New Clinical and Pathophysiologial Perspectives defining the Trajectory of Cirrhosis

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Abstract

Traditionally, the complications of cirrhosis were thought to result predominantly from circulatory disturbances consequent upon portal hypertension and the associated circulatory dysfunction resulting in alteration hepatic and organ perfusion. These culminated in the main complications of cirrhosis, namely, variceal bleeding, ascites and hepatic encephalopathy. Over the past two decades, large, international prospective studies have indicated the importance of systemic inflammation and organ immunopathology as additional features that are important in organ dysfunction of cirrhosis manifesting not only in the liver, brain, circulation and the kidneys but also affecting the immune system, gut, muscles, adrenal glands, sexual function, heart and the lungs. This review provides an overview of the traditional and emerging concepts around the initiation and maintenance of organ dysfunction of cirrhosis and proposes a potential new paradigm based upon better understanding of acute decompensation of cirrhosis. The interaction between the traditional concepts and the emerging perspectives remains a matter of great interest and the basis of future research.
Lay Summary

This review aims to describe new knowledge gained from several prospective studies along with the traditional view of why patients with cirrhosis develop complications by introducing the importance of inflammation as an important mechanism. These new studies suggest that in patients with cirrhosis, the occurrence of ‘decompensation’ marks the onset of a phase of rapid deterioration in about 50% patients. The new hypothesis provides insights into potential outcomes of patients following a decompensating event, which can range from low risk of short-term mortality to almost 100% risk.
Cirrhosis represents the culmination of decades of liver injury and is thought to represent an irreversible disease. Traditionally, the occurrence of the first major complications identified by portal hypertension and associated variceal bleeding, ascites and hepatic encephalopathy are thought to change the natural history of cirrhosis with the transition of the patient from a ‘compensated’ to a ‘decompensated’ state (1,2,3). This identified a clinical condition, which is associated with a high risk of mortality over the subsequent 5-years. Over the past two decades, following the clinical, prognostic and pathophysiologic characterisation of acute on chronic liver failure (ACLF), this classical view of the clinical course of cirrhosis needs to be revisited (1,3).

From a clinico-pathophysiologic perspective, the complications of cirrhosis have been thought to be directly related to severity of liver dysfunction and changes in portal hemodynamics that involves portal hypertension, portosystemic shunting, hepatic and extra-hepatic organ perfusion (4). Recently, the importance of systemic inflammation, particularly in cirrhotic patients who present with acute decompensation has been highlighted and shown to be independently associated with high-risk of short-term mortality (1,2,5,6). Perhaps, the greatest change in our understanding of the clinical course of cirrhosis comes from the demonstration of the importance of extra-hepatic organs in defining the short-term outcomes of cirrhotic patients with acute decompensation (1,3). Although there is some debate in the diagnostic criteria of ACLF the best studied and validated in studies across the world is the EASL-CLIF Consortium criteria, which will be referred to for the most part in this review [reviewed in (1)]. These extrahepatic manifestations of cirrhosis have been shown to be
associated with evidence of inflammation and cell death within these extrahepatic organs, collectively referred to as organ immunopathology (7,8,9,10).

There are three relevant clinical features that are important to highlight as introductory statements of the current review. The first is 'acute decompensation', which frequently signals the transition of cirrhotic patients from compensated to decompensated state, and subsequently develops in a recurrent form during the entire clinical course. It is classically defined as the acute development ascites, gastrointestinal hemorrhage or hepatic encephalopathy, or any combination of these, and may run widely different clinical courses. The second is ‘stable decompensated cirrhosis”, which defines a frequent type of patients with decompensated cirrhosis who, while receiving sustained prophylaxis with diuretics, and/or lactulose or rifaximin, and/or non-selective betablockers or repeated endoscopic treatment of esophagogastric varices, do not present episodes of AD for a long-time period. The concept of stable decompensated cirrhosis should be differentiated from 'recompensated cirrhosis', which is the clinical phase of the disease prior to the resolution of cirrhosis induced by successful treatment of the etiology of the disease (1,3,10). The aims of this review are to elaborate how our evolving understanding of cirrhosis and its complications is changing and to provide an overview of the traditional and emerging concepts around the initiation and maintenance of organ dysfunction of cirrhosis and propose a potential new paradigm.

**Insights into the clinical course of decompensated cirrhosis: The traditional view**
Cirrhosis may result from any type of chronic insult to the liver through inflammation, parenchymal necrosis, fibro/angio-genesis, and progressive vascular changes. Once established, cirrhosis is initially characterized by the absence of symptoms and good/acceptable quality of life until the appearance of one or more of its clinical manifestations. At this point, the disease acquires a rapidly progressive course with deterioration of liver function, repeated hospital admissions and poor quality of life (2,11). In the most advanced disease, the appearance of other organ dysfunction predicts imminent mortality (2,5,6). Since the very early descriptions of the natural history of cirrhosis, the disease has been termed compensated in the absence of symptoms and decompensated in their presence. In the last decades, long-term prospective studies have shown that liver-related mortality in cirrhosis only occurs after decompensation but can occur after first decompensation (1,2,3,11,12). Median survival of patients with compensated disease is in the order of 12-years compared with 2-4 years for those diagnosed at decompensation (2,11,13). Therefore, the most important outcomes are decompensation for compensated and death for decompensated cirrhosis. These marked differences have prompted the perspective that compensated and decompensated cirrhosis, defined by the absence and, respectively, presence or history of variceal bleeding, ascites, encephalopathy or jaundice, are distinct clinical states of the disease (2,3,13). Further disease states with increasing death risk have then been recognized in either compensated or decompensated cirrhosis and transitions across them have been described (12,14).

In compensated cirrhosis, two clinical states have been defined based on the presence or absence of gastro-esophageal varices. Absence of varices defines state 1 while their presence defines state 2: 5-year death risk is 1.5% and 10% respectively (13).
Patients in state 1 may be sub-classified in mild PH (MPH) (HVPG >5 mmHg and < 10 mmHg) with minimal or no risk of clinical events and clinically significant portal hypertension (CSPH) with HVPG ≥10 mmHg (15), the threshold for the development of esophageal varices and decompensation (16,17). This sub-classification has clinical relevance since in MPH, hyperdynamic circulation is not yet established and no response to non-selective beta-blockers (NSBB) is detected (18), leaving the etiological treatment of cirrhosis (19) as the only rational approach in this state (15). However, while NSBBs reduce HVPG in patients with CSPH, a significant reduction of decompensation has been shown only in state 2 (20,21). Importantly, liver stiffness measurement (LSM) ≥20-25 KPa alone or in combination with low platelet count and increased spleen size may non-invasively identify CSPH (specificity 0.90) (22) in compensated cirrhosis without varices, thus allowing state 1 sub-classification in clinical practice.

Given its associated risk of further clinical events and death, decompensation is a critical point in the clinical course of cirrhosis. In decompensated cirrhosis, clinical states with increasing risk of death have been defined by the type and number of decompensating events (Figure 1). When decompensation presents with variceal bleeding alone, state 3, 5-year mortality is 20%; for patients decompensating with any single non bleeding event (mostly ascites), state 4, 5-year mortality is 30%; after any second decompensating event or when decompensation occurs with any 2 or more decompensating events at once, 5-year mortality is 88%, state 5 (12). A late decompensation state was previously proposed after two meta-analyses (23,24) showing that infections and renal failure occurring in decompensated cirrhosis are associated with 1-year mortality of 63%. It is now clear that bacterial infections play a
relevant role throughout the course of cirrhosis by precipitating or aggravating
decompensation and that any organ dysfunction beyond the liver is associated with a
very high risk of imminent mortality (1,3), with acute on chronic liver failure (ACLF)
being the most significant expression of this disease progression (1,3). It is therefore,
the recurrence of infections, the appearance of extrahepatic organ dysfunction, ACLF,
refractory ascites, persistent encephalopathy or jaundice that may define *this late
decompensation state*; although heterogeneous, this group of patients share a very
high 1-year risk of death, ranging from 60% to 80%(2), and very high inflammatory
markers (2,5,6,).

**Relevance and diagnostic criteria of organ failures (OFs). Relation with
precipitating events and mortality**

The CANONIC and the PREDICT studies are two large scale prospective
observational studies performed in patients hospitalized with AD. The PREDICT data
(10), showed that most patients (60.7%) presented one or more organ failures (OFs,
severe impairment in organ function) or organ dysfunctions (moderate impairment of
organ function), according to the CLIF-Consortium Organ Failure score (CLIF-C OFs)
diagnostic criteria. The CANONIC data showed that among the 22% of patients
hospitalized with organ failure, 64.9% had a single organ failure, 24.4% had 2 organ
failures, and 10.6% had 3 organ failures or more (3). The most frequent OF at hospital
admission were liver and kidney *failure* followed by coagulation and cerebral failures
(3,10). Likewise, in patients with AD who develop ACLF after hospital admission, the
commonest OFs were renal failure (56%), followed by liver, coagulation, cerebral,
circulatory, and respiratory failures (44%, 28%, 24%, 17%, and 9%, respectively) (3).
The type and the rate of OFs is strongly related to the nature of the precipitating
event/s (PE). Thus, in the European studies (3,10), where the commonest PE is a bacterial infection and active alcoholism, kidney failure is a common OF. However, in China, where the commonest PE is the reactivation of HBV infection, liver and coagulation failures are the commonest OFs (1,25).

**Recompensation of cirrhosis.**

The clinical course of cirrhosis has been typically linked to progressive accumulation of fibrosis and portal hypertension 2). The recognition of a dynamic component (26) of portal hypertension led to its pharmacological treatment and, more recently, etiologic treatments have shown that also fibrosis may be substantially reduced (12;27), progressively introducing the concepts of *reversion of cirrhosis* (28) in compensated and in decompensated disease.

The outcome of patients recovering from (acute) decompensation is not yet clearly known and hence, there is no consensus on how to define *recompensation* as follow up time is limited to 1-year at present. It would require a symptom-free time-interval since the (only) previous decompensation and the ability to maintain this state without treatment. While such a situation might be expected after etiologic cure that may result in progressive reduction of fibrosis and portal hypertension, and even reversion of cirrhosis (19;27,28,29); this is unlikely with ongoing exposure to the etiological agent. In fact, stable recompensation has been reported after effective antiviral treatment in patients with HBV- (29) or HCV (30) related cirrhosis and with abstinence in those with alcohol-related cirrhosis (31). Therefore, accurate predictors of the risk of further decompensation are needed to define *recompensation*. The inflammatory pattern may be one of such predictors, as recently suggested by the PREDICT study (10), but long-
term prospective validation is needed. For now, patients recovering from
decompensation should still be included in the decompensated population and be
considered to have lower life expectancy compared with patients who have never
experienced any decompensation, unless they have successfully undergone
etiological treatment. However, even following successful etiologic cure, occurrence
of esophageal varices, decompensation and HCC has been reported. In patients with
HCV-related cirrhosis, the risk of de novo/additional acute decompensation is still
about 7% two years after the achievement of sustained virological response, being
associated with baseline HVPG≥16 mmHg and previous ascites (33). Therefore,
prognostic indicators of further decompensation are needed also in these patients, for
whom watchful follow-up is currently recommended (34,35).

The current understanding of the pathophysiological basis of decompensated
cirrhosis, AD and its limitations.

Cirrhosis as a systemic disease.
The current understanding of the pathophysiological basis of decompensated cirrhosis
originated from investigations by Pavlov in Saint Petersburg and Starling in London at
the end to the 19th century[36-40], who described hyperammonemia and portal
hypertension associated with exaggerated production of hepatic lymph as the main
mechanisms of encephalopathy and ascites, respectively. Three modern concepts
developed over these theories are of major interest for this review. The first was the
functional component of portal hypertension, which is related to under-expression of
vasodilators in the hepatic microcirculation, leading to increased intrahepatic vascular
resistance, and overexpression of vasodilators in the splanchnic circulation, leading to
overflow of blood into the portal venous system and the hyperdynamic systemic circulation of cirrhosis[36,37]. The second was the identification of new mechanisms of hyperammonemia, of ammonia entry into the brain, and on the deleterious effects of ammonia on neuronal function, which led to better understanding of brain dysfunction in cirrhosis[41-46]. Finally, the third important modern concept was the Peripheral Arterial Vasodilation Hypothesis, which reformulated the traditional pathophysiology of ascites and hepatorenal syndrome into a more complex sequence of events, proposing splanchnic arterial vasodilation and left ventricular dysfunction as the initial mechanism of effective arterial hypovolemia, the homeostatic activation of the renin-angiotensin-aldosterone system, sympathetic nervous system and antidiuretic hormone the intermediate processes, and renal fluid retention the final consequence[4]. These new concepts had great impact in the treatment of decompensated cirrhosis within the last decades.

Soon after this proposal, however, investigators began to understand the limitations of this pathophysiological paradigm of decompensated cirrhosis. Among the major arguments against this new view of the pathophysiology of AD and ACLF, the new concept of cirrhosis as a systemic disease stands out. A systemic disease is a condition that affects the whole body, and there were clear observations suggesting that this definition fits well for patients with decompensated cirrhosis. Typical examples of extrahepatic manifestations of cirrhosis are renal dysfunction (47-50), hepatic encephalopathy (HE) (51,52), cirrhotic cardiomyopathy (53,54), hepato-pulmonary syndrome (55,56), porto-pulmonary hypertension (57,58), gut dysfunction, sarcopenia, and endocrine dysfunction, most of which have negative impact on survival (59-64). Such widespread organ/system dysfunction fit badly into the
paradigm derived from the peripheral arterial vasodilation hypothesis and other independent mechanisms proposed by each organ dysfunction. Secondly, this paradigm did not offer a reasonable explanation for the extremely high incidence of bacterial infections at admission and during early follow-up (roughly 60%) in patients hospitalized with AD[1,3,10]. Such a high risk of bacterial infections was proposed to be related to severe impairment of the immune system, which was also not satisfactorily explained in the context of the other complications. Finally, the clinical observation that ascites, encephalopathy, gastrointestinal hemorrhage and infections frequently develop simultaneously in combinations of two, three or even four complications in about 50% of patients hospitalized with AD[10] is more compatible with a common pathophysiological mechanism rather than with specific mechanisms for each complication.

**Background of systemic inflammation in decompensated cirrhosis**

Systemic inflammation is a condition in which there is inflammation throughout the body. It may be acute or chronic, mild, moderate or severe, cause or consequence of various pathological processes, is characterized by activation of the innate immune system, increased circulating levels of inflammatory mediators and, in severe cases, proliferation of neutrophils, monocytes and dendritic cells. The culminate in systemic marked neuroendocrine and metabolic changes that aim to conserve metabolic energy and allocate more nutrients to the activated immune system. Systemic inflammation is a major pathophysiological process in many clinical conditions including infections, obesity, atherosclerosis, metabolic syndrome, diabetes, non-alcoholic steatohepatitis, chronic pulmonary obstructive disease, depression and
neurodegenerative diseases, osteoporosis, autoimmune diseases and cancer, and it is considered the most significant cause of death in the world today.

Systemic inflammation is a topic of growing interest in cirrhosis. The first studies were published in the 1970s and since then a large body of investigations has been reported[65-83]. The interest of clinical hepatologists on systemic inflammation is logical considering the predisposition of patients with decompensated cirrhosis to developed translocation of viable bacteria and bacterial products from the intestinal lumen to the systemic circulation due to quantitative and qualitative changes in the microbiota, increased permeability of the mucosa and impaired function of the submucosal immune system. The intestinal flora is, therefore, a formidable source of systemic inflammation in these patients.

In this second part of the article we summarize current data supporting that the clinical course of decompensated cirrhosis occurs in a context of severe chronic systemic inflammation associated to transient episodes of acute inflammatory bursts, during which, patients may develop AD or ACLF[5].

The systemic inflammation hypothesis: A new perspective in defining the clinical course of acute decompensation of cirrhosis.

As indicated above, the current paradigm of AD and organ failure in cirrhosis does not satisfactorily explain the complexity of AD, particularly the simultaneous development of two or more major complications (ascites, encephalopathy, gastrointestinal hemorrhage or infections) together with widespread impairment in the function of most extrahepatic organs, including the kidney, brain, lungs, heart, thyroid, adrenal glands, immune system, circulation and coagulation. For such a complex systemic syndrome, this paradigm only offers individual mechanisms specific for each complication or
organ dysfunction. Systemic inflammation, in contrast, is a systemic syndrome that may lead to severe impairment of all these organs/systems. In addition, it mainly increases portal hypertension and liver failure, impairs cardiocirculatory and renal function, increases the permeability of the blood brain barrier, and impairs neuronal function, exerting a synergistic effect with hyperammonemia[72-75].

This section summarizes the clinical course of AD, stratified into 6 phenotypes with different prognosis, and a new pathophysiological paradigm of AD and ACLF proposed by the EASL-CLIF consortium, in which systemic inflammation plays a predominant role[5]. This paradigm, named “The Systemic Inflammation Hypothesis”, largely based investigations derived from the CANONIC and PREDICT studies[3,10] (Table 1), does not exclude the traditional specific mechanisms of ascites, encephalopathy or variceal hemorrhage (i.e. portal hypertension, circulatory and renal dysfunction and hyperammonemia) but propose that they would act synergistically with systemic inflammation in the development of these complications and of the widespread impairment of in the function of extrahepatic organs.

**Stratification of patients with AD**

Due to the complexity of AD and the ACLF syndrome, the large number of patients included in the PRECIT and CANONIC studies, and the need for a strategy to correlate the severity of systemic inflammation with patients’ clinical course and mortality, the first analysis in both studies was to develop and propose a new stratification criteria for patients with ACLF (AD-ACLF group) and with AD without ACLF (AD-No ACLF group) (Figure 2). AD was diagnosed as the development of ascites, encephalopathy or gastrointestinal hemorrhage or any combination of these complications. The ACLF syndrome was defined as an episode of AD associated with single or multiple organ
failure and high risk of short-term patient mortality (>15% in 28 days). Patients with AD-ACLF into three grades (ACLF 1, 2, and 3) according to the number of organ failures at admission. Six organ/system failures (liver, kidney, brain, coagulation, circulation, and respiration) were considered for this stratification, and the CLIF-C Organ Failure Score was specifically designed to diagnose organ/system failures[84]. The PREDICT study patients did not permit to stratify patients with AD-No ACLF into subgroups with different prognosis at the time of hospital admission. Therefore, they were stratified according to clinical course during the three-month follow-up period. Three subgroups of patients with different prognosis were identified: Pre-ACLF subgroup including patients developing ACLF within 3 months after admission; Unstable Decompensated Cirrhosis (UDC) subgroup, including patients dying in hospital or requiring re-hospitalization for reasons other than ACLF during the 3-month follow-up period; and Stable Decompensated Cirrhosis (SDC) subgroup, including patients who were discharged alive and did not require re-hospitalizations during the 3-month follow-up period. These six subgroups showed marked differences in cumulative 1-year mortality (figure 3A). Figure 3B shows the cumulative development of ACLF and mortality during the 3-month follow-up period in the pre-ACLF group.

The CANONIC AND PREDICT studies did not considered patients with mild decompensation not requiring hospitalisation such as mild ascites [35], Grade 1 hepatic encephalopathy [85,86] or clinically significant portal hypertension with or without varices [17]. However, this subgroup identifies a set of patients with higher risk of acute decompensation and therefore increased risk of mortality. Additionally, Tonon et al. suggest the existence of a new entity referred to as ‘acute kidney disease’ that affects about 30% cirrhotic patients during routine clinical follow up. About 78% of
these patients develop this syndrome without any episode of acute kidney injury and have have 5-year survival of about 12\%\[87\].

**AD correlate with systemic inflammation.**

**Hospital admission:** Patients with compensated cirrhosis show no evidence of systemic inflammation, as estimated by the frequency of inflammatory cells in blood and the plasma concentration of markers of systemic inflammation and inflammatory cytokines. In contrast, systemic inflammation is severe in all subgroups of AD-No ACLF and increased further in patients with AD-ACLF [10](**Figure 3C and 3D**). The systemic inflammation is higher in patients with pre-ACLF than in patients with SDC and UDC. In patients with AD-ACLF, severity of systemic inflammation increased in parallel with the number of organ failures [3](**Figure 3E**). Therefore: 1. Evolution of compensated to decompensated cirrhosis represents the transition from a status with unremarkable to one with severe systemic inflammation; 2. Severity of systemic inflammation at hospital admission correlates closely with severity of AD and short-term mortality during follow up.

**Precipitants.** Bacterial infections and acute alcoholic hepatitis, the two most important pro-inflammatory precipitants, are present either alone, in combination, or associated with other precipitants in approximately 95\% patients with AD-No ACLF or AD-ACLF with identifiable precipitants at admission[3,10]. The percentage of patients without identifiable precipitants (indeterminate precipitants[10]) is much higher in AD-No ACLF (61\%) than in AD-ACLF (29\%)\[3\]. Sequential measurement of the plasma levels of interleukin-6 (IL-6) in patients with AD-No ACLF followed-up for 12 weeks detected frequent and intense peaks of systemic inflammation of variable duration (between
days or weeks) in the absence of apparent clinical events in a significant number of patients, indicating that chronic systemic inflammation in patients with decompensated cirrhosis is not a steady process likely as consequence of transient episodes of severe bacterial translocation [88]. The number of precipitants at admission correlates with the severity of systemic inflammation and 90-day mortality[10]. Therefore: 1. Bacterial infections and acute alcoholic hepatitis are the major precipitants of AD-No ACLF and AD- ACLF. Other precipitants are present in a small proportion of patients; 2. The number of precipitants correlates directly with the severity of systemic inflammation at admission and the 90-day mortality, suggesting an additive effects of precipitants in systemic inflammation; 3. Most patients with AD-No ACLF (70%) but only one-third of patients with AD-ACLF do not present identifiable precipitants, suggesting that AD likely develops in the context of acute bursts of bacterial translocation and systemic inflammation in a significant number of patients.

**Clinical Course.** The distinct clinical courses of AD-No ACLF and AD-ACLF (Figure 2) subgroups correlate with differences in the progression of systemic inflammation[3,10,88]. Patients with SDC follow an excellent clinical course with very low mortality in the context of marked reduction in the grade of systemic inflammation (Figure 3E). In contrast, patients with pre-ACLF develop the most severe clinical course among the AD-No ACLF patients in the setting a significant increase of systemic inflammation (Figure 3F). The UDC subgroup shows relevant differences with the other two AD-No ACLF subgroups. They present a complicated course and relatively high mortality despite moderate systemic inflammation at hospital admission and significant improvement during follow-up (Figure 3E). On the other hand, they show surrogates of severe portal hypertension (gastrointestinal hemorrhage,
treatment with transjugular portosystemic shunt, and hypovolemic shock as cause of
death) more frequently than the other two groups. Therefore, the clinical course of
patients with UDC likely depends on the progression of portal hypertension and not of
systemic inflammation. The clinical course of the AD-ACLF subgroups also correlates
with the course systemic inflammation (Figure 3F). Thus, whereas resolution or
improvement of ACLF occur in the setting of significant decrease of systemic
inflammation, worsening of ACLF develops in parallel with aggravation of the
inflammatory markers. Therefore: 1. The clinical course of most patients with AD
(SDC, Pre-ACLF, ACLF-1, ACLF-2 and ACLF-3) Idepends on the evolution of
systemic inflammation; 2. In patients with UDC, however, clinical course likely
depends on a rapid progression of portal hypertension.

**Immunosuppression is the likely mechanisms of bacterial infections in AD**

Immunosuppression, a mechanism to limit vigorous systemic inflammation, was first
proposed in patients with severe sepsis to account for unexplained aggravation of the
primary infection or the development of secondary infections after the resolution of the
initial infection[89,90,91]. Among 407 patients with AD-ACLF in the CANONIC study,
the incidence of infections at admission or during hospitalization was 65%[3]. The
corresponding incidence of infection in the 1071 PREDICT study patients with AD-No
ACLF was 53%[10]. Such extremely high incidence of infections strongly suggests
immunosuppression. Indeed, among the soluble molecules contributing to
immunosuppression, the anti-inflammatory IL-10 and quinolinate were markedly
increased at hospital admission in patients with AD-No ACLF and even more in those
with AD-ACLF[88,92]. Moreover, alterations of the innate immune cells that may
contribute to immunosuppression have also been reported in patients with AD[93-99].
These features are already present at the time of hospitalization, which suggests that immunosuppression coincides with the onset of systemic inflammation and AD development in most patients and that both bacterial infections present at hospital admission and those developed thereafter are likely due to this immune dysfunction.

Systemic inflammation causes AD through acute metabolic dysregulation affecting energy production by the peripheral organs.

As indicated, AD develops in the context of acute bursts of systemic inflammation associated with identifiable precipitants or likely secondary to acute episodes of bacterial translocation. AD can develop in patients with compensated cirrhosis and therefore without baseline systemic inflammation or in patients decompensated cirrhosis and chronic systemic inflammation. It has been suggested that there is a critical threshold of systemic inflammation beyond which AD develops [100]. Patients with compensated cirrhosis would therefore require a more severe burst of systemic inflammation to develop AD than patients with decompensated cirrhosis. Indeed, patients with ACLF without prior history of AD develop the syndrome in the context of higher concentration of white cell count and c-reactive protein and showed higher mortality rate at 28 days than patients with ACLF with prior history of AD[3].

The metabolomic and lipidomic fingerprints of patients with ACLF, either infected or not infected, identified the three characteristic metabolic dysregulations observed in patients with severe sepsis or other clinical conditions associated with systemic inflammation and multiorgan failure[101-103]. The first is an intense systemic catabolic reaction in response to the effect of pathogen and damage associated molecular patterns (PAMPs and DAMPs), cytokines and other inflammatory mediators on the
sympathetic nervous system, the hypothalamic-pituitary-adrenal axis and glucagon secretion[104,105]. This leads to intense glycogenolysis, lipolysis and proteolysis and increased circulating levels of glucose, fatty acids and amino acids to fuel the inflammatory reaction and the function of peripheral organs.

The second metabolic characteristic is the prioritization of glucose metabolism to the immune system[104,105]. Systemic inflammation is an energetically expensive process due to the synthesis of a myriad of pro- and anti-inflammatory molecules and acute-phase proteins, activation and proliferation of the immune cells and phagocytosis. The energetic metabolism (ATP synthesis) by the activated immune cells largely depend on glucose metabolism by the cytosolic aerobic glycolysis pathway and not on mitochondrial oxidation of acetyl-CoA through the Krebs cycle and Oxidative Phosphorylation (OXPHOS) pathway (Figure 4A). There are two reasons for this change. The first is that energy production by aerobic glycolysis, although energetically inefficient, is extremely rapid, a feature of critical importance to confront an acute process requiring high energy consumption. The second is that metabolites derived from aerobic glycolysis are channelled through specific pathways that increase the nucleotide and RNA synthesis (i.e. the pentose phosphate pathway, PPP) required for the inflammatory reaction,

The third metabolic characteristic is a consequence of the prioritization of glucose metabolism to the activated immune system[106,107]. Energy production by peripheral (non-immune) organs, therefore, must rely on fatty acids and amino acids catabolism in the mitochondria. However, severe systemic inflammation adversely affects the mitochondrial metabolic pathways. Indeed, the entry of fatty acids into the
mitochondria is severely impaired in AD and particularly in patients with AD-ACLF[67] (Figure 4A). Systemic inflammation also inhibits mitochondrial β oxidation of fatty acids and accordingly OXPHOS and ATP synthesis[108]. Finally, mitochondrial generation of NO, carbon monoxide and other reactive molecules that increase during systemic inflammation, damage mitochondrial DNA and proteins of the electron transport chain, and cause generalized mitochondrial dysfunction[108]. This likely explains that whereas the cytosolic amino acid catabolism is markedly increased in AD-No ACLF, it is impaired in the mitochondria, as reflected by the lack of increase in ketone bodies by the liver.

The expression of the metabolic dysregulation in AD, therefore, is characterized by increased circulating levels of metabolites derived from glycolysis, increased concentration of carnitines, reflecting and impaired transport of cytosolic fatty acids into the mitochondria, and increased concentration of metabolites derived from the cytosolic catabolism of amino acids [67] (Figure 4B). Interestingly, whereas the metabolome fingerprint of patients with compensated cirrhosis is almost normal, it is significantly altered in patients with AD-No ACLF, and severely altered in patients with AD-ACLF (Figure 4B).

In summary, while glycolysis and energy production by the immune cells are markedly activated in patients with AD, severe metabolic dysregulation with hypometabolism in peripheral organs develops as consequence of systemic inflammation. Since the homeostasis of cell function is energy-dependent, the systemic inflammation hypothesis proposes that metabolic dysregulation is the cause of impairment in the function of peripheral organs in AD-No ACLF and of single or multiple organ failure in
AD-ACLF[5]. Metabolic dysregulation may operate by itself or in combination with organ specific mechanism (e.g. hyperammonemia for brain failure or effective arterial hypovolemia for ascites and renal failure). However, it is the predominant mechanism of the widespread impairment in organ function AD.

Conclusions and Future Perspectives

The traditional multistate models for prognosis of cirrhosis have been validated in several studies and are currently widely used in clinical practice but mainly focus of the natural history of patients that are relatively stable. Recent studies have focussed on better understanding the outcomes of cirrhotic patients with acute decompensation adding to the traditional models. The new understanding of the revised trajectory of cirrhosis helps to stratify patients into clinical and pathophysiological groups. The associated scoring systems, the CLIF-OF score to diagnose ACLF [3], the CLIF-AD (CLIF acute decompensation) score to prognosticate on patients with AD no-ACLF [84] and the CLIF-C ACLF score (CLIF Consortium acute on chronic liver failure score) to provide prognostic information about patients with ACLF are likely to help stratify patients for admission to intensive care, liver transplantation, defining futility of ongoing intensive care and very importantly for selection in clinical trials.

For instance, patients with AD no-ACLF could run 3 distinct courses with very widely differing mortalities [10]. Likewise, the severity of ACLF may vary from a very low risk of death to a risk that nears 100% [3]. The recognition that these clinical courses are associated with relatively distinct pathophysiological states allows attempts at drug development targeting specific patient populations appropriately. Taking into account
the data presented here, it is possible that the failure to find an efficacy signal in large trials of steroids in alcoholic hepatitis (STOPAH study) [109], extracorporeal liver support devices such as molecular adsorbents recirculating system (MARS, RELIEF trial) [110], PROMETHEUS (HELIOS trial) [111] and Extracorporeal Liver Assist Device (ELAD) in patients with ACLF [112] was because of a lack of stratification, i.e. the inclusion of patients with widely varying mortality rates. Several clinical trials of novel therapeutics based upon the new understanding of the trajectory of cirrhosis are underway, such as APACHE and DIALIVE, which targets patients with ACLF Grades 2-3; PRECIOSA, which targets AD no-ACLF patients with UDC and TAK-242, a toll-like 4 receptor antagonist, which targets patients with pre-ACLF and ACLF 1-2. Additionally, recent studies have indicated that patients with ACLF Grade 3 can achieve excellent survival rates after transplantation and are disadvantaged by the current organ allocation system [113]. This has led to a re-think about how organs should be allocated leading to a pilot programme being introduced in the UK where patients with severe ACLF will be prioritized. We suggest that this new understanding would help to reduce the death of patients with cirrhosis.

Although one of the aims of this paper was to try and build links between the traditional hypothesis and the new paradigm described here, we were not able to do so. Future studies should address this aim to allow harmonisation between the traditional views of the trajectory of cirrhosis and the new understanding.
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# Table 1. The proposals of the Systemic Inflammation Hypothesis

1. AD is a clinical entity with common pathophysiological background for all complications and organ failures.

2. In the majority of patients, systemic inflammation is a major driver in the progression of compensated to decompensated cirrhosis, the recurrence of AD during the clinical course of the disease, and the development of single or multiple organ failure.

3. Once the first episode of AD develops, systemic inflammation follows a chronic course, with transient periods of aggravation due to proinflammatory precipitants or bursts of bacterial translocation resulting in repeated episodes of AD.

4. The clinical course of AD largely depends on the evolution of systemic inflammation.

5. AD-ACLF is the extreme expression of systemic inflammation.

6. Systemic inflammation perturbs peripheral (non-immune) organ function and causes organ failures mainly through a severe metabolic dysregulation leading to mitochondrial dysfunction and impaired energy production. Other mechanisms include direct tissue damage by the systemic inflammatory process (immunopathology) or the synergistic effects of organ specific mechanisms such as hyperammonemia in encephalopathy.
Figure legends

Figure 1. The traditional perspective of the multistate model of clinical trajectory of decompensated cirrhosis across different clinical states with increasing risk of death.

Clinical states are defined according to the type of decompensation and increasing mortality. Decompensation may be precipitated by acute or non-acute events. Acute on chronic liver failure (ACLF) may occur at any disease state. The relative incidence of acute and non-acute decompensation is not yet known. State 3 is defined by the occurrence of variceal bleeding alone, state 4 by any single non-bleeding event, state 5 by any 2 or more events and the late decompensate state by any event with organ failures either with or without ACLF. 5-year mortality across states from 3 to 5 is in the order of, respectively: 20%, 30%, 88%. With late decompensation mortality ranges between 60% and 80% in one year.

The arrows at the bottom indicate the intensity of some major mechanisms of disease progression, respectively: hyper/hypodynamic circulation, Bacterial translocation and risk of infections, systemic inflammation, organ failures.

Figure 2. Clinical trajectory of cirrhosis based on the new understanding of acute decompensation of cirrhosis. This figure describes that patients with compensated cirrhosis have different risk of developing an episode of acute decompensation on the basis of whether they have clinical features of cirrhosis such as mild to moderate ascites, grade 1 hepatic encephalopathy or clinically significant portal hypertension. Following acute decompensation, the patients may either have ACLF or no ACLF. No-ACLF phenotype: patients with AD without ACLF which may
follow 3 clinical courses (a) stable decompensated cirrhosis sub-phenotype: patients not requiring further hospital readmission during a 90-day follow-up period (b) unstable decompensated cirrhosis sub-phenotype: patients requiring one or more hospital readmissions unrelated with ACLF development during a 90-day follow-up period (c) pre-ACLF sub-phenotype: patients with AD no-ACLF developing ACLF during a 90-day follow-up period. The second is the ACLF phenotype, which is defined by single renal failure or single non-renal organ (liver, brain, coagulation, circulation, respiration) failure if associated with renal dysfunction and/or brain dysfunction (chronic-liver failure organ failure organ failure score). Its severity and the patient’s risk of mortality is defined by the number of organ failures.

Figure 3. Outcome of acute decompensation and role of inflammation. Panel A. Cumulative incidence of mortality curves of the six subgroups of patients with AD. Patients with SDC, UDC and Pre-ACLF were included in the Predict study. Patients with ACLF1, ACLF2 and ACLF3 were included in the Canonic study. Panel B. Cumulative percentage of patients with Pre-ACLF developing ACLF or dying during the 3-month follow-up period per week. Panel C. Severity of systemic inflammation at admission, estimated by the plasma concentration of C Reactive Protein (CRP), in patients with ACLF1, ACLF2 and ACLF3 included in the Canonic study (No-ACLF: patients without ACLF at admission). Panel D. Severity of systemic inflammation, estimated by the plasma concentration of Interleukin 6 (IL-6) in a control group of patients with compensated cirrhosis (CC) and in patients with SDC, UDC and Pre-ACLF included in Predict study. Panel E. Plasma concentration of C Reactive Protein (CRP) at hospital admission and at the last visit during the 3-month follow-up period in patients with Stable Decompensated Cirrhosis (SDC), Unstable Decompensated
Cirrhosis (UDC) and pre-ACLF included in the Predict study. Panel F. Plasma concentration of interleukin 6 (IL-6) at hospital admission and at the last follow-up visit in patients with ACLF included in the Canonic study who develop improvement of worsening of ACLF.

Figure 4. Evidence of severely deranged metabolism in cirrhosis patients with acute decompensation. Panel A. Major abnormalities of cell metabolism in AD. In the cytosol there is activation of glycolysis, pentose phosphate and glucuronic pathways, and ATP and lactate synthesis. This occurs predominantly in the immune cells. In the mitochondria there is downregulation of carnitine-acylcarnitine translocase, and inhibition of β-oxidation, leading to fatty acid hypometabolism by the Krebs cycle and impaired oxidative phosphorylation and ATP synthesis. There is also increased mitochondrial oxidative stress and protein damage, which further impairs mitochondrial function. This occurs in the cells of peripheral organs. The net effect of the whole process is an increased production of energy by the immune system and hypometabolism and decrease energy production by peripheral organs. These changes explain the widespread dysfunction of peripheral organs in non-severe cases (AD-No ACLF clinical phenotype) and multiorgan failure (AD-ACLF clinical phenotype) in cases with extreme mitochondrial dysfunction. Upregulated mechanisms are represented in green and downregulated mechanisms are represented in red. (Modified from Arroyo V et al, N Engl J Med 220; 382:2137-2145). Panel B. Cleveland Plots. The right plot shows the whole set of annotated metabolites ranked according to their fold changes in patients with AD-ACLF versus healthy subjects (HS) (the highest fold changes on the top, the lowest at the bottom). Fold changes of AD-No ACLF vs HS and compensated cirrhosis (CC) vs HS are also showed. Left inset,
zooming of the 50 top metabolites in the three comparisons. The dotted vertical line represents values in HS. Metabolites from carbohydrates, fatty acids and amino acids are identified by colors (Moreau R, et al J Hepatol 2020; 72:688-701).
Any transition may be precipitated by acute decompensation which is associated with worse outcome. ACLF may occur at any disease state.
Stable Decomp Cirrhosis: 100% Survival over 3-months
Unstable Decomp Cirrhosis: 70% Survival over 3-months
pre ACLF: 50% Survival over 3-months

CSPH:
Clinically significant portal hypertension
Large proportion undiagnosed
Time: Years

Emergency hospitalization with acute decompensation
Variceal Bleeding
Infection

60% Stable decomp. cirrhosis*
70% No ACLF
20% Unstable decomp. cirrhosis **
20% Pre-ACLF
70% Alive at 3 months
30% Death or transplant

High risk of further decompensation and mortality
Low risk of further decompensation and mortality

3-12 months from acute decompensation

Stable decomp. cirrhosis*  60%
Alive at 3 months70%
20% No ACLF
20% Pre-ACLF
30% Death or transplant

Unstable decomp. cirrhosis ** 20%
ACLF

Clinical signs
CSPH/Varices
Mild-Moderate ascites
Grade 1 HE

Long–term outcomes
Time: Months to years

* Stable Decomp Cirrhosis: 100% Survival over 3-months  ** Unstable Decomp Cirrhosis: 70% Survival over 3-months  *** pre ACLF: 50% Survival over 3-months
CSPH: Clinically significant portal hypertension

Large proportion undiagnosed
Time: Years

Starts with hospitalization
Time : 3 months

Ascites
Hepatic Encephalopathy

No clinical signs
Low risk
High risk

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