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Abstract: The spectrum of alcoholic liver diseases (ALD) includes steatosis, steatohepatitis, progressive liver fibrosis, and cirrhosis. Acute-on-chronic liver failure (ACLF) is a recently defined entity occurring in patients with chronic liver diseases and characterized by acute decompensation, organ failures and high risk of short-term mortality. Active alcohol consumption, alcoholic hepatitis and bacterial infections are the most frequent precipitating events of ACLF in the context of ALD (ALD-ACLF). The specific management of this entity remains unknown and the place of salvage liver transplantation controversial. This overview details the current knowledge on specific aspects of epidemiology, pathophysiology, prognosis and management of ALD-ACLF.

Acute-on-Chronic Liver Failure in Patients with Alcoholic Liver Disease

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Abbreviations: ABIC, age, serum bilirubin, international normalized ratio and serum creatinine; ACLF, Acute-on-Chronic Liver Failure; ALD-ACLF, alcohol-related ACLF; APASL, Asian Pacific Association for the Study of the Liver; EASL-CLIF, CRP, C-reactive protein; CS, corticosteroids; DAMPs, damage associated molecular patterns; European Association for the Study of the Liver – Chronic Liver Failure consortium; FMT, fecal microbiota transplantation; G-CSF, granulocyte colony stimulating factor; GAHS, Glasgow alcoholic hepatitis score; LT, liver transplantation; NACSELD, North American Consortium for the Study of End-Stage Liver Disease; OFs, organ failures; PAMPs, pathogen associated molecular patterns; PIRO, Predisposition, Injury, Response, Organ Failure; PTX, pentoxyfilline; RCT, randomized controlled trial; sAH, severe alcoholic hepatitis; WCC, white cell count.

Abstract

The spectrum of alcoholic liver diseases (ALD) includes steatosis, steatohepatitis, progressive liver fibrosis, and cirrhosis. Acute-on-chronic liver failure (ACLF) is a recently defined entity occurring in patients with chronic liver diseases and characterized by acute decompensation, organ failures and high risk of short-term mortality. Active alcohol consumption, alcoholic hepatitis and bacterial infections are the most frequent precipitating events of ACLF in the context of ALD (ALD-ACLF). The specific management of this entity remains unknown and the place of salvage liver transplantation controversial. This overview details the current knowledge on specific aspects of epidemiology, pathophysiology, prognosis and management of ALD-ACLF.

1) The concept of Acute-on-Chronic Liver Failure

Acute on chronic liver failure (ACLF) is a recently defined entity that occurs in patients with cirrhosis and is characterized by acute deterioration, organ failures and high risk of short-term mortality [1,2]. Currently different definitions have been created by several scientific societies (the Asian Pacific Association for the Study of the Liver [APASL], the European Association for the Study of the Liver – Chronic Liver Failure consortium [EASL-CLIF], the North American Consortium for the Study of End-Stage Liver Disease [NACSELD], reviewed in details elsewhere [3]). The syndrome is characterized pathophysiologically by systemic inflammation and altered host response to injury. From the clinical perspective, the condition can be described using the Predisposition, Injury, Response, Organ Failure (PIRO) concept [4]. Factors such as age, aetiology of the underlying liver disease, previous decompensation constitute *P*redisposition. The event precipitating the development of ACLF in a previously stable cirrhosis constitutes *I*njury. Whether ACLF is associated with infection, inflammation and/or immune failure describes *R*esponse and the type and number of organ failures constitutes *O*rgan failure. In alcohol related ACLF (ALD-ACLF), the underlying liver disease is alcohol related cirrhosis. The following section describes the clinical features, prognosis, pathogenesis and treatment of ALD-ACLF. Finally, this article also discusses the current controversies in the concept about ACLF.

2) The precipitating events for ALD-ACLF.

2.1. Active alcohol consumption as a trigger event of ACLF (including severe alcoholic hepatitis [sAH])

In the CANONIC European observational study, active excessive alcohol consumption (defined by more than 14 units per week in women and 21 units per week in men) within the past three months was recognized as the second most frequent precipitating event (~25%) of ACLF after bacterial infection [2]. Patients with acute decompensated alcoholic cirrhosis and active excessive alcohol consumption were younger and more marked biological alterations (higher total bilirubin, leukocyte count and INR). The prevalence and the severity of ACLF were also increased in this subgroup compared with the rest of patients, suggesting that alcohol *per se* triggered liver damage responsible of ACLF [2]. In South Asia, alcohol consumption is currently the most frequent acute hepatic insult (~50%) responsible of ACLF [5]. Alcoholic hepatitis (AH) could be the underlying entity induced ACLF but very few liver biopsies (proving the diagnosis) were performed in these studies. We know that AH frequently progresses to multiple organ failures, which are a leading cause of death [6]. In a prospective cohort of patients with severe AH (sAH, modified discriminant function ≥ 32), EASL-CLIF ACLF was reported in 65% of cases either at the time of sAH diagnosis or within 6-month follow-up [7]. Currently, we do not know if some alcohol-induced ACLF is a specific form of ALD or a merely clinical progression of sAH. To answer to this question, we need high-quality liver histological and molecular data correlated with well-defined clinical entities. A study of hospitalized patients with alcohol-related cirrhosis with liver biopsy suggested an association between specific histological features (ductular bilirubinostasis

and cholangiolitis) and ACLF [8]. More recently, histological studies have demonstrated marked evidence of cell death due to apoptosis and necroptosis [9,10].

2.2. Other trigger events of ACLF in patients with ALD (alcoholic cirrhosis)

Patients with ALD are prone to develop infection due to multiple defects in their innate and adaptive immune system. This susceptibility is reviewed in details elsewhere [11]. In Europe and North America, bacterial infections are the most identifiable precipitating factor of ACLF in patients with cirrhosis from all etiologies, in particular alcoholic cirrhosis [2,12]. Moreover, bacterial infection is the only independent predictor of the occurrence of ACLF in a cohort of patients with sAH [7]. In China, bacterial infection is considered as a precipitating factor of ACLF in 44% [13]. In other parts of Asia, these data are lacking due to the fact that the APASL definition of ACLF requires an acute hepatic insult and bacterial infection is not considered as a part of the syndrome.

Superimposed acute viral hepatitis A or E, hepatitis B flare, drug-induced liver injury are other potential precipitating event of ACLF in patients with alcoholic cirrhosis. A classical diagnostic workup must be made to exclude these etiologies.

3) Specific mechanisms of ALD-ACLF

The specific clinical and pathophysiologic feature of ACLF irrespective of aetiology is the presence of organ failure (s) and evidence of systemic and hepatic inflammation [2,4]. The pathogenic mechanism underlying the development of ACLF is unclear and the mechanism underlying systemic inflammation is unknown. Based upon the existing data,

one can start to build a hypothesis, which is described in Figure 1 and will be explored further in this section.

3.1. Evidence of systemic inflammation and immune dysfunction in ALD-ACLF and its association with mortality

Systemic inflammation: It is clear from many studies that systemic inflammation is a particular feature of ACLF in general and significantly over represented in ALD-ACLF [2,4,6]. Data from the CANONIC study clearly demonstrated that patients with ACLF have more marked systemic inflammatory response manifested by elevated white cell count (WCC) and C-reactive protein (CRP) [2]. Indeed, the study confirmed that WCC was indeed an independent predictor of mortality and this has been incorporated into the CLIF-C ACLF prognostic scoring system to define the risk of death of patients [14]. It is not clear whether this represents an alteration of host response to injury or whether it is due to an inability to resolve inflammation as other studies suggested that a lack of reduction in CRP was associated with increased mortality [3]. It is intriguing to note that the increase in WCC is predominantly due to neutrophilia. The neutrophil/lymphocyte ratio was shown be predictive of increased mortality in ALD-ACLF study [15,16]. The mechanism underlying this discrepant and important alteration in WCC is unclear but may be due to the effect of increased granulocyte colony stimulating factor (G-CSF) that was observed in ALD-ACLF patients as G-CSF is known to act on the bone marrow to increase granulopoeisis whilst reducing the lymphocyte and monocyte lineages [17]. This hypothesis would argue for a deleterious effect of administering G-CSF to ALD-ACLF patients but the available clinical data suggest the opposite [18]. More studies are

needed to better define the mechanisms underlying alterations in the cellular phenotypes in ALD-ACLF and the role of G-CSF.

Circulating cytokines: These changes in WCC and CRP are also associated with increases in the circulating cytokines in patients with ACLF [19–21]. The changes in the pattern of cytokines are however not consistent and depend upon the severity of ACLF, the underlying cause of the liver disease and the precipitating event. Data from a sub-study of the CANONIC study demonstrated clearly that both pro and anti-inflammatory cytokines were elevated in ALD-ACLF patients suggesting the existence of a mixed inflammatory response [21]. IL-8 tended to be more elevated in patients when alcohol abuse was the main precipitating event, whereas IL-6 was more likely to be elevated in the patients in whom infection was the precipitating event. In the patients with no identifiable precipitating events, cytokinemia was limited suggesting perhaps that this group of patients are pathophysiologically different [21]. The mechanism underlying these widely varying cytokine profiles are unclear but suggest the existence of a complex alteration of the immune system. It was therefore not surprising to note that large studies using corticosteroids, pentoxifylline or targeting TNFα have not been successful in patients with alcoholic hepatitis, which is an important cause of ALD-ACLF [22–24]. Studies targeting IL-1β are currently underway and the results of these studies are awaited.

Immune cell dysfunction: These changes in circulating markers of inflammation are associated with changes in the functional characteristics of the circulating inflammatory

cells in ALD-ACLF. It is becoming clear that with increasing severity of ACLF, there is a shift of the immune cellular function from a pro-inflammatory to an anti-inflammatory phenotype, which may explain the very high risk of infection in these patients, which is frequently the cause of death [2,7,22,25]. All cell lineages and both the innate and adaptive immune defects are observed in ALD-ACLF but the mechanisms underlying these changes are unclear. The available data are summarized in Table 1. In general, it appears that although cellular functional defects are measurable evidenced by an inability of the cells to kill and clear bacteria, they also generate pro-inflammatory molecules and these defects are due in part to circulating humoral factors [26–33]. In *in vitro* studies, removal of endotoxin from plasma was shown to restore neutrophil function and monocyte function could be rescued by albumin as it binds to prostaglandin E2 [26,27]. Circulating ligands of PD1 and TIM3 receptor, which alter lymphocyte function have been shown to be present in ALD-ACLF [29]. Taken together, these studies point to the potential of developing targeted interventions to address cellular dysfunction and also to more general strategies such as plasma exchange and use of extracorporeal liver assist devices such as DIALIVE, which are underway and their results are awaited.

Although it is clear that dysregulated inflammation is a key pathophysiological mechanism underlying the pathogenesis of organ failure and risk of infection, it is not clear whether it is the cause of ACLF or its effect. In future studies, it will be important to perform longitudinal studies to better define the role of dysregulated inflammation in ALD-ACLF.

3.2. Possible mechanisms underlying systemic inflammation in ALD-ACLF

Role of cell death: It has become clear that molecules released following cell death, so-called damage associated molecular patterns (DAMPs) have immunogenic properties and can result in systemic inflammation. As ACLF is associated hepatocyte cell death, the type and severity of cell death is important in determining their immunogenicity (Figure 2). Although early small studies suggested that apoptosis is the predominant form of cell death in ACLF [9], a large study using plasma samples obtained from the CANONIC study has shown incontrovertibly that the predominant mechanism of cell death in in ALD-ACLF is non-apoptotic, which may provide an explanation for the severity of systemic inflammation observed [10]. Recent studies have provided evidence for the importance of hepatocyte necroptosis, which is a form of regulated necrosis that requires the proteins RIPK3 and MLKL. It is induced by interferons, death receptors, toll-like receptors, intracellular RNA and DNA sensors, and other mediators such as lipopolysaccharides [34]. In preliminary studies, necroptosis was aboserved to be an important mode of cell death in ACLF patients and the inhibition of RIPK3 phosphorylation, a key regulator of necroptosis prevented the occurrence of ACLF in an animal model [35]. Pyroptosis is a lytic type of regulated necrosis which is inherently associated with severe inflammation. It is mediated by the “inflammatory caspases” such as caspase-1, and caspase-5 in humans (and caspase-11 in rodents) [36]. In an unbiased RNA sequence analysis in an animal model of alcoholic hepatitis, Casp11 (CASP4 in humans) was identified. Caspase 11 in mice and Caspase 4 activation was observed in alcoholic hepatitis mice and patients respectively. Inducing Caspase 11 deficiency was associated with protection of animals from alcoholic hepatitis [37]. The

data suggest that hepatocyte cell death may precede systemic inflammation and may be its cause rather than its consequence.

Role of bacterial translocation: Many studies have shown evidence of bacterial translocation in patients with cirrhosis and targeting the gut with poorly absorbed antibiotics such as norfloxacin and rifaximin prevents the major cirrhosis complications such as acute kidney injury and hepatic encephalopathy [38,39]. The bacterial products referred to as pathogen associated molecular patterns (PAMPs) can activate the pathogen recognition receptors on the immune cells resulting in systemic inflammation and subsequent immunopathology. The importance of this pathway in the pathogenesis of ACLF is illustrated by the fact infection is the commonest precipitant factor for its development. More recently, studies in patients with alcoholic hepatitis has clearly demonstrated that increased concentrations of circulating lipopolysaccharides is associated with more marked systemic inflammatory response and increased risk of death [6].

Role of changes in metabolism: Ammonia is the best-studied metabolic toxin. It is produced predominantly in the gut, in which the microbiome plays a role [40]. It has widespread pathological effects not only on the brain but also on the immune system, muscle metabolism and has been shown to be associated with stellate cell activation and worsening portal hypertension, all features of ACLF [41–43]. More recently, studies have addressed the metabolic basis of immune dysfunction in ACLF. Studying the

metabolomic signature of the plasma of ACLF patients has revealed a marked dysfunction of the tryptophan / kyneurenin pathway, which has a key role in monocyte function although its exact role is not yet defined [44]. ^{1}HNMR spectroscopy metabolomic signature accurately discriminated between patients that died following an episode of acute decompensation [45]. The spectra that distinguished non-survivors from survivors were attributed to reduced phosphatidylcholines and lipid resonances, with increased lactate and altered amino acid metabolism. Interestingly, the lysophosphatidyl choline levels correlated inversely with biochemical and histological markers of liver cell death. Whether these changes are a cause or effect is not clear.

4) Prognosis of ACLF in patients with ALD

Prognostic tools have been developed to try and better predict outcomes of patients with ACLF. According the CANONIC study, the initial grade of ACLF, the clinical course, and a specifically designed score (CLIF-Consortium ACLF score [CLIF-C ACLFs]) seemed to accurately estimate outcomes [2,14,46]. The number of organ failures (OFs) defined by the CLIF-C OFs and the presence of kidney and/or neurological dysfunction defined the grade of ACLF (see Table 2). We observed also that ACLF was an extremely dynamic syndrome associated with potential resolution, improvement, stabilization or deterioration and the grade of ACLF between the 3rd and 7th day after diagnosis seemed to predict outcomes more accurately than the initial one [46]. Finally, investigators combined CLIF-OFs with age and white cell count to design a specific ACLF score, the CLIF-C ACLFs (web calculator at http://www.efclif.com) [14]. This score improved significantly prediction for short and medium-term mortality compared with classical

scores (MELDs, MELD-Nas, and Child-Pugh score) in ACLF patients of the CANONIC cohort and in a validation cohort of ICU-admitted cirrhotic patients. The type of precipitating event, in particular active excessive alcohol consumption within the past three months, did not influence the mortality rates or the clinical course of ACLF [2,46]. Another score has been developed by the AARC in a large cohort of patients with APASL-defined ACLF (50% had active alcohol consumption as precipitating event) [5]. The score is composed by total bilirubin, grade of HE, INR, lactate and serum creatinine (http://www.aclf.in/?page=doctor_aarc_grade_cal) and performed better than Child-Pugh score, MELDs, SOFAs, and CLIF-SOFAs in the prediction of 28-day mortality. Similar to the CLIF-C ACLFs, the changes in the score during the first week increase its accuracy.

The presence of ACLF and its grade makes it possible to stratify patients with sAH into prognostic groups. In a prospective cohort of patients with sAH, the 28-day cumulative incidences of death of patients without ACLF or with ACLF-1, ACLF-2 or ACLF-3 were 10, 31, 58 and 72% respectively [7]. In this observational study, the accuracy of CLIF-C ACLFs was relatively poor (C-index 0.68) for early identification of patients at high risk of death at 28 and 168 days. In the STOPAH trial, the area under the curve of CLIF-C ACLFs relating to 28-day and 90-day mortality was 0.79 and 0.77 respectively, similar to other classical AH scores measured at baseline (MELD, Glasgow alcoholic hepatitis score [GAHS], age, serum bilirubin, international normalized ratio and serum creatinine [ABIC] score) [47].

5) Therapeutic impact of ACLF in the treatment of patients with ALD

5.1. Treatments of sAH in the context of ACLF

Currently, corticosteroids (CS) remain the first line therapy of sAH. In a prospective cohort of consecutive unselected patients with biopsy-proven sAH, the probability of response to CS according to the Lille model was reduced in patients with compared to those without ACLF and progressively among grades of ACLF (77% for patients without ACLF, 52% for ACLF-1, 42%for ACLF-2 and 8% for ACLF-3) [7]. This critical point raises concerns about CS administration to patients with ACLF-3. In the STOPAH trial (RCT assessing the efficacy of CS in patients with sAH), patients were selectively recruited and those with severe renal impairment and those with inotropic support were excluded [22]. A sub-analysis of this trial confirms a reduced probability to response to CS and higher risk of infection in patient with ACLF but, if a response to CS was achieved (observed in 37% of patients with ACLF-2 or 3), the survival benefit was maintained irrespective of ACLF grade [47]. With the current data, we cannot state on a systematic use of CS in sAH with ACLF (in particular high grades ACLF) or an absolute contraindication. We suggest to balance risks and benefits on case-by-case basis.

Pentoxyfilline (PTX) has been suggested as an alternative treatment when CS is contraindicated but recent trials and meta-analysis concluded that PTX administration alone or in combination with CS is unable to improve short-term survival in patients with sAH [22,48]. Moreover, PTX is also ineffective in non-responders to CS [49]. Currently, PTX has not been assessed especially in patients with sAH and ACLF.

5.2. Potential specific treatments of ACLF

Based on the hypothesis that released endogenous substances contribute to propagation of liver dysfunction and extrahepatic organ failures, detoxification devices have been assessed. Albumin dialysis (molecular adsorbent recirculating system, MARS®) improved liver biochemistry, renal and cerebral functions and attenuated hyperdynamic circulations in alcohol-related ACLF [50,51]. In RCTs, devices (MARS® and fractionated plasma separation and adsorption system, Prometheus®) did not demonstrate a survival benefit for ACLF patients (the majority of patients having alcoholic cirrhosis and/or alcohol as a precipitating event) [52,53]. These trials have been designed before establishment of a validated definition of ACLF.

Granulocyte-colony stimulating factor (G-CSF) has been recently proposed as a potential treatment of ACLF. G-CSF promotes mobilization of bone marrow stem cells and proliferation of hepatic progenitor cells in patients with AH [54]. G-CSF is also able to increase circulating and intrahepatic myeloid and plasmacytoid dendritic cells and T lymphocytes in patients with ACLF [55]. Some small RCTs have observed reduction of infectious episodes, improvement of liver function and also significant survival benefit compared with standard medical treatment in patients with APASL ACLF [18,56,57]. Nevertheless, additional randomized trials are needed to confirm these observations before establishment of recommendations.

Some pilot studies suggest that health donor fecal microbiota transplantation (FMT) has a beneficial effect on the outcome of patients with alcohol-related ACLF [58,59]. A retrospective uncontrolled study on 23 patients with sAH and ACLF not eligible for corticosteroids and not undergoing liver transplantation (LT) but receiving salvage FMT showed promising survival rates of 73% for patients with ACLF-1 and 58% for ACLF-2 or 3 at 548 days [59]. Unfortunately, high-quality trials are lacking to make clear recommendation about this emerging therapy.

6) Liver transplantation for ACLF in the context of patients with ALD

Due to poor short-term outcomes, the option of LT for ACLF patients is frequently considered but highly controversial. We can state that LT in sicker patients is unquestionably associated with substantial survival benefit but could impact the survival of other potential recipients on the waiting list and result in less acceptable longer term results after LT [60]. Experiences with LT in selected patients with ACLF or multiple organ failures (including ACLF-3 patients) were associated with acceptable 1-year post-LT survival (from 75 to 84%) [46,61,62]. In expert centers, results of living-donor LT are reported as equivalent as deceased-donor LT for ACLF patients [63,64]. On the other hand, some publications reported significantly lower post-LT survival rates for patients with ACLF-3 [65,66]. Currently, the question about the objective limits where the patient is considered as too sick to be transplanted and LT as futile, remains unanswered. Another main issue about LT in ACLF is the timing. Indeed, early LT is preferred to avoid clinical deterioration impacting the post-LT results but the potential recovery or improvement observed in ACLF after critical management has been suggested to

maximize the chance of LT success. Some authors proposed to prioritize patients with ACLF on the waiting list after an initial stabilization [67].

Active alcohol consumption and sAH is a frequent precipitating event of alcohol-related ACLF. The controversial 6-month rule of alcohol abstinence and the acceptable published results about alcohol relapse in highly selected patients are reviewed in details in another article of this *Special Issue*. Particularly, patients with ACLF are frequently in very poor clinical condition (severe hepatic encephalopathy, unstable status) and have a short time window making precise assessments about type of alcohol consumption, social network, and familial supports very challenging. We need to prospectively validate a fast-track multidisciplinary protocol to assess these different aspects to guarantee acceptable alcohol relapse rate after LT in the context of ACLF.

7) Controversies

The term “acute on chronic liver failure” (ACLF) designates a condition where acute liver injury is superimposed upon chronic liver disease with or without cirrhosis. One perspective is that the main organ dysfunction in ACLF is liver injury and organ failures are secondary to that. However, data from the CANONIC study suggests that nearly 50% patients have renal failure as the presenting organ failure in ALD-ACLF [2]. Sepsis is widely recognised as the main precipitating event of ACLF [2]. Some investigators argue that sepsis is secondary to liver injury and should not be considered a precipitating event. Again, the data from the NACSELD consortium and CLIF group have shown that sepsis is one of the most important precipitating events [2,25,68]. There is

also a suggestion that there should be an element of reversibility such that reversal to baseline hepatic function can potentially occur with or without liver support. Therefore, it was suggested that the term ACLF should not be applied to patients with decompensated cirrhosis. This assertion is not supported by the studies of the CLIF consortium who show that the short-term outcome of ACLF patients with or without previous decompensation is similar indicating a degree of reversibility even for previously decompensated patients [46].

A uniform definition of ACLF that can be applied world-wide is required. The current variability in definitions makes it appear that ACLF is a different disease depending on which continent the patient lives in. The variability in the definitions as well as the criteria for organ failure has been compared in a recent publication [3]. Current disagreements between definitions of different societies are because the so-called “defining” criteria like organ failure are, in fact, “prognostic” criteria. Since ACLF can progress to multiple organ failure, liver specific scoring systems such as the Child-Pugh or MELD scores are unlikely to be optimal. Inflammation is likely an early critical event and therefore markers such as WBC count, CRP, or procalcitonin may be helpful as early prognostic tests that herald the onset of extra-hepatic failure. Once extra-hepatic organ failures set in, organ failure specific scores like the CLIF-OF score are prognostic.

8) Conclusions

In conclusion, the occurrence of ACLF in patients with ALD who present with acute deterioration changes their prognosis and identifies a distinct subset of patients with extremely high risk of short-term mortality. These patients have a distinct pathophysiology characterised by intense systemic inflammation, immune failure and high risk of infection. The prognosis of these ALD-ACLF patients is defined by the number of organ failures and the current therapies such as steroids for those with alcoholic hepatitis in association with ACLF is likely to be ineffective and associated with increased risk of infection. Liver transplantation saves the lives of ALD-ACLF patients but future studies are needed to better define selection criteria.

9) Figure legends

Figure 1: Overview of the current hypothesis concerning the pathophysiology of Acute-on-Chronic Liver Failure (ACLF) in the context of Alcoholic liver diseases.

Figure 2: Description of pathways and immunogenicity associated with three types of cell death (apoptosis, necroptosis and pyroptosis).

Table 1: Cellular basis of immune dysfunction in ALD-ACLF, associated mechanisms and possible therapeutic targets (Modified from [11]**)**

Cell Type	Main functional derangement	Mechanism	Therapeutic target
Lymphocytes [29]	Reduced T-cells IFN production in response to LPS Increased T-cells producing IL-10	Increased expression of PD1 and TIM-3	• Antibodies to PDI and TIM-3 restored function
Monocytes and Macrophages [27,28,30,31]	Reduced LPS induced TNF production Reduced pro-inflammatory cytokine secretion and bacterial killing Reduced pro-inflammatory cytokine secretion in response to LPS Reduced monocyte oxidative burst and bacterial killing Reduced phagocytic capacity	Reduced DR3 expression Increased Prostaglandin E2 Increased expression of MERTK Reduced $gp91^{phox}$ subunit of NADPH oxidase Metabolic reprogramming and altered cellular bioenergetics	• Reduce bacterial translocation • PGE2 receptor antagonists • COX-2 inhibitors • Albumin infusion • Inhibition of MERTK, UNC569 • NADPH modulators • Glutamine synthase inhibitors
Neutrophils [26,32,33]	Increased resting burst but reduced E.Coli induced oxidative burst and reduced phagocytosis Reduced bactericidal activity	Involvement of humoral factor possibly LPS and toll-like 4 receptors Defect of myeloperoxidase release and the AKT/p38 MAP kinase pathway	• Bacterial translocation • Removal of LPS using plasma exchange or specific filters • Toll-like 4 receptor antagonists • TLR7/8 agonists

Table 2. The EASL-CLIF definition of Acute-on-Chronic Liver Failure (ACLF) (adapted [2,14]**)**

The CLIF Consortium-organ failure scoring system (CLIF-C OFs)			
Organ/system	Subscore=1	Subscore=2	Subscore=3
Liver (total bilirubin, mg/dL)	< 6	≥ 6 - < 12	≥ 12
Kidney (creatinine, mg/dL)	< 2	≥ 2 - < 3.5	≥ 3.5 or RRT
Brain (West-Haven grade HE)	0	1 - 2	3 - 4
Coagulation (INR)	< 2	≥ 2 - < 2.5	≥ 2.5
Circulation (MAP, mmHg)	≥ 70	< 70	vasopressors
Lung PaO_2/FiO_2 or SpO_2/FiO_2	> 300 or > 357	≤ 300 - > 200 or ≤ 357 - > 214	≤ 200 or ≤ 214

The shaded area describes criteria used to define organ failures.

Grade of ACLF

- ACLF grade 1 (ACLF-1):

- Patients with single kidney failure

- Patients with non-renal organ failure plus renal dysfunction (creatinine 1.5 – 1.9 mg/dL) and/or brain dysfunction (grade 1 – 2 HE).

- ACLF-2: patients with two organ failures
- ACLF-3: patients with three or more organ failures

CLIF, chronic liver failure; RRT, renal replacement therapy; HE, hepatic encephalopathy; INR, international normalized ratio; MAP, mean arterial pressure; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; SpO_2, pulse oximetric saturation.

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Figure

Pathophysiologic basis of ALD-ACLF

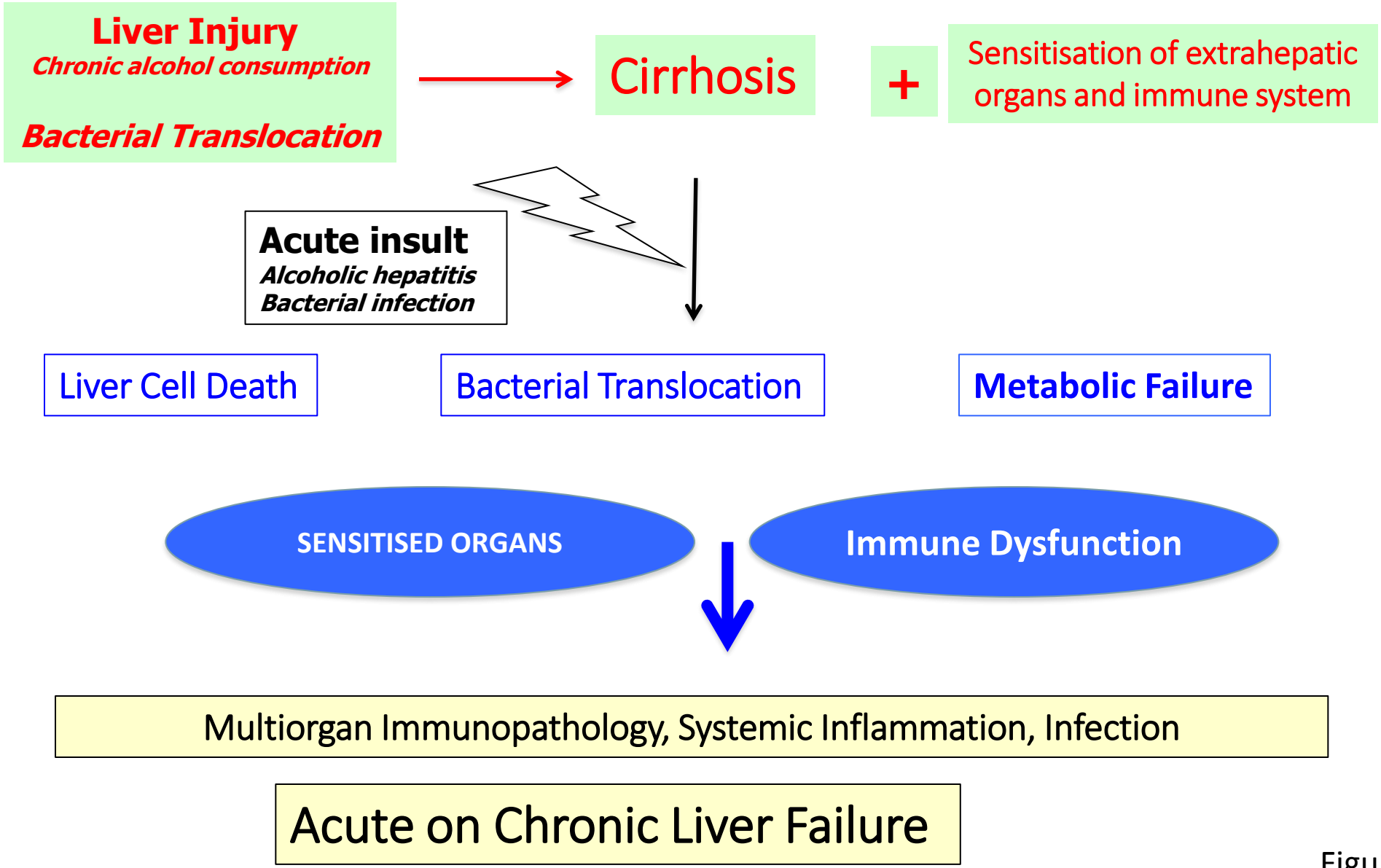
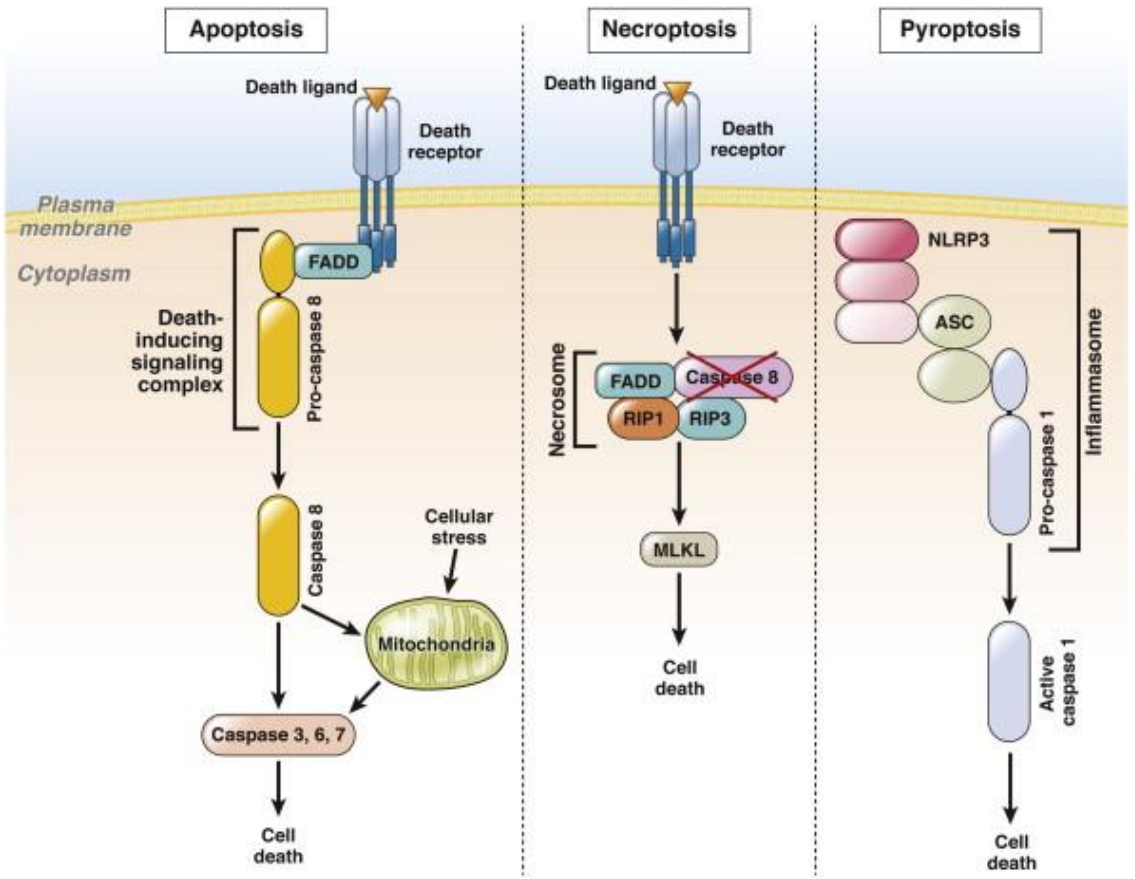


Figure 1



Immunogenicity

Figure 2