# Cuidados Intermédios

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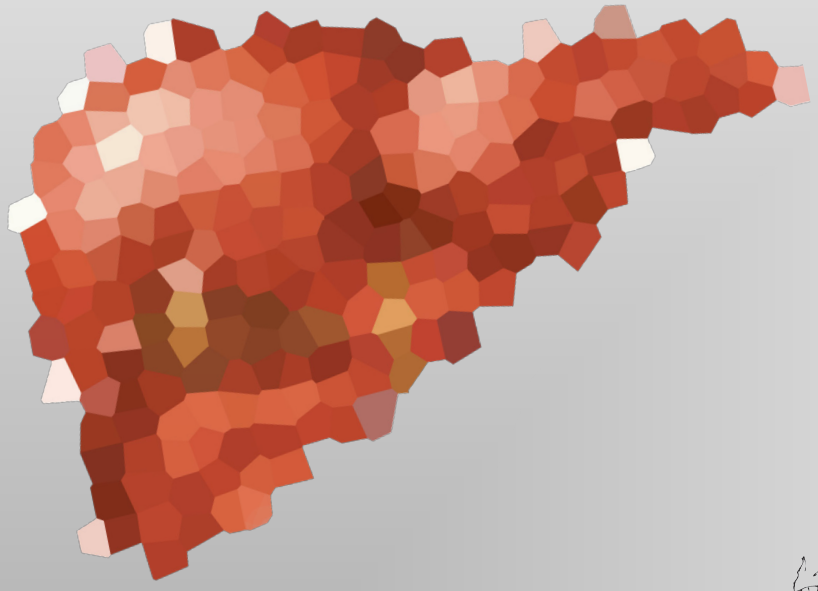
- Monothematic Conference

ACUTE ON CHRONIC LIVER FAILURE | resumos



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# PROGRAMME

**8:00** | Registry

**8:30** | Opening ceremony

**Where it all begins: the CANONIC Study**

**8:40** | Main fundaments: acute decompensation vs old and new definition(s) of ACLF.
Vicente Arroyo, Barcelona

**9:00** | SOFA vs CLIF-SOFA vs MELD: which score is the best to predict the outcome.
François Durand, Paris

**9:20** | Why is systemic inflammation related to ACLF? Back to the basics.
Thierry Gustot, Brussels

**9:40** | Clinical Case and discussion.
Diana Valadares, Porto

**Infection and ACLF**

**10:00** | Gut microbiota and individual susceptibility to liver disease: consequences to be expected and new biomarkers.
Gabriel Perlemuter, Paris

**10:20** | Antibiotics and cirrhosis complications prevention. Where do we stand?
Laure Elkrief, Geneva

**10:40** | Is ACLF a risk factor for fungal infections? When to prevent, how to treat.
Javier Fernandez, Barcelona

**11:00** | Clinical Case and discussion
Pedro Vita, Porto

**11:20** | Coffee-break

**Alcohol and ACLF**

**12:00** | The burden of alcohol consumption in Europe. Local and European strategies to lower consumption.
Helena Cortez-Pinto, Lisboa

**12:20** | Medical treatment for acute alcoholic hepatitis: where do we stand?
Julia Wendon, London

**12:40** | Liver transplantation as the last stronghold for acute alcoholic hepatitis?
Philippe Mathurin, Lille

**13:00** | Clinical Case and discussion.
Arlindo Guimas, Porto

**13:20** | Lunch

**Factors associated/ inducing decompensation in cirrhosis**

**14:20** | Hepatic encephalopathy and its role in acute decompensation, ACLF and prognosis: why the differences?
Manuel Romero-Gómez, Seville

**14:40** | Portal vein thrombosis and cirrhosis decompensation: is there really a cause-effect relationship?
Filipe Nery, Porto

**15:00** | TIPS in cirrhosis: state of play!
Arnulf Ferlitsch, Vienna

**14:20** | Clinical Case and discussion.
Teresa Moreira, Porto

**Special treatments for special patients**

**15:40** | Albumin use in specific settings in cirrhosis: shall we rationalize or generalize?
Rajiv Jalan, London

**16:00** | May new DAAs avoid LT in listed HCV patients with decompensated cirrhosis?
Marina Berenguer, Valencia

**16:20** | Is ACLF a motif to prioritize or temporary contraindicate patients in list for LT?
Luís Tomé, Coimbra

**16:40** | Clinical Case and discussion
Sofia Ferreira, Porto

**17:00** | **Closing ceremony**

INDEX

CUIDADOS INTERMÉDIOS
EM PERSPECTIVA

ACIM

junho 2015 | Volume 6 | Página 1 - 44



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Associação de Cuidados Intermédios Médicos

Porto is becoming not only a magnificent city to be and visit, but also, a place that embraces science. Porto Liver Meeting, this year, on its second edition, is a great example of that. As for 2014, when we first started with this project, we invite speakers that are the ones who write and who give all the expertise to the subject.

For 2015, we propose a very new and actually theme, as a monothematic conference: Acute on Chronic Liver Failure. This is the first meeting all consecrated to this subject and where we will approach the basics (as the definition, pathophysiology), the factors that may induce acute decompensation and evolution to organ failure and ACLF, as well generic and specific treatments.

Also, this meeting will have some particularities, as it will be co-chaired by Prof. Helena P Miranda (Medical head of the liver transplantation unit of Centro Hospitalar do Porto) and Prof. Richard Moreau (researcher and the first author of the CANONIC study). Each panel will be discussed with the aid of a clinical case.

Be very welcome to the 2nd Porto Liver Meeting – Acute on Chronic Liver Failure, monothematic conference, and we will see you in the 23rd June 2016 for the 3rd Porto Liver Meeting!"

Be very welcome,

Filipe Nery

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# Where it all begins: The canonic study

## Main Fundaments: Acute Decompensation vs Old and New Definition(s) of ACLF

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### ACLF: Concept

Approximately 10% of patients admitted to hospital for acute decompensation (AD) of cirrhosis (ascites, encephalopathy, bacterial infections or gastrointestinal hemorrhage) die during hospitalization in relation to impairment in liver function and/or the function of other organs, particularly the kidney and the brain. The term ACLF is frequently used to define this condition. However, and until recently, definitions have been based on expert opinion or consensus statements [1-3]. To provide a definition based on clinical data, the European Association for the Study of the Liver (EASL)-Chronic Liver Failure (ACLF) Consortium has recently performed a prospective observational study (CANONIC study) in a large series of patients with cirrhosis (1343 cases) consecutively admitted to 21 European Hospitals with acute decompensation to define the prevalence, diagnostic criteria, natural course, mechanism and prognosis of ACLF [4]. The current chapter is based on this study.

### Methodology Used for the Definition of ACLF

Due to the lack of data, some important features had to be pre-specified in the CANONIC study based on clinical experience. The first was a delineation of the major characteristics of the syndrome:

1. ACLF can observed either at hospital admission or during hospitalization but always in patients with AD;

2. The development of organ failure(s) is the most relevant specific characteristic;

3. Diagnostic criteria ACLF should differentiate patients with AD in two groups with different prognosis, the group with ACLF having relatively high short-term mortality rate.

The sequential Organ Failure Assessment (SOFA) Scale was the model selected for the assessment of organ failure [5-8]. Since components of the SOFA score do not take into account some pathophysiological and clinical features of cirrhosis, it was adapted for liver patients (Chronic Liver Failure Consortium – Organ Failure score (CLIF–C OFs, Table 1).

| Organ System | Score = 1 | Score = 2 | Score = 3 |
|---|---|---|---|
| Liver (mg/dl) | Bilirubin < 6 | 6 ≤ Bilirubin ≤ 12 | Bilirubin >12 |
| Kidney (mg/dl) | Creatinine <2 | Creatinine ≥2 <3.5 | Creatinine ≥3.5 or renal replacement |
| Brain (West-Haven) | Grade 0 | Grade 1-2 | Grade 3-4 |
| Coagulation | INR < 2.0 | 2.0 ≤ INR < 2.5 | INR ≥ 2.5 |
| Circulation | MAP ≥70 mm/Hg | MAP <70 mm/Hg | Vasopressors |
| Respiratory: PaO2/FiO2 or SpO2/FiO2 | >300 >357 | ≤300 - > 200 >214- ≤357 | ≤200 ≤214 |

Table 1 - Criteria to define organ failure (in grey) in cirrhosis according to the CANONIC study [4, 23]

The issue "relatively high short-term mortality rate" was defined as a mortality rate equal or greater than 15% within a period of 28 days. This figure represents approximately 50% of the short-term mortality rate associated with severe sepsis or septic shock in the general population [9].

Table 2 shows the short-term mortality in patients included in the Canonic Study. Mortality rate was clearly related to the presence and number of organ failures. Also, renal dysfunction (as defined by a serum creatinine of 1.5-1.9 mg/dl) and/or moderate (grade 1-2) hepatic encephalopathy, when associated to organ failure, were also found to predict prognosis. Based on the presence of organ failure and of short term mortality-rate the following groups of patients were excluded and included from the diagnosis of ACLF:

1. Excluded: (a) No organ failure; (b) Single non-renal organ failure with serum creatinine < 1.5 mg/dl and no hepatic encephalopathy.

2. Included: (a) Single renal failure; (b) Single non-renal organ failure plus renal dysfunction and/or grade 1-2 hepatic encephalopathy; (c) 2 or more organ failures.

| Number and types of organ failures | No kidney dysfunction and no mild-to-moderate hepatic encephalopathy | Kidney dysfunction and/or mild/moderate hepatic encephalopathy |
|---|---|---|
| No organ failure | 20/577 (3.5) | 19/329 (5.8) |
| Single liver failure | 4/75 (5.3) | 11/36 (30.6) |
| Single cerebral failure | 2/26 (7.7) | 1/5 (20.0) |
| Single coagulation failure | 1/22 (4.6) | 2/11 (18.2) |
| Single circulation/lung failure | 1/18 (5.6) | 2/8 (25.0) |
| Single kidney failure | 9/58 (15.5) | 7/30 (23.3) |
| Two organ failures | 19/75 (25.3) | 12/32 (37.5) |
| Three-four organ failures | 19/25 (76.0) | 6/12 (50.0) |
| Five-six organ failures | 6/8 (75.0) | 2/2 (100.0) |

The highlighted area in grey shows the sub-groups of patients defined as having Acute-on-Chronic Liver Failure (ACLF). HE: Hepatic encephalopathy grade 1-2

Table 2 - Diagnostic criteria of ACLF [4]

Table 3 shows the classification of patients with ACLF according to grades of severity. The prevalence of ACLF among patients admitted to hospital with decompensated cirrhosis is 30% (20% at admission and 10% during hospitalization) and the overall 28-day mortality rate is 33%. According to the number of organ/system failures, ACLF is stratified into three grades with different prognosis: Grade-1 (one organ failure, 28-day mortality rate 22%), Grade 2 (two organ failures, 28-day mortality rate 32%) and Grade 3 (three or more organ failures, 28-day mortality rate 73%). The overall short-term mortality rate of patient without ACLF was 1.9%.

| Grades of ACLF | |
|---|---|
| No ACLF | - No organ failure<br>- One organ failure (liver failure, coagulation, circulatory or respiratory failure) with creatinine <1.5 mg/dL and no hepatic encephalopathy.<br>- Single cerebral failure and creatinine <1.5 mg/dL |
| ACLF grade 1a | - Single kidney failure without mild or moderate hepatic encephalopathy |
| ACLF grade 1b | - Single organ failure with serum creatinine ranging from 1.5 mg/dL to 1.9 mg/dL) and/or mild-to-moderate hepatic encephalopathy |
| ACLF grade 2 | - Presence of 2 organ failures |
| ACLF grade 3 | - Presence ≥ 3 organ failures |

Table 3 - Grades of ACLF [4]

**Precipitating events**

The most common precipitating events were bacterial infections, particularly spontaneous bacterial peritonitis and pneumonia, occurring in 33% of patients with ACLF vs. 22% in patients without ACLF. The second precipitating event in frequency was active alcoholism prior to enrolement. It was present in approximately 25% of patients with ACLF vs 15% in patients without ACLF. Interestingly in patients with ACLF the prevalence of alcoholic cirrhosis (60%) was higher than the prevalence of active alcoholism, indicating that alcoholic hepatitis accounts for only part of cases of ACLF in patients with alcoholic cirrhosis. There was a small proportion of other precipitating event (8%). As a trigger, gastrointestinal hemorrhage was less frequent in patients with ACLF (13%) than in patients without ACLF, suggesting that hemorrhage, if not associated to other complications (i.e. active drinking and/or bacterial infections) is not clearly related to ACLF development. Finally, and most interestingly, in a significant proportion of patients (45%) ACLF developed in the absence of any identifiable trigger. Mortality was similar in the presence or absence of precipitating events, indicating that although triggers are important in the development of ACLF, once it develops mortality depends of other factors, such as the clinical course (see below) and number of organ failures.

**ACLF is not a terminal event of a long-standing cirrhosis**

A traditional concept is that ACLF is the final event in a long-standing history of decompensated cirrhosis in most patients. This concept is not supported by the CANONIC study since it revealed that almost half of patients with ACLF did not have a prior history of decompensation or had developed first acute decompensation within 3 months prior ACLF. An interesting feature was that patients with no history of decompensated cirrhosis developed a more severe form of ACLF than patients with previous episodes of decompensation.

**Clinical course of ACLF**

The clinical course of 388 CANONIC patients with ACLF at enrolment or developing ACLF during hospitalization was assessed during the first 28 days to understand the natural history of the syndrome. Four major findings were observed [10]. The fist was that ACLF is an extraordinarily dynamic syndrome. In only one-third of patients ACLF had no change between diagnosis and final follow-up. In most cases ACLF either improved (50%) or worsened (20%). The second was the demonstration of the reversibility of the syndrome. Resolution of ACLF was observed in 40% of patients. The frequency of resolution was high (55%) in patients with ACLF-1 at diagnosis, middle (35%) in patients with ACLF-2 and low (15%) in patients with ACLF-3. The third is that changes in ACLF grade following occur very rapidly (1-2 days) or rapidly (3-7 days) following diagnosis in more than 65% of the patients. Since short-term survival of patients with ACLF more dependent on the final than on the initial grade of ACLF, early course of ACLF is therefore, the major determinant of prognosis.

**ACLF is associated to systemic inflammation**

The CANONIC study has also provided important data to understand the mechanisms of ACLF. The finding of higher WCC and serum CRP levels in patients with ACLF than in those without suggests that systemic inflammation plays a role in the development of the syndrome (10). This is also supported by the finding that WCC and CRP levels raise across ACLF grades, the higher the intensity of systemic inflammation the higher the number of failing organs (10). Unpublished studies from the CANONIC study show that ACLF development and grade correlate closely with the plasma levels of pro-inflammatory cytokines, markers of endogenous vasoconstrictor molecules (renin, copeptin) and of systemic oxidative stress.

In approximately 30% of patients with ACLF, systemic inflammation was chronologically related to bacterial infections. In these patients, therefore, systemic inflammation is probably due to activation of the innate immune system cells (by products released by the bacteria (Pathogen Associated Molecular Patterns, PAMPs; i.e. lipopolysaccharide, lypoteichoic acid, peptidoglycan) [11]. In another 25%, ACLF is related to excessive alcohol consumption. Although some of these patients may be infected, many of them do not fulfill criteria of a bacterial infection. In these cases, the systemic inflammatory response is probably related to a “sterile inflammation” related to tissue damage (acute alcoholic liver injury) [11]. The pathogenesis of sterile inflammation in alcoholic hepatitis is probably related to the release of intracellular molecules (Damaged Associated Molecular Patterns, DAMPs) from dying hepatocytes that activate the innate immune systems acting as true “internal pathogens”. However, as indicated previously, in approximately 40% of cases with ACLF no clear precipitating event can be identified. Although the cause of systemic inflammation in these patients is unknown, it is possibly related an acute translocation of bacterial products (PAMPs) from the intestinal lumen into the systemic circulation. Translocation of PAMPs in the absence of infection is a well recognized feature in patients with advanced cirrhosis related to intestinal hypo-motility and bacterial overgrowth, increased mucosal permeability and impaired intestinal immune system function [12].

Impairment in organ function associated to systemic inflammation (e.g. in severe sepsis) is complex and probably related to several mechanisms.

1. Organ hypoperfusion due to cardiovascular dysfunction (impairment in left ventricular function, arterial vasodilation and impaired vascular response to endogenous vasoconstrictor systems) due to the overproduction of vasorelaxant substances within the heart and the arteriolar walls (nitric oxide, prostaglandins and bradykinin) [13];

2. Extension of the inflammatory process to organs. The local release of inflammatory mediators and reactive oxygen species impair cell metabolism and may cause cell necrosis or apoptosis [14];

3. Cirrhosis is associated with a procoagulant state, i.e., an increase in thrombin generation [15]. It is possible that the procoagulant state could be enhanced in patients with ACLF since inflammation is known to be associated with increased tissue factor synthesis in innate immune cells and endothelial cells [16-19]. The resulting microthrombosis favors tissue hypoperfusion and organ failure. Moreover, the coagulation cascade has intrinsic pro-inflammatory thus leading to a vicious circle by which activation of inflammatory cells leads

to endothelial dysfunction, increase in thrombin generation and more inflammation [20];

4. An increased circulating concentration of microparticles (MPs) is an additional potential mechanism in the development of complications associated with systemic inflammation in cirrhosis and in ACLF [21]. MPs are membrane vesicles of cell origin with a diameter ranging from 0.1 to 1 μm that are released to the extracellular space following immune cell activation or apoptosis. Circulating MPs (mainly derived from leuko-endothelial and hepatic cells) are increased in patients with acute decompensation of cirrhosis and correlate directly with the severity of cirrhosis and systemic inflammation. There is evidence that circulating microparticles (MPs) may play a role as a mechanism of ACLF-associated circulatory alterations [21-22]. MPs are also pro-coagulants because they expose phosphatidylserine, an anionic phospholipid that activates coagulation.

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# SOFA vs CLIF-SOFA vs MELD: which score is the best to predict the outcome?

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## Prognosis in ACLF: why is it important?

Acute-on-chronic liver failure (ACLF) is not only liver failure. This syndrome is characterized by failures of organs/systems other than the liver in patients with underlying cirrhosis. Cirrhosis is a predisposing factor for the occurrence of organ failures [1]. Organ failures contribute to further impairment in liver function leading to a vicious cycle. Mortality rate varies according to the number of organ failures. For instance, 1-month mortality ranges from about 22% in patients with single kidney failure or single organ failure with creatinine from 1.5 to 1.9 mg/dL to more than 75% in patients with 3 organ failures or more [1]. Overall, the prognosis of ACLF with more than one organ failure is poor. On practical grounds, simple assessment of organ failures in patients with ACLF could be considered an easy way to address the issue of prognosis in ACLF. However, more accurate prognostic tools are needed for several reasons. Firstly, the prognosis of multiple organ failure in patients with cirrhosis may be especially poor, even with aggressive management. Since the access to intensive care units (ICU) is limited by necessity, who justifies and who does not justify an aggressive management is still a source of controversy. Therefore, survival probability in the ICU should be precisely assessed. Secondly, since the implementation of a MELD score-based allocation policy, the sickest patients (including those with ACLF) may have a rapid access to transplantation. The possibility to transplant ACLF patients brings new issues including how to bridge patients to transplantation and who is too sick to be transplanted. Again, static and/or dynamic prognostic tools are needed. Finally, robust prognostic tools may help standardize studies in the field and also help compare different series [2, 3].

## Prognostic tools

The MELD score, which is based on the objective values of bilirubin, INR and creatinine, is a robust prognostic system that is widely used in the management of cirrhosis. However, the MELD score has a number of limitations for predicting outcome in ACLF. Apart from creatinine, the MELD score does not take into account organ failures other than the liver. In addition, by definition, the MELD score is capped at 40 points [4]. A MELD score capped at 40 covers a wide spectrum of disease severity. “Uncapped” MELD score could be superior to the existing MELD score in the sickest patients. However, objective data are missing.

General ICU scores such as SAPS, APACHE and SOFA [5] which include basic markers of organ failure are more relevant in ACLF. In critically ill cirrhotic patients, the SOFA score was found to be superior to MELD and APACHE II scores [6-8]. However, the SOFA score also has limitations in cirrhosis. Creatinine and bilirubin are weighted according to general ICU patients, which is a possible source of inaccuracies. For instance, cirrhotic patients with normal or near normal serum creatinine may have markedly impaired renal function [9]. Coagulopathy, which is a pivotal marker of liver dysfunction, is not included in the SOFA score. Finally, the interpretation of neurological status and platelet count is misleading in cirrhotic patients. Neurological changes can occur at an earlier stage as a result of hepatic encephalopathy. Platelet count is generally lower as a result of portal hypertension and hypersplenism.

Following a large European multicenter study, which represents the cornerstone in the definition of ACLF, a liver oriented modified SOFA score, termed CLIF-SOFA score has been proposed. The main differences between SOFA and CLIF-SOFA scores are changes in the limits of bilirubin, serum creatinine, platelet count, doses of vasopressors and PaO2/FiO2 that define different categories [1]. Then, a simplified and more specific score termed CLIF-C ACLF score has been proposed to better assess mortality risk in patients with cirrhosis and ACLF (Table 1) [10]. The CLIF-C ACLF is calculated on the basis of the CLIF-organ failure score system (CLIF-OFs) with the following equation: CLIF-C ACLF = 10 x (0.33 x CLIF-OFs + 0.04 x Age + 0.63 x ln(WBC count) – 2). Interestingly, this score includes WBC count, which was found to be independently associated with outcome in ACLF [1] while neither the SOFA score nor the CLIF-SOFA score include this variable. The predictive discrimination of the CLIF-C ACLF score was superior to that of the CLIF-OFs, MELD, MELD-Na and Child-Pugh scores. However, the C-index for predicting 28-day mortality was of 0.76, which can be considered as relatively low. The prognostic value of the CLIF-C ACLF score measured at 48 hours and at 3-7 days was superior to that of the CLIF-C ACLF score at the time of diagnosis of ACLF [10].

Whether a cirrhotic patient with multiple organ failure should or should not be admitted in the ICU is still a matter of debate. The overall prognosis is poor. However, several studies have shown that outcomes have improved over time [11-13]. In addition selected critically ill cirrhotic patients can be safely bridged to transplantation [14, 15]. Cirrhosis and multiple organ failure should not be considered a contraindication for

admission in the ICU. A practical approach consists in managing critically ill cirrhotic patients in the ICU with unrestricted life sustaining treatments for at least 3 days. However, due to an especially poor prognosis, in patients with 3 or more organ failures (other than decreased platelet count) on day 3, withdrawal or limitation of life sustaining treatments may be recommended [11].

| Organ/system | Subscore = 1 | Subscore = 2 | Subscore = 3 |
|---|---|---|---|
| Liver | Bilirubin < 6 mg/dL | Bilirubin 6-12 mg/dL | Bilirubin ≥ 12 mg/dL |
| Kidney* | Creatinine < 2 mg/dL | Creatinine 2-3.5 mg/dL | Creatinine ≥ 3.5 mg/dL |
| Brain (grade of encephalopathy)** | Grade 0 | Grade 1-2 | Grade 3-4 |
| Coagulation | INR < 2 | INR 2-2.5 | INR ≥ 2.5 |
| Circulatory | MAP ≥ 70 mmHg | MAP < 70 mmHg | Use of vasopressors |
| Respiratory*** Pa02/FiO2 or SpO2/FiO2 | > 300 >357 | > 300 >357 | ≤ 200 ≤214 |

* Patients on renal replacement therapy are considered as subscore 3

** According to West-Haven classification

*** Patients on mechanical ventilation are considered as subscore 3

Table 1 - The CLIF-organ failure score system [10]

**Recommendations and perspectives**

General ICU scores (such as SOFA) are superior to the MELD score, and ACLF-specific ICU scores (such as CLIF-C ACLF) are superior to general ICU scores in predicting the outcome of patients with ACLF. However, discrimination of the current CLIF-C ACLF might be improved since a relatively high variability persists in terms of survival rate in patients with similar scores. Prognostic scores should be interpreted according to which a precipitating factor (that can be potentially cured) can be identified or not. Scores should also be interpreted according to which liver transplantation is an option or not. Dynamic evaluation is central in the decision for continuing or discontinuing aggressive life sustaining support. Selected critically ill cirrhotic patients can be transplanted with an excellent outcome in the long term. However, prognostic tools are needed to better identify who is likely to benefit from transplantation and who is too sick to be transplanted; namely, at too high risk to justify organ allocation in a context of organ shortage.

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## Why is systemic inflammation related to ACLF? Back to basics.

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A common feature of Acute-on-Chronic Liver Failure (ACLF) is an intensive systemic inflammatory response characterized by high leukocyte count and plasma C-reactive protein (CRP) level and correlated with mortality. [1] Furthermore, there is a correlation between these inflammatory parameters and the number of failing organs. Triggers of this inflammation are largely unknown. Bacterial infection might explain a part of it (about 30% of cases), but the association between severity of ACLF and systemic inflammation is also observed in non-infected ACLF patients. There are several potential scenarios.

First, infection might be an under-recognized cause. Indeed, the diagnosis of bacterial infection in cirrhosis is challenging for several reasons. The classical parameters assessing the inflammatory host response to infection (systemic inflammatory response syndrome (SIRS) are not specific for the diagnosis of infection in cirrhosis. SIRS has a low sensibility (57-70%) as a tool of diagnosis of infection in patients with decompensated cirrhosis (and low specificity (10-30%) in those patients without infection. [2,3] Moreover, common early markers of infection used in the general population, as CRP and procalcitonin, are not sufficiently adequate to distinguish infected from non-infected patients.

Secondly, Bacterial translocation (BT) without overt infection seems to be a major trigger of this systemic inflammation. Viable bacteria have been frequently isolated from mesenteric lymph nodes, and bacterial products or pathogen-associated molecular patterns, such as lipopolysaccharides (LPS) and bacterial DNA, have been detected in the blood of patients with decompensated cirrhosis. [4,5,6]

Several years ago, Albillos et al. demonstrated that administration of norfloxacin in order to achieve selective intestinal gut decontamination reduces plasma levels of pro-inflammatory cytokines, and other surrogate markers of BT (LPS-binding protein and soluble CD14) in cirrhotic patients with ascites. [7]

Finally, inflammation might be “sterile” and drive by mediators released by injured liver (damage-associated molecular patterns, DAMPs). Liver injuries due to drugs, alcohol or hepatotropic virus, are associated with hepatocyte cell death and release of molecules in the extracellular space able to trigger an inflammatory response. [8,9] Currently, data about involvement of DAMPs in systemic inflammation of ACLF are lacking.

Decompensated cirrhosis is classically associated with systemic inflammation characterized by enhanced expression of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β and IL-18) in the serum and in peripheral blood mononuclear cells which over-produce ex vivo pro-inflammatory cytokines in response to LPS, the TLR4 ligand. [10,11,12] A defect in mechanisms of immunotolerance at least partially explain this overexpression. LPS-stimulated monocytes from patients with cirrhosis display a lack of interleukin-1 receptor-associated kinase (IRAK)-M induction, decreased Akt activity, defects in glycogen synthase kinase (GSK)3β phosphorylation, and reduced expression of IL-10 contributing to the loss of counter-regulatory mechanisms of the TLR4 pathway and the hyper-production of TNF-α. [13-14] The consequence of this excessive inflammatory response is the development of organ failures, a process called immunopathology. Indeed, in spontaneous bacterial peritonitis, higher levels of proinflammatory cytokines in the plasma and ascitic fluid are associated with increased risk of renal failure. [15]

Another hypothesis to explain the link between systemic inflammation and organ failures in ACLF is a failed tolerance of organs to damage. Tissues have several tolerance programs to reduce inflammation-induced damage and defect in these mechanisms induce a sensitization to organ failure. [16] In a rat model of cirrhosis, LPS challenge induced in vivo apoptosis of 30-40% of hepatocytes, an effect not observed in normal animals. [17] This failed tolerance was mainly caused by endoplasmic reticulum stress of cirrhotic hepatocytes.

Beside this pro-inflammatory profile, patients with ACLF display a “sepsis-like” immune paralysis characterized by a down-regulation of HLA-DR expression on circulating monocytes and decreased secretion of pro-inflammatory cytokines (TNF-α) after lipopolysaccharide stimulation. [18] This feature seems to be conserved among the different etiologies of ACLF. Neutrophil dysfunction is also observed in patients with an alcoholic hepatitis superimposed on cirrhosis. [19] Recently, an adaptative immune dysfunction with an increase of proportion of regulator T cells compared to conventional CD4+ T cells is described in HBV-related ACLF. [20] Other key players of host response against

microbes are myeloid and plasmacytoid dendritic cells (mDCs and pDCs). A decrease of functional mDCs is observed in HBV-related ACLF and is associated with poor outcome. [21] This multiple immune defect contributes to the increased risk of secondary infection, perpetuating systemic inflammation and organ failures in ACLF patients.

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# Infection and ACLF

# Gut microbiota and individual susceptibility to liver disease: consequences to be expected and new biomarkers

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Excessive alcohol consumption and overweight are the main causes of chronic liver disease in Western countries. Despite these major public health concerns, the factors that link alcohol consumption, overweight and the onset and progression of liver injury are poorly understood. Thus, among subjects with heavy alcohol drinking or overweight, only 10 to 35% will develop inflammation (hepatitis) and 8 to 20% will evolve to cirrhosis. These data show that other factors than the only amount of alcohol intake or the importance of overweight are involved in the occurrence of liver damage.

The human gastro-intestinal tract hosts a complex and diverse microbial community (1014 bacterial cells, more than 1000 different bacterial species), called the intestinal microbiota (IM). The genetic coding capabilities far exceed those of the human genome. Thus, the IM is considered a full organ with many metabolic, immunological and endocrine roles that affect human health. Activation of the innate immune system by lipopolysaccharide (LPS) of the digestive system has emerged as a key factor in triggering alcoholic hepatitis (AH). An increased gut permeability and associated endotoxemia has been observed in humans and animals following alcohol consumption. Impairment of the intestinal barrier by ethanol involves the IM. This increase in permeability increases the translocation of bacterial toxins (LPS particular), which may in turn alter the intestinal barrier, leading to a vicious circle.

We have shown that, in alcoholic patients, a specific dysbiosis was associated with severe AH. By transferring the human IM in germ-free mice, we showed that this dysbiosis was not a mere consequence of AH but drives the susceptibility to liver injury. Metabolomic studies suggested that changes in the enterohepatic circulation of biliary acids due to dysbiosis participate in the onset of liver damages.

We also studied the involvement of IM in the heterogeneity of ALD in mice. We have shown that the presence of liver damage was associated with decreased population of Bacteroidetes. In addition, inhibition of Bacteroidetes decrease by prebiotics of fecal transfer experiments could prevent ALD. By similar methods, we have also the importance of IM in NASH.

In parallel, other teams have demonstrated that cirrhosis was associated with a specific dysbiosis and modifications of biliary acid metabolism.

The IM is easily modifiable by using pre-, pro- or antibiotics or by fecal transplant. These various findings open new possibilities for manipulating the IM of patients with liver diseases. Indeed, the study of IM in such patients could be envisaged to improve diagnostic tools and/or to treat liver diseases, as already used for recurrent *Clostridium difficile infections*.

# Antibiotics to prevent complications of cirrhosis: where do we stand?

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## Introduction

Bacterial infections have a major clinical impact on the outcome of patients with cirrhosis, who are at high risk of severe sepsis and death [1]. Infection may also precipitate variceal bleeding [2] and plays a major role in the pathogenesis of hepatic encephalopathy and acute-on-chronic liver failure [3].

Since the 1980's, antibiotic prophylaxis has been proposed to prevent the occurrence of spontaneous bacterial peritonitis (SBP) in patients with cirrhosis. Norfloxacin, an oral fluoroquinolone, has been the most widely used [4]. However, a marked increase in the prevalence of multiresistant bacterial infections in patients with cirrhosis has emerged. Furthermore, infections caused by multiresistant bacteria have poorer prognosis than those caused by susceptible bacteria, with higher in-hospital mortality [5,6]. Long-term use of antibiotic prophylaxis with norfloxacin clearly increases the risk of multiresistant bacterial infections [6].

This presentation will review the old and recent data on the effects of antibiotic prophylaxis in patients with cirrhosis. We will also review the major issues with the long-term use of fluoroquinolones in patients with cirrhosis.

## Indications for antibiotic prophylaxis in patients with cirrhosis

Antibiotic prophylaxis refers to the administration of an antimicrobial agent to patients without established infection in order to reduce its risk, inpatients at high-risk of developing of infection or in whom infection is associated with a poor outcome.

### *Prophylaxis of spontaneous bacterial peritonitis*

Patients at high risk of SBP include patients with advanced cirrhosis (namely those with Child Pugh class C cirrhosis) [7], those with low protein count in ascites (below 10-15 g/L) [8]. Older age and co-morbidities, namely diabetes mellitus, alcohol abuse [9] are risk factors for SBP in patients with cirrhosis .

### Primary Prophylaxis

The term « primary prophylaxis » refers to the prevention of the first episode of SBP. The indications for primary prophylaxis of SBP are essentially based on two double-blind placebo-controlled trials [10,11]. The inclusion criteria were different in these trials. In the Spanish study [10], patients had a more severe cirrhosis than those included in the Argentinian study [11]. Terg *et al* included patients with cirrhosis and low protein in ascites (< 15g/L) [11]. Fernandez et al included patients with cirrhosis at high risk of developing SBP and hepatorenal syndrome, namely patients with low protein ascites (<15 g/L) and advanced liver failure (Child–Pugh score ≥9 points with serum bilirubin ≥3 mg/dl) or impaired renal function [10]. In the latter study, norfloxacin reduced the 1-year probability of developing SBP and hepatorenal syndrome and improved short-term survival (94% vs. 62%) [10]. Importantly, antibiotic prophylaxis did not improve long-term outcome of these patients.

### Secondary prophylaxis

The term « secondary prophylaxis » refers to the prevention of the recurrence of SBP after a first episode of SBP. After a first episode of SBP, the risk of recurrence of SBP is up to 74% after 2 years [12]. Antibiotic prophylaxis with norfloxacine decreases the rate of SBP recurrence. In a double-blind, placebo-controlled trial including 80 patients, the incidence of SBP was significantly lower in the group norfloxacin than in the group placebo (12% vs. 35%) [13].

### *Variceal bleeding*

Cirrhotic patients with upper gastrointestinal bleeding are predisposed to develop SBP and other infections during or immediately after the bleeding episode (during the first week after bleeding). Approximately 20% of them are infected at admission and 50% develop infections during the first days of hospitalization in the absence of antibiotic prophylaxis [2]. Moreover, bacterial infections predict failure to control bleeding and variceal rebleeding. Antibiotic prophylaxis is effective in the prevention of SBP and other infections in this setting and that it improves survival [14]. A beneficial effect of antibiotic prophylaxis on control of bleeding and prevention of rebleeding has also been reported [15].

### *Alcoholic hepatitis*

Bacterial infection is a major issue in patients with alcoholic hepatitis. Indeed, 25% of the patients have infections at admission, and 23% develop infection under steroids. Moreover, patients who develop bacterial infections have a lower survival than those who do not develop infections [16]. In a recent case-control study, it has been found that patients with alcoholic hepatitis and variceal bleeding had a better outcome than those with alcoholic hepatitis and no bleeding. All patients who had variceal bleeding had received antibiotic prophylaxis [17]. This study suggests that antibiotic prophylaxis may improve the outcome of severe alcoholic hepatitis.

## Major issues with the use of antibiotic prophylaxis in patients with cirrhosis

*Emergence of multiresistant bacterial infections*

Long-term use of antibiotics increases the risk of multiresistant bacterial infections. Furthermore, long-term use of a fluoroquinolone not only promotes the emergence of fluoroquinolone-resistant *enterobacteriaceae*, but also promotes the emergence of other multiresistant bacteria, including Methicillin-resistant *Staphylococcus aureus* (MRSA), Extended Spectrum Beta Lactamase (ESBL) *enterobacteriaceae and Pseudomonas aeruginosa* [18]. In patients with cirrhosis, the prevalence of multiresistant bacteria has increased all over the world [5,6,19]. The long-term use of antibiotic prophylaxis of SBP with fluoroquinolone (mostly norfloxacin), is an independent risk factor for multiresistant bacterial infections, as well a nosocomial or healthcare acquisition, and previous therapy with beta-lactams [6].

Long-term use of SBP prophylaxis has also been independently associated with *Clostridium difficile* infection in a large cohort study from the US. *Clostridium difficile* infection is associated with a longer hospital stay, and increased mortality in patients with cirrhosis [20].

## Conclusion

Multiresistant bacterial infections became a major issue in patients with cirrhosis. As antibiotic prophylaxis is a major risk factor for multiresistant bacterial infections, the indications need to be restricted to patients at very high risk. Moreover, short-term prophylaxis (in case of an acute complication at high-risk of infection, namely variceal bleeding, or severe alcoholic hepatitis), should probably be preferred to long-term antibiotic use. Long-term prophylaxis of SBP using fluoroquinolone should probably be restricted to patients awaiting liver transplantation, as this procedure does not improve long-term survival.

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# Is Acute-On-Chronic Liver Failure a Risk Factor for Fungal infections? When to Prevent, How to treat?

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List of abbreviations:

IFI: invasive fungal infections;
HIV: human immunodeficiency virus;
ACLF: acute-on-chronic liver failure (ACLF),
ICU: intensive care unit;
KPC: Klebsiella pneumoniae carbapenemase;
BDG: ß-D glucan;
IA: invasive aspergillosis;
GM galactomannan;
BAL: bronchoalveolar lavage

## Introduction

Invasive fungal infections (IFI) occur frequently in immunocompromised hosts, mainly patients with hematological malignancies (most notably during prolonged neutropenia), solid tumors, HIV and those undergoing allogeneic stem cell or solid organ transplantation. However, in recent years IFI have also been increasingly recognized in critically ill patients admitted to the ICU, including cirrhotic patients.[1-4] IFI develop in these patients in the absence of any apparent predisposing immunodeficiency, other than the alteration in immune mechanisms observed in the late phase of critical illness (immunoparalysis). In the general population, between 5 and 15% of health-care associated infections are caused by fungi. *Candida* accounts for 70-90% of all invasive fungal infections and *Aspergillus* for 10-20%. [1,2]

Patients with cirrhosis, particularly those with decompensated cirrhosis, are at increased risk of bacterial infections that may further precipitate other liver decompensations including acute-on-chronic liver failure (ACLF) and constitute their main cause of death.[5-8] The risk of fungal infections in these patients seems to be substantially lower than that reported for bacterial strains. However, the real incidence of IFI (invasive candidiasis and aspergillosis) in patients with decompensated cirrhosis with and without ACLF is poorly know, as well as its risk factors and clinical impact on short-term outcome. This short review summarizes the current knowledge on the incidence, risk factors and prognosis of IFI in cirrhosis and suggests potential prophylactic and therapeutic strategies.

## Invasive Candidiasis

### 1. Epidemiology, prevalence and risk factors

*Candida* is part of the normal skin, vaginal and gastrointestinal flora, what explains why the vast majority of invasive *Candida* infections are endogenous. Modification of the endogenous flora by antibiotic therapy is a major risk factor of IFI allowing for fungal overgrowth on mucosal and skin surfaces. Disruption of the integrity of skin and mucous membrane barriers by intravascular or urinary tract devices and surgery are other key pathogenic factors that facilitate the development of fungal infections caused by *Candida*. On ICU, 5-15% of patients are colonized by *Candida spp*, but only 5-30% of them will develop invasive candidiasis, the higher the grade of colonization the higher the risk of IFI. [1,2]

Candidemia is the most frequent form of invasive candidiasis, frequently secondary to central venous line infection, followed by Candida peritonitis. Pleural and ocular candidiasis and *Candida* endocarditis are much less frequent. *Candida albicans* is the most frequent species isolated but non-albicans *Candida* strains are now responsible for up to 50% of all cases in some geographical areas, species that have intrinsic resistance to azoles. Invasive *Candida* infections are associated with high morbidity and mortality, especially in the ICU, with a crude mortality that ranges from 40% to 60%. Critical-illness severity (APACHE II score), cirrhosis (HR 2.15) and HIV infection have been described as independent predictors of mortality. [1,2]

Administration of broad-spectrum antibiotics, colonization by *Candida*, prolonged ICU stay, diabetes mellitus, presence of intravascular access devices, parenteral nutrition, renal replacement therapy, mechanical ventilation, abdominal surgery, acute necrotizing pancreatitis and treatment with steroids and chemotherapy all are well-known risk factors for the development of invasive candidiasis in the general population. Acute liver failure also predisposes the patient to the development of fungal infections. Cirrhosis itself has not been identified as a risk factor of invasive candidiasis, although the majority of critically ill cirrhotic patients present one or more of the risk factors described previously. [1,2]

Fungal infections have been scarcely reported in the literature in patients with decompensated cirrhosis. As expected, patients admitted to the ICU seem to have a higher risk of fungal infections, but real incidence and specific risk factors for invasive candidiasis (i.e. liver failure, ACLF) have not yet been described. In a recent sub-analysis of the EPIC II study (Extended Prevalence of Infection in Intensive Care; a 1-day point-prevalence survey) by Gustot et al, fungi (particularly *Candida*), were isolated more frequently in cirrhotic patients than in the non-cirrhotic population (25% vs. 19%; p=0.06). [9] However, prevalence of suspected or proven fungal infections was 13%, in the upper limit of that described in other studies involving non-cirrhotic patients (8-

13%). Bajaj at al reported in 2012 a marked increase in the prevalence of fungi in second infections compared to the first infectious episodes (14% vs. 3%; p<0.05). [10] All fungal infections described in the study were caused by Candida. The majority were urinary infections followed by esophagitis and cellulitis. Only one case of candidemia was reported in this series. Finally, Bartoletti et al have reported recently the epidemiology and outcome of bloodstream infections in patients with decompensated cirrhosis. [11] Among the 162 bloodstream infections, sixteen (10%) were caused by fungi. Candidemia was mainly primary (n=11); 3 episodes were secondary to spontaneous bacterial peritonitis and 2 to catheter infection. Crude mortality at 30-day of patients with candidemia was 53%, comparable to that observed in bacteremia episodes caused by KPC-producing Enterobacteriaceae (60%) and significantly higher than that observed in the rest of bloodstream infections. Invasive candidiasis was more common in patients with prolonged hospital stay (> 6 days), prior surgery, central venous catheter, neutropenia and previous broad-spectrum antibiotic therapy.

No data exit in the literature on the incidence and risk factors of invasive candidiasis in ACLF. A preliminary analysis of the Canonic database did not show a high prevalence of fungal infections in this subset of patients.

### 2. Diagnosis, scoring systems and prophylactic strategies

As commented before, invasive candidiasis is often fatal unless treated promptly with appropriate antifungal agents. However, early diagnosis is extremely difficult due to the lack of specific clinical manifestations, the low sensitivity of blood cultures (50%) and the delay in obtaining positive microbiological results. [1,2] Therefore, non-culture-based methods with improved sensitivity and specificity are needed to enable earlier diagnosis and improve IFI prognosis. (1,3)-ß-D glucan (BDG), a cell wall component of *Candida* and other fungi, has been proposed as a biomarker of IFI. FDA has approved BDG for the diagnosis of invasive mycoses although its sensitivity and specificity varies widely (from 55 to 95%). Mannan antigen and anti-mannan antibodies, antimycelial antibodies and *Candida* DNA have also been suggested as biomarkers of invasive candidiasis but they are not commonly used in clinical practice.

Taking into account the important difficulties that exist in the early diagnosis of invasive candidiasis, some authors have proposed different clinical scores to enable to identify patients at high-risk of fungal infection and to exclude invasive candidiasis. Among them, the easiest to use is the *Candida* score that relies in four risk factors of IFI: total parenteral nutrition, surgery, multifocal *Candida* colonization and severe sepsis. The incidence of invasive candidiasis is around 17% with a *Candida* score of 4 and of 24% with 5 points. Early and appropriate empirical antifungal therapy is recommended in these high-risk patients. [1,2]

Antifungal prophylaxis may be reasonable in ICU patients with a risk of fungal infection > 10%. Fluconazole administration reduces the rate of *Candida* infections but promotes the selection of azole-resistant yeast and has not demonstrated a clear survival benefit. [1,2]

Stewardship programs to avoid over-treating patients with broad-spectrum antibiotics and minimization of invasiveness, removing unnecessary central lines and urinary catheters, are without doubt easy to achieve measures that can contribute to prevent invasive candidiasis in the general and in the cirrhotic populations. [5,6]

### 3. Therapy of invasive candidiasis

Management of invasive candidiasis in the cirrhotic population must follow the international guidelines described in the general population, that recommend an initial treatment with echinocandins (caspofungin, anidulafungin or micafungin) for all critically ill patients and reserve azoles for de-escalation in stable patients with isolates showing susceptibility to these agents. There is no significant benefit of combining antifungals for the treatment of invasive candidiasis. Duration of treatment is 14 days from the first negative blood culture in proven cases without abscesses or dissemination. All patients with candidemia must undergo a dilated eye exam to rule out dissemination. Another basic point in the management of these patients is the removal of central lines and the drainage of any identified collection. [1,2]

## Invasive Aspergillosis

### 1. Epidemiology, prevalence and risk factors

As occurs with invasive candidiasis, invasive aspergillosis (IA) has been increasingly recognized as an emerging disease in non-neutropenic patients and in patients admitted to the ICU, in the absence of an apparent predisposing immunodeficiency. Chronic pulmonary obstructive disease, decompensated cirrhosis, diabetes, alcoholism, malnutrition, solid cancer with or without treatment and steroid therapy are now considered risk factors for the development of IA. In the ICU, the incidence of IA ranges from 0.3% to 6%. Mortality is around 60% in immunocompromised patients compared to 80-90% in non-neutropenic patients. In these hosts, in contrast to patients with neutropenia, angioinvasion, specific radiological signs, fever and other symptoms are uncommon. Therefore, many cases follow a relatively indolent course and IA progresses over weeks. Consequently diagnosis is often not suspected. [3,4]

A careful review of the literature suggests that IA is a potential fatal complication of severe liver diseases

(decompensated cirrhosis or severe alcoholic hepatitis). Several case series show that IA can complicate the evolution of patients with alcoholic cirrhosis and alcoholic hepatitis receiving steroids. [12,13] A recent paper published by Gustot et al shows that IA is a frequent complication of severe alcoholic hepatitis and is associated with an extremely poor prognosis. [14] The study included 94 patients with biopsy proven severe alcoholic hepatitis. Fifteen IA infections were observed (16%), 6 were classified as proven, 6 as probable and 1 as possible. IA was diagnosed a median of 26 days after liver biopsy and involved the lungs in 11 cases, the central nervous system in 2 and was disseminated in other 2 patients. The majority of IA occurred in the context of steroid treatment (81%), but non-response to steroids at day 7 was not a risk factor for aspergillosis. IA was independently associated to poor liver function at baseline (MELD score ≥ 24 at day 0: incidence of 27% vs. 4%) and to ICU admission, what suggests that IA occurs in the most severe patients, many of them probably with ACLF. All non-transplanted patients died, and only 1 out of the 3 transplanted patients survived, thus confirming the huge mortality of this entity.

## 2. Diagnosis

Clinical manifestations of IA may be initially indistinguishable from those of bacterial pneumonia. The isolation of an *Aspergillus* species from the respiratory tract in critically ill patients should indicate a probable case of IA and must promote further investigations, such as a chest CT scan, galactomannan antigen test (GM) in serum and bronchoscopy with bronchoalveolar lavage (BAL) for GM determination and PCR techniques. BAL GM sensitivity ranges from 60 to 93% depending on the cut-off value used (88% using a cut-off index of 0.5) whereas PCR techniques have a sensitivity that ranges from 85 to 100%. BAL GM at a cut-off of 0.8 is more sensitive than fungal culture or serum GM for the diagnosis of IA. Moreover, more than one positive respiratory test (culture or GM levels) is usually an indication of IA whereas 2 negative respiratory sample tests almost always rule it out.[3,4]

## 3. Treatment and prophylactic strategies

IA must be considered a devastating infectious disease in patients with liver disease. Treatment of IA is challenging in these patients. The drug of choice is voriconazole, but it is potentially hepatotoxic and is metabolized by cytochrome p-450. Thus it is contraindicated or must be used with extreme caution in patients with severe liver failure. Other options are represented by lipid formulations of amphotericin and echinocandins. Although only caspofungin has been approved for the treatment of IA, the 2 other echinocandins (anidulafungin or micafungin) are also used in clinical practice. In breakthrough IA, refractory disease and in our opinion in patients with liver failure (ACLF and severe alcoholic hepatitis), combination therapy (echinocandin plus liposomal amphotericin or voriconazole) must be prescribed, since combinations increase the response to treatment. Optimal duration of therapy is not known, but in non-neutropenic patients is typically a minimum of 12 weeks. [3,4]

Prophylactic strategies are currently recommended in neutropenic patients and in those undergoing allogeneic stem cell or solid organ transplantation. Echinocandins or low dose IV liposomal amphotericin and nebulized amphotericin are prescribed in an attempt to decrease the rate of IA in well-established high-risk populations. The efficacy of these strategies in critically ill cirrhotic patients or in severe alcoholic hepatitis has not been evaluated. Before giving this step, prospective studies must be conducted to clarify the real incidence and risk factors of IA in critically ill liver patients.

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# Alcohol and ACLF

## The burden of alcohol consumption in Europe. Local and European strategies to lower consumption.

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The WHO report 2014, estimates that about 3.3 million deaths were caused by alcohol consumption in 2012, corresponding to 5.9% of all deaths (7.6% for men, 4.0% for women), worldwide. In Europe, the proportion of alcohol-attributable deaths relative to all deaths is the highest among the WHO areas, with 13.3% of alcohol-attributable fractions (AAFs) for all diseases.

This is in parallel with the reported consumption, since while the average worldwide consumption is 6.2 liters of pure alcohol per year (13.5 grams of pure alcohol per day), in Europe it is about 10.9 liters of pure alcohol per year. Also, this consumption associates with a very heavy economical burden, with alcohol-attributable costs that have been estimated at about 125 billion euros in the European Union for 2003.

According to report from OCDE 2015, the overall per-capita alcohol consumption in the OECD countries has decreased, although there has been divergent trends, with some countries having seen a decrease and others an increase. However, a major concern is the observed increase in certain patterns of risky drinking, particularly in young people and females. Also, some countries with emerging economies have observed an increase in alcohol consumption, although starting from lower levels. Probably as a consequence of this, in the years between 1990 and 2010, harmful consumption of alcohol rose from eight to fifth leading cause of death and disability.

Worldwide, alcohol is the leading cause of liver diseases including cirrhosis, and it is also the most common cause (responsible for 33 to 45%) of hepatocellular carcinoma (HCC) in several countries of Europe and USA.

In fact, globally, in 2010, if we consider deaths or DALYs (disability adjusted life years), it was found that alcohol-attributable liver cirrhosis was responsible for 493,300 deaths (156,900 female deaths and 336,400 male deaths) and 14,544,000 DALYs (4,112,000 DALYs for women and 10,432,000 DALYs for men), representing 0.9% (0.7% for women and 1.2% for men) of all global deaths and 0.6% (0.4% for women and 0.8% for men) of all global DALYs, and 47.9% of all liver cirrhosis deaths (46.5% for women and 48.5% for men) and 46.9% of all liver cirrhosis DALYs (44.5% for women and 47.9% for men). In what concerns alcohol-attributable malignant neoplasm deaths, 80,600 deaths (14,800 deaths of women and 65,900 deaths of men) were caused by liver cancer and were attributable to alcohol consumption.

In Europe, it was estimated that more than 75% of all liver cirrhosis in 2004 were caused by alcohol. In Portugal it was found that 84% of hospital admissions for cirrhosis were due to alcohol, during the period from 1993 to 2008.

More recently it was found that Central Europe had the highest proportion of liver cirrhosis deaths and DALYs attributable to alcohol consumption, with 72.3% of all liver cirrhosis deaths (62.6% for women and 77.1% for men) being attributable to alcohol consumption and 74.6% of all liver cirrhosis DALYs (67.8% for women and 77.4% for men) being attributable to alcohol consumption.

Another evidence of the high prevalence of alcoholic liver disease in Europe is that it represents one-third of liver transplantation due to liver cirrhosis, although there is evidence that patients with liver disease due to alcohol are less frequently transplanted. Furthermore, alcohol is also a very important contributing factor to other liver diseases, such as viral hepatitis, accelerating progression and increasing the risk for HCC, although difficult to exactly quantify its contribution.

The last decade has witnessed an increase in alcohol-related cirrhosis in several countries such as Estonia, in Denmark and UK, directly relating to the increase in alcohol consumption, since 1990s in those countries.

Interestingly, in what relates to the risk for incidence of liver cirrhosis in relation with consumption, the risk curve is much flatter than for mortality from liver cirrhosis. This suggests that individuals that are drinking at low or moderate levels have a relatively low risk of liver cirrhosis opposite to the risk with heavier drinking where it is exponentially increased. However, if a person already has cirrhosis, independently of the cause, the risk of progression or death is very much increased even at moderate levels of alcohol drinking.

Looking at the devastating effect that alcohol consumption, concerning several diseases but particularly, liver diseases it becomes evident that measures are needed to reduce alcohol consumption. In general, it is possible to identify the measures that are effective, although it is often very difficult to implement them. It is also of interest that some of these measures target heavy drinkers while others have a broader target. In fact, according to the OECD report

2015, the majority of alcohol is drunk by the heaviest-drinking 20% of the population.

The World Health Organization has launched a global strategy to reduce the harmful use of alcohol, that is based on several major points: a) health services' response and community action, but focus on preventive public health actions such as drink-driving policies and countermeasures; b) reductions of availability of alcohol; c) ban of marketing of alcoholic beverages; d) increase of prices mostly through increases in taxation. It also includes harm reduction measures to reduce the negative consequences of drinking and alcohol intoxication of those who drink. Other important measures include a reduction of unrecorded illicit and informally produced alcohol, and the establishment of a monitoring and surveillance system.

Among these measures, it has been shown that the more effective measures are increasing taxation/price, reducing availability, and reducing advertising in media, mostly publicity targeting young people.

An important point to bear in mind is that many public health strategies to prevent alcohol-attributable harm tend to be quite unpopular among politicians and the media. It is also important to acknowledge that since the alcoholic-beverages industry is very powerful and has a strong economical power, they may have a strong influence in advising on measures that have already proved not to effective. In fact it is frequent to observe that politicians and the alcohol industry tend to focus on education or individual -based responses that proved not to be effective. On the opposite, measures such as the minimum price per unit, implemented in Scotland, that has already proved to be very effective, has been strongly opposed by the alcohol-industry and by politicians in several countries.

Related with that, comes the issue if the alcohol-related harm reduction organizations should allow alcohol-industry representatives in their constitution. On that respect the WHO has already firmly ruled against, prohibiting that alcohol industry stakeholders are present on their organizations.

In the European Union (EU), there are several organizations to deal with the problem. The Committee for National Alcohol Policy and Action (CNAPA) was established to ensure coordination of government-driven policies between Member States and the European Commission and to contribute to policy development. The additional value of an EU strategy is the work on policy areas where Member States need EU support to act effectively, in particular on cross-border issues, which need to be central in a new strategy.

Another important organization is the European Alcohol and Health Forum (Forum or EAHF) that consists of stakeholders, mainly industry, and health NGOs who make commitments to work to reduce alcohol related harm. Very recently, there was a joint position of all the health NGOs, including the European Association for the Study of Liver diseases (EASL), to walk out of EU alcohol Forum, based on the fact that no effective steps were being taken in order to reduce alcohol consumption in Europe, what might be partially due to the influence of alcohol-industry.

To minimize the burden of ALD, reducing alcohol consumption is undoubtedly the more effective measure. However, the timely treatment of its initial, reversible, stages of disease would also be of great benefit to reduce the ALD morbidity/mortality. The major difficulty is that the disease is mostly asymptomatic until its more advanced phases and these individuals tend not to regular health check-ups. Consequently, an emphasis on screening for alcohol use disorders and their treatment would be the more appropriate.

Recommended reading:

© OECD (2015), Tackling Harmful Alcohol Use: Economics and Public Health Policy, OECD Publishing. doi: 10.1787/9789264181069-en

Global Status Report on Alcohol and Health – 2014 ed.

Rehm J, Samokhvalov A , Shield K. Global burden of alcoholic liver disease. J Hepatol 2013; 59:160-8

# Medical treatment for acute alcoholic hepatitis: where do we stand?

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**Diagnosis, Stratification and Scores**

Although we describe alcoholic hepatitis, as a homogeneous disease the reality is that frequently the patient achieves the label based upon history and clinical diagnosis supported by laboratory results – elevated neutrophils, bilirubin, fever and hepatomegaly. Unfortunately, however, the number of studies where liver biopsy has been used to define the diagnosis is by no means universal.

Great improvements have been made in severity scoring of these patients using generic and specific scores. We have at our disposal the Maddrey Score, Glasgow hepatitis score, Lille score and MELD score. Such scores are used to stratify patients and assess response to any given intervention. However as clinicians we need to recognize the variability of such scores both across centers and changes as a result of interventions. Examples being a fall in bilirubin due to fluid resuscitation, a change in prothrombin time due to laboratory variables or administration of coagulation factors, wbc count and steroids, urea and creatinine being dependent upon fluid status and muscle mass.

Many studies utilize an alcoholic hepatitis score but without context of time line re other treatment modalities, nutritional status or reference to underlying severity of liver disease (MELD, delta MELD, Child Pugh score) and or development of extra hepatic organ dysfunction (renal, neurological, coagulation disturbances, gastro-intestinal bleeding, cardiovascular or respiratory). These hepatic and extra hepatic organ failures can be assessed with SOFA and CLIF-SOFA scores and potentially give further information as to optimal treatment and response patterns.

**Early Treatment and screening**

The patient firstly needs to be assessed and other aetiological factors excluded. Axial imaging will allow assessment of liver volume and exclude pancreatitis. Use of contrast in order to obtain optimal images will need to be balanced against risk of contrast-induced nephropathy. A liver biopsy should be actively considered, often via the trans-jugular route.

Assessment of extra hepatic organ dysfunction / toxicity should be addressed specifically looking for cardiac dysfunction (echo-cardiography), respiratory function (CXR, gases) and renal injury (urinalysis and assessment of GFR), chronic / acute pancreatitis and muscle function. Consideration must be given early to the nutritional status of the patient and the need for nutritional supplements along with vitamin and trace metal requirements. Support may be needed for alcohol withdrawal syndromes and other dependencies that may result in withdrawal.

The presence or absence of sepsis is a daunting proposition in the context of a significant inflammatory response as part of the disease presentation. Cultures should be taken and sources of sepsis examined through clinical review and radiological assessment. Unfortunately at the present time none of the commonly available biomarkers clearly separate inflammation and infection.

Choice of agents depends on local and patient factors. Attention to good hygiene practice is essential, hand hygiene, line care etc.

**Ethnicity, Organ Failure, Treatment and Prognosis**

At present we are unable to comment with any certainty as to whether their are ethnic variations in response to treatment, nor to whether the presence of standard exclusion to steroid therapy, renal failure or active gastro-intestinal bleeding, should result in different therapies, doses or only supportive therapy.

**Immunological dysfunction.**

There is considerable data to suggest that the immune dysfunction of alcoholic hepatitis may be different from that of other aetiologies of Acute on Chronic Liver failure (ACLF). Certainly there are lowered levels of complement and some immunoglobulin fractions, but in addition there appear to be differences in monocyte, neutrophil and lymphocyte function as compared to other groups of ACLF. As to whether these are pertinent to therapeutic choice and timing of treatment intervention is yet to be determined.

## Disease Related Treatment options

**Nutrition :**

Malnutrition associated with poor outcome. Ensure adequate nutrition and vitamin supplementation. Role of specific nutritional supplements are not clearly proven of benefit in ACLF/ alcoholic hepatitis.

**Avoidance of hepatic encephalopathy and renal dysfunction**

Difficulty in diagnosis of acute kidney injury as opposed to waiting for specific factors for diagnosis of HRS. Relationship between renal dysfunction and ammonia clearance. Need to maintain no, or low level encephalopathy – increasing levels associated with non compliance, use of pharmacology to allow treatment and increased risk of micro-aspiration and chest sepsis. Consideration of early low dose terlipressin for acute kidney injury to facilitate urine output and water clearance

**Avoidance of intra-abdominal hypertension (IAP)**
Measure IAP and consider renal perfusion pressure; low volume paracentesis may be required as compared to large volume with the inherent cardiovascular risks.

**Optimize fluid status**
Assess fluid status at the bedside – use of echocardiography. Central venous saturations are not useful in prediciting volume status in a hyperdynamic state.

**Assessment of coagulation status**
Need for coagulation factors should be considered in the totality of a coagulation profile utilizing measures of pro and anticoagulant factors and dynamic testing (RoTEM, TEG) as opposed to routine administration of coagulation support.

**Role of antimicrobials & Screen for viral, fungal and bacteria**
Separation of inflammation vs infection can be complex. Biomarkers lack sensitivity and specificity. Sequential tracking of fungal biomarkers allow greater risk assessment for fungal sepsis. In patients in receipt of steroids or other immune modulating treatment screening for viral replication (CMV, HSV) utilizing PCR is beneficial allowing treatment to be instituted for those with rising copies.

**Role of albumin**
The role of albumin as a volume therapy is not clear; it does however have potential roles as an immunomodulatory agent. Choice of patient and dose is yet to be clarified in alcoholic hepatitis.

**Mobilization and rehabilitation**
As with all acute illnesses early mobilization and rehabilitation is essential to facilitate recovery. Patients with alcoholic hepatitis are no different in this regard and early mobilization and exercise programmes should be encouraged.

**Disease specific treatment options**
**N-acetyl cysteine and Anti-oxidant cocktail**
Conceptually the role of a mild anti-inflammatory agent with anti-oxidant properties is attractive in the management of alcoholic hepatitis. Unfortunately a variety of randomized trials have failed to demonstrate any clear benefit. A large RCT of steroids with or without NAC did not show mortality benefit at 3 months (22 vs 38%), but was significant at 1 month and with an associated decrease in renal failure (9 vs 22%) (Nguyen-Khac et al). Cocktails of anti-oxidants have also been examined, also without significant benefit being demonstrated. Moreno et al compared enteral nutrition with or without NAC and did not demonstrate benefit. Philips et al compared an anti-oxidant cocktail to streroids with the latter group showing improved outcome (70 vs 54% survival).

**TNF monoclonal antibody**
The blockade of inflammatory mediators, and specifically TNF-alpha is an attractive option in a disease process where there are clearly elevated levels of TNF and an active inflammatory process resulting in liver damage. Its role on the pathogenesis was supported by animal studies where blockade resulted in improved survival. Although case series were supportive of its role subsequent RCTs failed to show benefit, and a study comparing steroids plus TNF blockade vs steroids alone was halted early due to increased infections and mortality. The study of Boetticher et al showed similar outcome at 1 month but the 6-month mortality was higher in the TNF blockade group (58 vs 22%). These poor outcomes may relate to inappropriate dosing regimes but it should be emphasized that blockade of inflammatory mediators have failed to show benefit in any acute inflammatory process as compared to chronic inflammatory states; as suchTNF-alpha mediator blockade is not recommended as a treatment option.

**Pentoxyifylline (Ptx)**
This agent, a little akin to NAC, provides low-level suppression of TNF-alpha through inhibition of TNF gene expression. In a large single centre RCT administration of oral pentoxifylline for 28 days was associated with improved outcome (76 vs 54% survival) and a decreased incidence of HRF. A further study of De et al also suggested benefit of Ptx although the study design and blinding render the results less clear. More recent studies did not show any benefit for Ptx and steroids as compared to steroids alone (Sidhu et al, Mathurin et al). The data from the Mathurin paper clearly again demonstrates that survival is associated with response to treatment intervention as assessed, on this occasion, using the Lille score. This raises the question as to whether in the context of an environment where sepsis (multi drug resistant) is a significant risk factor, likewise reactivation of hepatitis B as to whether give equivalence in response Ptx may still be considered as a useful therapeutic agent.

**Steroids**
Comparison of enteral nutrition with steroids showed an early benefit to steroids but this was lost over time, potentially related to increased sepsis.
The role of steroids has been shown in a meta-analysis by Mathurin et al to have a survival benefit (79 vs 65% survival); steroids, DF, leucocytes, Lille score and hepatic encephalopathy were associated with survival on multivariate analysis. 28-day survival was strongly

associated with delta response, allowing separation into full, partial and none responders. Similarly the work of Forrest et al using the Glasgow hepatitis score allows definition of a group of patients who will benefit from steroid therapy. Response to therapy and outcome is again emphasized in the work of Louvet at el. It was of note that in this study infection per se did not result in poor outcome; as compared to response to therapy; questioning the long held view that infection is an absolute contradiction to use of steroids.

Some patients are clearly steroid non-responders and in this group treatment should be discontinued to avoid side effect risk without measurable benefit. A small study by di Mambro et al demonstrated steroid resistance, which could be resolved with IL-2 blockade. The recent STOPAH study published by Thurz et al, raises further questions as to optimal treatment for these patients. They compared Ptx, steroids, Ptx and steroid and placebo groups. Baseline characteristic showed a MELD of 20-21, DF > 60 and Glasgow alcoholic hepatitis score of 8.4 - the data shows no mortality benefit for steroids or Ptx over placebo. There was a trend to improved survival in the 28-day outcome for steroids but this did not achieve significance and there was no benefit at 90 days or 12 months. In a secondary multi-variate analysis of determinants of survival at 28 days steroids were shown to offer significant benefit whilst encephalopathy, wbc, creatinine, urea, age and prothrombin time were associated poor outcome.

**Liver support systems**

Liver support systems in ACLF have not yet been shown to demonstrate any survival benefit. Studies are at present ongoing looking specifically at alcoholic hepatitis. Conceptually they have the opportunity to impact on disease course with beneficial outcome.

**Immune manipulation**

As we gather more information pertaining to immune dysfunction in ACLF and alcoholic hepatitis specifically it is likely we will be able to tailor therapy dynamically to an individuals patient needs. This may be manipulation of monocyte, macrophage or T cell function, along side adsorptive techniques using dialysis systems and manipulation of regenerative capacity and pathways. Singh et al suggest beneficial outcome in patients treated with G-CSF, whilst Michelena et al demonstrate inflammatory response and lipopolysaccharide levels are clear determinants of outcome. The recent publication of Dubuquoy et al present data that those patients who are not responsive to steroid therapy also have low levels of cytokines associated with regenerative pathways, lack of proliferative hepatocytes and profound mitochondrial damage.

**Prognosis after the development of extra hepatic organ failure**

The data from the CLIFF consortium studies would suggest that alcohol related liver disease, did not have worse outcomes than other aetiologies regardless of the active or inactive alcohol consumption. However this has not been formally examined and active alcohol consumption certainly increases risk of bacteremia and chest sepsis in the general population.

Should the amount of organ support offered to patients with alcoholic hepatitis be exactly the same as for those with other precipitants for admission – certainly we have no evidence to suggest otherwise and this is by its very nature potentially reversible. The majority of data would suggest that development of cardiovascular, respiratory and renal failures carry a poor prognosis but even in this context, assessment of response after 72 hours of critical care support is justified.

# Liver transplantation as the last stronghold for acute alcoholic hepatitis?

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## Background

Alcoholic hepatitis represents one of the most serious forms of alcoholic liver injury and is characterized by the presence of lesions, generally located in the zone 3 of the lobule, such as hepatocyte necrosis or ballooning, polymorphonuclear neutrophil infiltration and intracellular Mallory inclusion bodies.

The cardinal sign of alcoholic hepatitis is rapid onset of jaundice that may be associated with fever, ascites and other symptoms such as encephalopathy in the severe forms [1]. The classical profile of AH comprises elevated serum aspartate aminotransferase up to twice the upper limit of the normal range, although rarely above 300 IU/ml, with an AST/ALT ratio typically greater than 2, biological parameters indicating impaired liver function such as hypoalbuminemia, elevated bilirubin, high INR and prothrombin time [1].

Several investigators have given priority to treatment of AH, as this entity is associated with significant early mortality; inpatient mortality can attain 50-75 % in the most severe forms [1]. The main causes of death are liver insufficiency, sepsis, hepatorenal syndrome and gastrointestinal bleeding. To improve the survival of patients with alcoholic liver disease, pharmacological treatments for controlling the alcohol-induced liver injury are required.

Patients at significant risk of early death are identified by the use of prognostic models. The available prognostic models include the Maddrey's discriminant function (DF), the Model for End-Stage Liver Disease (MELD), the Glasgow AH (GAH) score, the ABIC score [2-7]. The most widely used is the DF, which is calculated as 4.6 x (prothrombin time patient - prothrombin time control) + serum bilirubin [2]. A DF value ≥ 32 is indicative of evaluated short-term mortality around 20-35% at 1 month.

## MEDICAL THERAPY OF ALCOHOLIC HEPATITIS

### Corticosteroids

- Corticosteroids improve short-term survival

In fact, the main limit of meta-analysis of the literature in alcoholic hepatitis is that evaluation of any treatment effect on short-term survival is achievable only in the subgroup of patients with a significant risk of death in the short-term [8-10]. For that purpose, the use of reproducible tools is mandatory but this requirement was not met in most studies published before DF became available.

The use of meta-analyses combining individual data is warranted in order to overcome the limitations associated with using the literature for comparative purposes. The need for such an approach is confirmed by the fact that, 20-year truth survival of conclusions derived from meta-analysis from the literature was lower (57%) than that from non-randomized studies (87% %) ($p< 0.001$) or randomized trials (85%) [11]. Whenever possible, a meta-analysis of individual patient data should be done because this provides the least biased and most reliable means of addressing questions that have not been resolved satisfactorily by individual clinical trials. A recent international study combined individual data of patients with DF≥32 or encephalopathy from the five most recent randomized controlled trials comparing corticosteroids to placebo or any inefficient treatment [12]. 221 allocated to corticosteroids and 197 to non-corticosteroids were analyzed. The two groups were similar at baseline. 28-day survival was higher in corticosteroids than in non-corticosteroids patients (79.97% vs. 65.7%, $p=0.0005$). In multivariate analysis, corticosteroids, DF, leukocytes, Lille model and encephalopathy were independent predictive factors of 28-day survival [12].

- New management of patients according to the response to steroids

Early identification of responders with a substantial improvement in hepatic function following treatment with corticosteroids constitutes an advance in the management of severe AH [13]. In order to make progress in the management of severe AH, our group initially proposed a simple criterion for early identification of patients who do not benefit from corticosteroids, [13]. This criterion, termed "early change in bilirubin levels (ECBL)" is defined as a bilirubin level at 7 days lower than the bilirubin level on the first day of treatment. In a second step, our group generated a model, referred to as the Lille model, that was specifically designed for patients with severe AH treated with corticosteroids [14]. After 7 days of treatment, physicians may identify responders to medical therapy using this model [14].

The Lille model is highly predictive of death at 6 months and a score above 0.45 predicted 75 % of the deaths. This approach highlights the benefits obtained from strategy integrating the impact of treatment upon the evaluated endpoint.

The need for adapting corticosteroid therapy to response to treatment was confirmed by survival analysis according to the percentile distribution of the Lille score: ≤35th, 35-70th and ≥70th percentile [12]. Patients were classified as: complete responders (Lille score ≤0.16, ≤35th percentile); partial responders (Lille between 0.16-0.56, 35th-70th percentile); and null-responders (Lille >0.56, ≥70th percentile). This approach identified three patterns of responses, complete, partial and null, with significant differences in survival benefit: 91% vs. 79% vs. 53%, p<0.0001. Survival impact of corticosteroids was significant in complete and partial responders, whereas it appeared negligible in null responders [12]. This new classification raises questions concerning management of severe AH. It is speculated that corticosteroids may be sufficient in complete responders and that novel pharmacological therapies are relevant for intermediate responders. [12].

Up to now, in severe AH, infection has classically been viewed as a contraindication for corticosteroid treatment, although specific data are lacking. A recent prospective study of 246 patients with severe AH evaluated the incidence of infection in patients with severe AH before and after corticosteroid treatment, the predictive factors of development of infection and determine whether infection contraindicates corticosteroids. 246 patients with severe AH were prospectively included [15]. At admission, 25.6% of patients were already infected. Patients infected before using corticosteroids had 2-month survival similar to that of others. Infection occurred more frequently in non-responders than in responders: 42.5 vs. 11.1%. In multivariate analysis, only the Lille model independently predicted infection upon steroids. In summary, severe AH is associated with high risk of infection. Infection screening is warranted, but should not contraindicate steroids. In terms of mechanisms, non-response to steroids is the key factor in development of infection and prediction of survival [15].

## EARLY LIVER TRANSPLANTATION AND ALCOHOLIC HEPATITIS

### Liver transplantation: an efficient treatment for decompensated alcoholic liver disease

Orthotopic liver transplantation (LT) is considered as the first therapeutic option for improving survival of patients suffering from end-stage liver disease. In order to ration organs, most programmes require a 6-month period of abstinence prior to evaluation of alcoholic patients. The 6-month period of abstinence is presumed: a) to permit some patients to recover from their liver disease and obviate the need for LT; and b) to identify subsets of patients likely to maintain abstinence after LT. Nevertheless, data concerning the utility of the 6-month rule as a predictor of long-term sobriety are controversial. Progress in the management of alcohol dependence is mandatory to decrease the risk of any alcohol use after liver transplantation. Drinking habits of transplanted patients need to be routinely screened with tools of proven reliability. Despite the frequent use of the 6-month rule, the United Network for Organ Sharing (UNOS) [16], the EASL clinical practical guidelines on ALD [17] and the French Conference Consensus on Liver Transplantation {, 2006 #1262} do not consider this measure as a formal recommendation.

Given the organ shortage, it is necessary to identify patients who will derive significant survival benefit from LT. Among patients with Child class C, transplanted patients had higher 1- and 5-year survival than their matched controls, whereas among those with Child class A or B, there was no significant survival difference between transplanted patients and their matched and simulated controls [18]. At MELD 18-20, the mortality risk was lower among recipients compared to candidates [19]. Survival benefit increased with increasing MELD score. Taking into account that result, this American national conference stated that listing only patients with a MELD score ≥15 is the best option [19].

In the setting of LT for ALD, alcohol abstinence is viewed as a critical issue by physicians and drinking habits of transplanted patients need to be routinely screened by physicians with tools of proven reliability. One important facet is the absence of a consensus concerning the definition of alcohol relapse [20,21]. For some centres, all drinking is considered a relapse, whereas others have defined excessive drinking as alcoholism relapse, when considering that only heavy drinking is associated with alcohol-induced liver injury. At first, relapse was defined as any alcohol intake after LT. However, this definition contrasts with studies from the literature on addiction medicine in which relapse is considered only in the presence of heavy drinking recurrence. The wide variability in the rate of relapse may at least in part be attributed to this lack of a clear definition of alcoholic relapse. Indeed, the frequency of alcohol relapse after LT varied widely between studies from 10% to 50% within 5 years following LT {Burra, 2005 #1270;Burra, 2000 #1271}. A systematic review evaluated patterns of alcohol use among LT recipients with ALD and non-ALD. In patients reporting early alcohol use post-LT, there was no difference in the proportion of transplant recipients with ALD compared with those with non-ALD: 4% vs 5% at 6 months and

17% vs 16% at 12 months [22]. However, transplant patients with ALD were more likely to drink excessively [22]. Long-term studies showed that occasional or moderately heavy drinking did not impact graft function or patient survival. Conversely, the deleterious effect of excessive drinking is established at long-term. Indeed, initial studies focusing on short-term survival did not observe any survival difference between recipients who resumed heavy drinking and others. Conversely, recent studies evaluating long-term effects of the different patterns of alcohol relapse showed that recipients who resumed abusive drinking had significantly lower long-term survival than abstinent recipients or those with minor relapses. Analysis of causes of death revealed that recurrent ALD was responsible for approximately 90% of deaths in recipients who resumed abusive drinking. In summary, abusive drinking after LT has little effect on short-term outcome, but worsens long-term survival.

**Does the 6-month rule limit access to liver transplantation for the most severely ill patients?**

At present, liver transplantation is not considered a therapeutic option for patients with alcoholic hepatitis. A panel of experts noted that the potential role of liver transplantation in managing patients with severe alcoholic hepatitis remains unsettled [23]. In addition, members of UK liver transplant units listed alcoholic hepatitis as a contraindication for liver transplantation [24]. However, such recommendations have raised several concerns [25]. Indeed, optimal timing for liver transplantation in alcoholic patients varies drastically between transplant programs, and decisions on transplant eligibility should be made on an individual basis, with careful prediction of short-term survival. In the particular setting of non-responders to corticosteroids, strict application of a period of sobriety as a policy for transplant eligibility is unfair to such patients, as most of them will have died prior to the end of the 6-month sober period.

It is well established that doctors and the public do not share the same viewpoint on graft allocation. Indeed, a survey in the UK showed that healthcare professionals gave priority to disease severity, whereas the public gave low priority to patients with self-inflicted diseases such alcoholism [26]. Another study presented prospective jurors with multiple scenarios, asking them to distribute 100 transplantable organs among different groups [27]. The subjects allocated fewer than half the organs to patients with self-inflicted disease.

Clinicians fear that modifications in guidelines for liver transplantation of alcoholic patients, which are in conflict with public allocation preferences, may decrease public willingness to donate. It should be emphasized that such a concern was not raised in the setting of emergent liver transplantation proposed to patients with fulminant hepatic failure due to voluntary acetaminophen poisoning, or to active drug abusers with acute hepatitis B virus. It is important to make the public aware that most philosophers and ethicists feel that patients with self-inflicted diseases should have the same access to medical resources, and that personal responsibility should not influence the decision to transplant.

**Early liver transplantation improves survival of patients**

In severe alcoholic hepatitis, patients with severe alcoholic hepatitis failing to medical therapy can be early identified and have a 6-month survival around 30%. As most deaths occur within 2 months, early liver transplantation in those patients is attractive but highly controversial as it challenges the 6-month abstinence rule prior to LT. Seven liver transplantation centres performed early liver transplantation in patients with severe alcoholic hepatitis failing to medical therapy undergoing their first episode of liver disease and drastically selected using those criteria: absolute consensus of paramedical and medical staff, no co-morbidities, social integration and supportive family members. NRS were identified using Lille score ≥0.45 or worsening of liver function by day 7 [28]. This case controlled study showed a drastic improvement of survival in patients who were early transplanted. The investigators concluded that despite early LT challenges the 6-month abstinence rule, these results support future evaluation in drastically selected patients with severe alcoholic hepatitis failing to medical therapy [29].

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# Factors associated/inducing decompensation in cirrhosis

# Hepatic encephalopathy and its role in acute decompensation, ACLF and prognosis: why the differences?

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**Conflict of Interest**

Manuel Romero-Gómez was inventor of THDP-17, a glutaminase inhibitor, which was licensed by Janus Development, S.L. He has ongoing research collaboration with Umecrine, S.A., Sweden. He has also received speaker fees from Bama-Geve, Merz and Norgine, S.A.

**Introduction**

Hepatic encephalopathy (HE) is a major complication of liver cirrhosis, and is classified into three types: Type A (acute) HE is due to with acute liver failure (ALF); Type B (by-pass) HE is due to portal-systemic shunting without intrinsic liver disease; and Type C (cirrhosis) HE occurs in patients with underlying cirrhosis. However, the appearance of hepatic encephalopathy in patients with acute-on-chronic liver failure was not included in this classification.

HE manifests as a spectrum ranging from minimal disturbances in mental function that impacts on attention, cognition and quality of life to coma. Moreover, HE could complicate acute liver cirrhosis decompensation or acute-on-chronic liver failure (ACLF). ACLF is a complex syndrome in patients with liver cirrhosis characterized by acute hepatic decompensation resulting on liver failure (jaundice and coagulopathy) and one or more extrahepatic organ failures (liver, kidney, brain, circulation, coagulation and respiratory) that is associated with increased short-term mortality.

Hepatic encephalopathy is a complex neuropsychiatric syndrome in patients with liver dysfunction or porto-systemic shunts. Stages of HE have been defined by West-Haven criteria: Stage 0 means no abnormality detected. Stage 1 trivial lack of awareness with shortened attention span, euphoria and anxiety and inability to do easy calculations. Stage 2 is characterized by lethargy, disorientation for time, changes in personality, inappropriate behaviour. Stage 3 was defined by somnolence and semi stupor, keeping response to stimuli with confusion, gross disorientation for time and space and bizarre behaviour. Stage 4 was defined by coma. From an HE point of view, brain failure was considered when HE grade was 3 or 4, and in this case could add an organ failure to achieve definition of ACLF. In patients with brain failure, Glasgow scale could be useful to monitorize mental status progression.

From a clinical point of view, is mandatory to correctly classify patients with hepatic encephalopathy if suffering or not from ACLF. CLIF-C organ failure score is an easy-to-use tool to accurately make the diagnosis of ACLF.

**Hepatic Encephalopathy in Acute decompensation and ACLF**

HE in patients with cirrhosis decompensation without criteria for ACLF has been strongly related to previous episodes of hepatic encephalopathy and the abuse of diuretics, but not with hyponatremia, infections or alcohol binge. Interestingly, GI bleeding seems to protect against HE instead to promote it. Improvement in the management of variceal bleeding avoiding infections and controlling bleeding could explain, at least in part, this result. On the other hand, in patients with ACLF, HE was also associated with previous bouts of overt HE but not with diuretics abuse, GI bleeding, alcohol binge or infections. These precipitant factors were equally distributed in patients with and without HE.

The strong association between previous bouts of overt HE and HE support the hypothesis of the impact of gene alteration on the risk of developing HE. A microsatellite in the promoter region of gutaminase type K gene has been associated with increased risk of HE (form long-long of the microsatellite). However, other genes could be implicated on HE and a GWAS analysis is warranted to define the genetic profile associated with risk of overt HE in cirrhotics.

Diuretics-induced renal insufficiency seems to be a major cause of HE in cirrhotics with acute decompensation, highlighting the role of kidneys on HE.

Brain impairment appeared as consequence of hyperammonemia in the brain, oxidative stress, activation of microglia, hyponatremia and benzodiazepine-like substances able to promote an astrocyte-neuron dysfunction, neurological basis for HE.

HE in ACLF is not different from acute decompensation just for not sharing the same risk factors but also different mortality rate. Patients with HE and ACLF showed higher mortality in comparison with patients with HE without ACLF or patients without HE, suggesting a subset of patients with poorer prognosis and requiring more aggressive therapeutic options. Thus, in further consensus a new type of HE should be included: HE in patients with ACLF due to a different pathophysiology and prognosis.

## Management of he in ACLF

Taking care of patients with HE and liver dysfunction is mandatory to exclude other causes of neurological or psychiatric disorders and keep in mind other types of encephalopathy like sepsis or hyponatremia. Mental status should be explored using Glasgow scale. Nutritional assessment should also be included. Biochemical analysis include: full blood count, liver and kidney function, electrolytes, ammonia, thyroid function, inflammatory reactant, glycaemia, vitamin B12 and urine analysis. Patients with HE and ACLF should be admitted in the intensive care unit. The first step is removing any precipitant factor or treating it (infections by antibiotics; diuretics abuse: volume expansion; alcohol binge: thiamine and in cases of malnutrition nutritional support). If no precipitant factor was detected with have to focus on modulation of inflammation plus ammonia lowering drugs. In patients without response and preserved liver function, large porto-systemic shunts should be ruled out and embolised if present. Lastly, liver transplantation remained as the therapeutic option in patients with HE without response to all mentioned measures.

Several ammonia-lowering drugs are also able to avoid glutamine accumulation (that could serve as substrate for glutaminase transforming it into glutamate and ammonia –Trojan Horse hypothesis-) excreting by urine it in form of phenylacetyl-glutamine. Ornithine-phenylacetate and glycerol or sodium phenylacetate belonged to this type of drugs. CB-839 a glutaminase inhibitor demonstrated in portacaval shunted rats its ability as ammonia lowering drug. The role of these drugs in management of overt HE in patients with acute decompensation or in patients with ACLF requires future studies.

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# Portal vein thrombosis and cirrhosis decompensation: is there really a cause-effect relationship?

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Portal vein thrombosis (PVT) – the occurrence of a thrombus at any level of the portal vein tract, with any degree of obstruction – may arise in patients with cirrhosis or not, with or without associated malignancy. In cirrhosis and without malignancy, prevalence's have been described as high as 26%. [1] Reported incidence's seems to vary according to the severity of the liver disease, lower in the more stable patients, Child A and B with 1-, 3-, and 5-year cumulative incidence rates of 4,6%, 8,2% and 10,7% [2], and higher in the more severe ones, notably for those in a waiting liver transplantation list, with incidence's per year reported to be of 7,4%, 12,8% and 16,4%. [3-5] PVT also seems to be a dynamic entity, as it may spontaneously disappear in the course of the follow up, even without starting anticoagulation, in up to 70% of the patients. [2,5,6]

The consequences of PVT seem to be dependent on its extension. Intestinal ischemia results if there is an upstream extension of the thrombus, leading to 20-50% of death due to peritonitis and multiple organ failure if intestinal infarction emerges. [7] If there is a downstream thrombus extension, clinical picture depends on the existence of cirrhosis or not, varying from liver failure to an (almost) asymptomatic clinical course. [7] Compensatory mechanisms arise to overcome portal obstruction with an immediate vasodilatation of the hepatic arterial bed and the formation of collateral veins in the portal tract, the so-called portal cavernoma. [7,8] In spite of these mechanisms, portal pressure increases leading to portal hypertension and eventually its consequences (as oesophageal varices and gastrointestinal bleeding) as well as an increase in cardiac index like is seen in cirrhotic patients suggesting a hyperkinetic circulation. [9] Clinical biliary complications related to portal cavernoma may be present and also be an important problem to deal with. [10]

When a branch of the portal vein tract is intentionally occluded, as when portal vein ligation (PVL) or portal vein embolization (PVE) are performed for elective liver resection in the setting of the treatment of liver neoplasms, ipsilateral atrophy occurs and compensatory hypertrophy of the future liver remnant is achieved with an increase in up to 27% and 39%, respectively. [11] These procedures are relatively safe, but more often described in healthy livers than in cirrhotic ones. The parenchymal atrophy induced by the occluded segment has been described as the "extinction parenchymal theory". [12,13] In 61 explanted livers, intimal fibrosis was found in 36% of them, putting in evidence previously occurrence of PVT, which led to focal atrophy of the hepatic parenchyma, areas of hyperplasia and lower liver weight, which, by its turn may lead to cirrhosis progression. [13]

As previously expressed, PVT develops more often in liver transplantation candidates, putting a direct relationship between its occurrence and more severe patients. The studies that impact PVT and survival are more often retrospective, and not all gather consensus about its relationship, but some evidence points to the inexistence on survival impact on the waiting liver transplantation list, but with decreased survival after the procedure. [14] These last conclusion was best drawn in a very large study that retrospectively enrolled 22291 liver transplant recipients, and in which a strong association between PVT and higher posttransplant mortality was found, but not affecting waiting list mortality. [15]

Recent longitudinal published studies seem to show that when PVT develops it doesn't lead to liver decompensation. [2,5,6,16] In 2012, Luca et al found that, in a prospectively followed cohort of 42 cirrhotic patients diagnosed with PVT and for whom no anticoagulation treatment was started, PVT spontaneously improved in 45% of the patients and that no association existed between its occurrence and liver decompensation, and that were also the more severe patients (higher Child scores) by the time PVT was found that had also a more dismal prognosis and which decompensated most. [6] More recently, we also found, in a longitudinal study that enrolled 1243 Child A and B patients, no relationship between PVT occurrence and liver decompensation. Decompensation was defined as the appearance of clinically detectable ascites, hepatic encephalopathy, variceal bleeding, jaundice and/ or serum bilirubin > 45 µmol/L. This study found, in multivariate analysis that prothrombin time and oesophageal varices size (≥2 grade) were the only independent factors either for PVT development either for hepatic decompensation, reflecting that PVT and hepatic decompensation share the same common determinants but the first do not induce the second. PVT was also not related to progression (being rather a marker) of cirrhosis or death. [2]

In summary, PVT as inducing acute decompensation/ acute on chronic liver failure was not specifically addressed in the original description of the CANONIC study. [17] PVT seems not to impact mortality unless in the liver transplantation setting, after the procedure. Also, recent evidence with more robust studies does not allow admitting that PVT, itself, leads to decompensation of cirrhosis. Instead, there are same common determinants that are shared between PVT and liver decompensation, as are the more severe patients those who decompensates and develop PVT the most. Anticoagulation may, somehow, prevent not only PVT development but also liver decompensation in more severe patients, with a positive impact also in mortality. [18] Systemic inflammation, leaking gut hypothesis, microvascular thrombi development and the relationship between inflammatory and coagulation cascade may be the next step to work in, in order to prevent PVT, hepatic decompensation, liver disease progression or mortality.

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# TIPS - State of Play

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TIPS (transjugular intrahepatic portosystemic shunt) was introduced in 1988 as a treatment for uncontrolled variceal hemorrhage. Technically, a stent placed via the jugular vein to create a shunt from the portal vein to liver veins and inferior cava vein via an artificial communication through the liver. TIPS is used to treat complications of portal hypertension by reduction of portal pressure. Initially introduced as an uncovered metal stent with high rates of TIPS occlusion without anticoagulation, modern polytetrafluoroethylene (PTFE)–covered stents have overcome this problem and are used routinely in several indications:

TIPS implantation prevents rebleeding in high-risk patients (defined as patients with an Hepatic venous pressure gradient (HVPG) > 20mm Hg, Implantation of a TIPS early (within 72 hours) after the index variceal bleeding experience less bleeding with better mortality and even less complications compared to standard therapy with endoscopic band ligation and non selective beta blockers. TIPS implantation is an effective emergency treatment of esophageal and fundal variceal bleeding in patients who have failed conventional therapy.

In addition to treatment and (secondary) prophylaxis variceal bleeding, TIPS is recommended for the management of treatment-refractory or treatment-intolerant ascites or for patients with hepatic hydrothorax and in selected patients with Budd Chiari Syndrome.

### Technical and clinical considerations before implantation

Before TIPS implantation, hepatic functional insufficiency (Child Pugh Score >12 ; MELD>18) and clinically overt hepatic encephalopathy should be excluded. Older age, pre-TIPS HE and bilirubin >3 mg/dl are the most significant predictors of outcome and may be used as relative contraindications. Patients with Hepatorenal Syndrome (HRS) type 1 with serum bilirubin concentrations > 5 mg/dl have a clear contraindication for TIPS due to hepatic insufficiency. Portal and hepatic arterial anatomy should be investigated either by duplex ultrasonography, respectively CT or MRI angiography. Echocardiography should be performed to exclude significant diastolic or systolic cardiac failure, especially decompensation of the right heart. In patients with refractory ascites or hydrothorax, paracentesis and/or thoracentesis should be performed before TIPS implantation to facilitate cannulation of the liver vein and portal puncture.

### Intervention

Either with sedation using midazolam, piritamide, and propofol or general anesthesia TIPS implantation is performed. While Interventional hepatologists often perform ultrasound targeting to puncture the portal vein, radiologists mainly trust preinterventional imaging. To avoid shunt related complications, stents with a nominal diameter of 10 mm are dilated only to 8 mm to reduce the rate of TIPS-induced hepatic encephalopathy. Target is a portal pressure gradient of 12 mmHg or below. Technical complications are rare, most of them related to perforation of the liver capsule or stent migration.

### Post Intervention

While anticoagulation was standard of care when implanting bare metal stents, it is no longer recommended in PTFE covered stents, however occurrence of stent dysfunction an clinical relapse were reduced to approximately 10%. In general, in patients with variceal bleeding, ß-blockers are withdrawn and in patients with refractory ascites, diuretic medication is reduced by half. Duplex ultrasonography is performed before patient's discharge. Long term follow up includes ultrasonography every 6 months. The flow velocity in the stent is expected to be between 80 and 160 cm/sec shortly after TIPS. While primary factors (liver function and blood flow) inducing HE are expected to be worsened by the shunt, the shunt may improve some secondary factors such as the mean arterial pressure, serum sodium concentration, renal function, nutrition status, muscle mass, total body protein and albumin concentration.

### Complications

A post-TIPS portal vein flow velocity of less than 30 cm/sec or higher than 200 cm/sec suggests shunt dysfunction. When TIPS dysfunction is suspected, revision is not generally indicated in the absence of clinical symptoms. Certainly, revision should not be performed in patients who developed severe liver failure or hepatic encephalopathy at the time of TIPS patency. A few patients develop severe liver failure characterized by a rapid increase in bilirubin concentration. They require immediate TIPS occlusion to prevent death. The incidence of hepatic encephalopathy (HE) after TIPS varies from 15% to 48%. However a recent meta-analysis of individual

patient data showed that the cumulative probability of developing a first episode of HE during follow-up was not different between TIPS and paracentesis groups (p = 0.36) in patients with ascites, and a study by Kircheis et al. using critical flicker frequency test showed a stable HE-severity in the control group (no TIPS) while patients with TIPS showed no change in HE-severity in 44%, deterioration in 35%, and improvement in 21% of the patients. Reduction of shunt size and caution when decreasing portal pressure due to implantation of small stents improves post TIPS HE rates.

**Indications for TIPS**

i) Acute bleeding & Prophylaxis of rebleeding

RCT´s recommend the implantation in patients with an HVPG>20mmHg, the early TIPS RCT by Garcia-Pagan recommends to use early TIPS implantation within 72h hours after acute bleeding instead of Endoscopic band ligation and drugs to prevent rebleeding and improve mortality. The incidence of HE was lower in the TIPS group possibly due to the lower rate of rebleedings. The results of the study were confirmed by a post-RCT surveillance study. Consequently, the Baveno V and VI conferences in 2010 and 2015 recommended early TIPS to prevent early rebleeding. Bleeding from gastric varices often occurs with a low portal pressure gradient, TIPS should therefore preferably be used in patients with pre-TIPS pressure gradients above 12 mmHg. The use of TIPS for bleeding from portal hypertensive gastropathy is not proven by RCT´s but small studies and case reports suggest that TIPS may control bleeding in these patients.

ii) Ascites and related complications

In contrast to repeated paracentesis, TIPS implantation can improve renal function and systemic hemodynamics. Recent meta-analysis showed a complete response in 51% and a complete and partial response not requiring paracentesis in 68% of the patients. Analyzing the individual data of 4 randomized studies, the mean response to TIPS was even 76%. Recurrence of tense ascites occurred in 42% of patients allocated to TIPS and 89% of patients allocated to paracentesis. Recurrence is mostly seen in shunt insufficiency and can be effectively treated by TIPS revision. Complication rate related to portal hypertension (gastrointestinal bleeding, Spontaneous Bacterial Peritonitis (SPB) and Hepatorenal Syndrome (HRS)) is lower after TIPS Implantation (15% vs 29% in paracentesis), also mortality rates are better compared to paracentesis in recent meta-analyses. Patients with HRS type 1 with bilirubin levels >5mg/dl are contraindicated to undergo TIPS Implantation. In hepatic hydrothorax response rates were 65% after TIPS implantation.

iii) Rare indications

In patients with subacute or chronic Budd-Chiari syndrome (BCS), the complications of portal hypertension can be prevented or treated by TIPS in many cases. In a minority of patients, one or more hepatic veins are stenosed or occluded over a short segment only. This short segment Budd-Chiari syndrome may ideally be treated by angioplasty as long as cirrhosis has not developed. In contrast to patients receiving a transjugular shunt for variceal bleeding, where a graded reduction of the portal pressure may be advisable in BCS patients a larger diameter of the shunt may be recommended to allow decompression of both the sinusoidal and splanchnic beds and to facilitate arterial perfusion. BCS patients should receive anticoagulation and/or platelet aggregation inhibitors. Patients with BCS show a favorable survival with 90% after 5-years and 80% after 10-years.

Sinusoidal obstruction syndrome/veno-occlusive disease (VOD) can be treated with TIPS to improve liver disease, however large studies are needed to demonstrate a survival benefit.

In patients with portal vein thrombosis, which occurs in up to 28% of patients with cirrhosis. Newer studies state that TIPS can improve the patient's course in 87% with a complete recanalization in 57% without additional anticoagulation during or after the TIPS procedure, though these results need to be confirmed in larger trials.

TIPS treatment has also been applied to patients with cirrhotic or non-cirrhotic portal vein thrombosis with cavernomatous transformation. In patients with a relevant communication between an intrahepatic portal branch and the extrahepatic collaterals, TIPS may be effective in draining the varices and prevent bleeding in 35-83%.

# Special treatments for special patients

## Albumin use in specific settings in cirrhosis: Shall we rationalise or generalise

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Human serum albumin is a critical plasma protein produced by the liver with a number of accepted clinical indications in chronic liver disease including management of circulatory and renal dysfunction in patients with ascites. Traditionally, the biologic and therapeutic role of albumin in liver disease was attributed to its oncotic effects but it is now understood that albumin has a wide range of other important physiologic functions such as immunomodulation, endothelial stabilisation, antioxidant effects and binding multiple drugs, toxins and other molecules. Albumin has a complex structure, which is responsible for a variety of biological functions. In disease, the albumin molecule is susceptible to modifications that may alter its biological activity. During the last decades, different methods to measure albumin function have been developed. Recent studies have shown that not only albumin concentration but also albumin function is reduced in liver failure. This observation led to the concept of effective albumin concentration, which represents the fact that plasma albumin concentration does not reflect its function. Indeed, in liver disease albumin function is several times less than its concentration. In patients with cirrhosis, albumin infusion reduces mortality in patients with spontaneous bacterial peritonitis and improves outcome following large volume paracentesis. In combination with vasoconstrictors, albumin is useful in the management of patients with hepatorenal syndrome. Its role is being investigated in a large number of indications, which rely on its volume and nonvolume expansion functions such as stroke, severe sepsis, Alzheimer's disease, malaria, burns, and ovarian hyperstimulation syndrome. This talk explores the above concepts, reviews the available evidence for the use of albumin in liver diseases, defines therapeutic limitations, and explores the challenges that should be addressed in future research. Better understanding of the effects of albumin will define whether the use of albumin should be more generalised.

## May new DAAs avoid LT in listed HCV patients with decompensated cirrhosis

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Sustained Virologic Response (SVR) is associated with a favorable outcome in patients with chronic hepatitis C with or without cirrhosis, notably, if regression/stabilization of cirrhosis, which has been described in this setting, occurs. In addition, among the cirrhotic population, SVR is associated with a decreased risk of hepatic decompensation and hepatocellular carcinoma development and an increase in overall survival and liver-transplantation free survival (1-4). Finally, extrahepatic outcomes including health related quality of life, risk of diabetes, risk of cardiovascular diseases (5) and control of HIV replication by antiretroviral therapy are additional benefits of permanent HCV eradication. In patients with decompensated cirrhosis though, the clinical benefit of SVR is less clear and identifying the point of no-return where viral eradication is not followed by clinical improvement is extremely relevant, particularly for patients in the waiting list for liver transplantation. In this review, we will address if delisting is feasible in patients with decompensated cirrhosis with SVR using direct antiviral agents.

**Key Words:** Hepatitis C Virus, Sustained Virologic Response, decompensated cirrhosis, liver transplantation, organ allocation

### Introduction

Chronic hepatitis C virus (HCV) is one of the most common causes of end-stage liver disease and cancer in the world, and the leading cause of liver transplantation (LT) in most centers. While the primary goal of treatment is to achieve the cure of the infection or sustained viral response (SVR), the ultimate aim is to stop/reverse fibrosis progression, to prevent/reverse cirrhosis, prevent liver decompensation and hepatocellular carcinoma (HCC) and reduce need of LT and liver related mortality [1-4].

In the past few years, treatment has evolved from interferon (IFN)-based therapies to IFN-free combination of DAAs. All oral, IFN-free DAAs regimens are able to eradicate HCV in more than 90% patients depending on patient's characteristics. The best results close to 100% are achieved in naïve non-

cirrhotic patients while the worse have been described in the setting of hepatic decompensation.

Data based on IFN-based regimes have shown that viral eradication is associated with regression of fibrosis, possible reversibility of cirrhosis and a significant improvement in clinical outcomes and survival, with decreased incidence, although not complete elimination of complications [1-4]. However, in the era of IFN-based treatments, decompensated patients could hardly be treated.

**Treatment of patients with decompensated liver disease.**

The aims to treating HCV in list-waited patients are two-fold. First, to allow LT to be performed in a "virus-free environment", thus reducing the risk of graft reinfection. With newer oral antivirals, this is a strategy potentially applicable to all transplant candidates. Studies have shown that prevention of reinfection occurs in all patients who have achieved a SVR before transplantation, and in most of those who undergo transplantation with serum undetectability of HCV RNA. In the latter, undetectability of HCV RNA for more than one month is highly predictive of lack of HCV recurrence [6].

The second aim of antiviral therapy is to improve liver function, and in doing so, to delay or even obviate the need for LT, a situation already described in patients with decompensated hepatitis B virus infection (HBV) cirrhosis [7]. Studies performed with new oral antivirals have shown a clear decrease in MELD and Child scores [8-13] but whether these reductions lead to sufficient clinical improvement to delist the patient from the waiting list is still a matter of debate. In fact, certain centers have described a situation termed "the meld purgatory" where patients remain "eternally" in the waiting list as their MELD status improves and hence they loose priorities for LT in a MELD-based allocation system. The effect of viral eradication in patients with decompensated cirrhosis is likely heterogeneous, since this stage of disease includes a wide range of situations, ranging from patients with relatively well preserved liver function (for example patients with mild ascites) to patients with severely impaired liver function and a short life expectancy. It is likely that the in latter group, SVR might not significantly change patient's clinical outcomes or survival.

**Studies showing treatment outcomes with new DAAS in patients with decompensated cirrhosis**

In one of the first studies where decompensated patients were treated with all oral base therapy, 50 patients with HCV-cirrhosis and portal hypertension (hepatic venous gradient-HVPG- of > 6mmHg, presence of esophageal/gastric varices without bleeding for at least 6 months) were included randomized to receive SOF plus RBV for 48 weeks while the remainder were used as controls-observation group. [8] After 6 months of follow up, patients in the observation group crossed over to receive the same treatment. Most patients had undetectable HCV RNA by week 4; interestingly though, response was faster among those with compensated disease compared to those with decompensated disease. Platelet counts, albumin and bilirubin levels improved in the SOF arm, while slightly worsening in the untreated arm. A majority of treated Class B patients had a decline in their MELD scores. In addition, a decrease in the number of clinical decompensation events was observed in the treated group. No patient had worsening or new onset hepatic decompensation in the treatment group. Paired HVPG measurements were available in 37 patients. Reductions in HVPG ≥10% were observed in 38% of patients with paired measurements; 24% of patients had ≥20% HVPG reduction. The only significant factor associated with an HVPG decrease ≥20% was baseline MELD score <10. Interestingly, improvements in MELD score and liver function were seen in patients on treatment irrespective of change in HVPG. Whether the effect of SVR12 and viral suppression on HVPG may manifest later is being explored.

Another study analyzed the combination of Ledipasvir-LDV/SOF + RBV in 108 genotype 1 or 4 treatment-naïve or experienced patients with decompensated cirrhosis (CPT class B or C) (9). They were randomized to 12 vs 24 weeks of LDV/SOF + RBV. Patients were stratified by CPT score B (n=55) or C (n=53). 28 patients (26%) had a MELD score > 15 but none > 20. At baseline 96% of CPT class C patients had ascites and 88-91% encephalopathy. LDV/SOF + RBV resulted in high SVR12 rate in this population (87-90%) with 12 weeks results similar to those achieved in the 24 week arm. Clinical improvement, documented by an improvement in MELD score as well as an increase in serum albumin, was observed in SVR patients. Thus, Child-Pugh C patients may clinically benefit from viral eradication. Nonetheless, further CPT increase was observed in 4 patients and MELD increased in 12 (6 with initial CPT class B, 6 CPT class C) and in 4 patients (3 CPT class B and 1 CPT class C) of those treated for 12 and 24 weeks, respectively, suggesting that there is a point of no return for clinical improvement despite viral eradication.

The results of a very similar trial were recently presented in the EASL 2015 meeting (11). Sof/LDV plus daily RBV for 12 or 24 weeks was administered to patients with HCV GT1 or 4 decompensated cirrhosis and/or in those with recurrent HCV post-transplantation. Main inclusion criteria were CLcr ≥ 40 mL/min, platelets >30,000 x 103/μL, while patients with CPT score > 12 were excluded. 329 patients were randomized 1:1 to 12 or 24 weeks of treatment in 34 sites in 12 countries: 168 were post-transplant patients with F0-F3 fibrosis or CPT A cirrhosis and 160 had decompensated cirrhosis with CPT B or C (53 post-transplant). About

one-quarter of decompensated patients had a MELD score greater than 15. SVR12 rates of 85% and 88% were achieved in the 12 & 24 weeks of treatment, respectively. Participants with CPT B responded better than those with CPT C, and within the CPT C group, pre-transplant patients did better than post-transplant patients. In genotype 1, pre-transplant CPT B and C patients had an SVR12 of 87% and 98% (12 & 24 wks) and 85% and 72% (12 &24 wks), respectively. Again, SVR was associated with improved liver function: 35% of those initially classified as class B reverted to class A, while 48% of those classified as class C reverted to class B and 5% to class A.

In another study, 60 patients with advanced cirrhosis (Meld 8-40) were treated with SOF + DCV + RBV (12 CPT A, 32 CPT B, 16 CPT C) (12). As with prior studies SVR results were significantly better for Child A and B patients (around 90-95%) diminishing to 56% in Child C. In particular, SVR rates were lower in patients with albumin levels < 2.5 g/dl, in those with bilirubin levels > 3 mg/dl and in those with ascites or encephalopathy. Improvements of MELD score were seen in all CPT groups, particularly in those achieving SVR.

A real-world study describing results of combination therapies in patients with decompensated liver disease has shed some light in the issue of clinical improvement (13). In that study, 467 patients (GT 1 [n=235]; GT 3 [n=189]) with advanced disease and CTP score ≥7 (66% CPT B, 10% CPT C, mean MELD score of 12, range 6-36 ) were treated with 12 weeks combination of SOF + LDV or daclatasvir (DCV) ± RBV. A significant proportion of these very sick patients (71-80%) achieved a SVR. 42% of patients showed improvement (MELD >2) in liver function while 48% showed no significant change. Reduced albumin levels were associated with lack of clinical benefit.

While the number of patients who might be inactivated and further delisted is still under study, there is already one report of a 67 yr woman with advanced cirrhosis (Meld 16, Child C12) achieving significant biochemical and clinical improvement (CTP and MELD scores decreased to A6 and 12, respectively) and hence being able to be delisted for the WL for LT (14)

## Conclusions

In summary, most trials with IFN-based regimens excluded patients with decompensated cirrhosis. With new, well tolerated oral agents, sicker patients are being treated and the questions that remain are whether decompensated patients may become re-compensated, whether LT may be avoided, and in how many, and whether there is a point of no-return where no clinical benefit is achieved despite viral eradication. Patients with decompensated cirrhosis have short-term weak improvements in MELD scores but whether these will persist or increase in the long term and whether MELD modifications will result in a status of clinical compensation without the subsequent need for LT is still unknown. Identifying the point of no-return where viral eradication is not followed by clinical improvement is extremely relevant so that treatment is postponed post-transplantation in these patients.

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# Is Acute-On-Chronic-Liver Failure (ACLF) a motif to prioritize or temporary contra indicate patients in list for LT?

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### Acute decompensation of liver diseases and ACLF

The evolution of chronic liver diseases involves frequently a long-standing phase of compensated cirrhosis. In about 60% a specific complication occurs within 10 years of diagnosis. Once the patient progress to the decompensated phase, survival is markedly reduced. Acute decompensation is a heterogeneous entity with different clinical presentations and variable prognosis.

ACLF is characterized by the abrupt onset of organ failure in patients hospitalized for an acute decompensation of liver disease. It seems to be very frequent ( 30.9% in the seminal paper, 79. Moreau, 2013) It is associated with high short term mortality (3-month mortality of patients with ACLF was 51%, 79. Moreau, 2013). ACLF is considered a reversible component of acute deterioration with potential to recover to the state the patient was in prior to the acute event.

Renal failure is present in most cases of ACLF. For example ACLF grade 1 encompasses patients with kidney failure defined by a creatinine > 2 mg/dL or patients a failure of an organ other than the kidney when it is associated with a creatinine from 1.5 to 1.9 mg/dL (6. Moreau, 2013).

### Renal failure and the course after liver transplantation

- Impaired pre transplantation renal function: a poor prognostic indicator for survival after transplantation.

Relevant data on the impact of renal compromise in survival after liver transplantation were analysed by Nair et al (19 261 patients from UNOS database). 12 778 (67%) had normal eCrCl ( ≥ 70 ml.min). 6 483 (33%) had varying severity of renal impairment. Renal impairment was mild in 4419 (22%; mean 56 sd 8.5 ml.min); moderate in 1560 (8%; mean 30 sd 5.7 ,l.min); severe in 504 (3% mean 14 sd 3.6 ml.min).

Mortality within 30 days of transplant occurred in 5.2% of patients with normal renal function and in 7.3% of patients with mild compromise. It involved 14% of patients with moderate compromise and 17.3% of patients with severe compromise.

Patients with renal insufficiency (mild, moderate, severe) had a lower long-term survival rate when compared with patients with normal renal function. The survival of patients with moderate and severe renal insufficiency was similar but significantly lower when compared with patients with mild renal insufficiency (8. Nair, 2002 ).

- Renal insufficiency and the evolution after transplantation

The vast majority of patients with pre transplant renal insufficiency do not develop advanced chronic kidney diseases after liver transplantation even in the setting of calcineurin inhibitor based suppression. Only 13% of patients with significant renal dysfunction prior to transplant reached a GFR of < 20 ml.min at 36 week median follow up post transplant.

Severe renal dysfunction was particularly uncommon among patients whose pre transplant serum creatinine was elevated for less than 12 weeks: only 2 (5%) patients reached this end point. Among patients with kidney dysfunction for more than 12 weeks prior to transplantation, pretransplant serum creatinine > 2 mg/dL and the presence of diabetes are significant predictors of poor transplant renal outcomes (eGFR < 20 ml.min within 3 years after transplant). These patients qualify for combined liver kidney transplantation (1.Bahirwani, 2008).

- Patients in renal replacement therapy (RRT) by liver transplantation

Northup et al demonstrated that even cirrhotic patients in RRT recover renal function after transplant. They studied 1041 liver transplant recipients in RRT at the time of transplantation. 707 (67.9%) had spontaneous recovery of renal function. Of the 334 that did not recovered 26 eventually underwent renal transplantation.

Duration of RRT was the strongest independent predictor of spontaneous recovery. Recipients on pre transplant RRT for more than 90 days had an adjusted OR of 0.06 for spontaneous recovery (only a 11.5% chance of recovery). Other statistically significant pre transplant variables independently associated with recovery of renal function were recipient age (OR 0.98 per year); recipient pre transplant diabetes mellitus (OR 0.54); donor age (OR 0.98 per year).

It is suggested that the 90-day RRT duration could be used as guideline to combined liver kidney transplant (7. Northup, 2010)

**Combined liver kidney transplantation versus liver transplantation alone**

- Consensus Conference

Some patients need a liver transplantation alone but some patients need a simultaneous liver-kidney (SLK) transplantation. A consensus conference has been convened to devise guidelines for SLK transplantation. The conference recommended SLK for patients with a) ESRD (meant long term dialysis) with cirrhosis b) acute kidney injury with creatinine ≥ 2 mg/dL and dialysis for more than 8 weeks c) end-stage liver disease and chronic kidney disease with a kidney biopsy showing > 30% glomeruloesclerosis or 30% fibrosis; d) end stage liver disease and GFR < 30 ml.min for more than 12 weeks (2.Eason, 2008).

- Supporting the recommendations

Selecting liver transplant candidates who are not on dialysis but have evidence of CKD (recommendations c and d) remains difficult. The recommendations do not address the common scenario of renal function that fluctuates above and below 30 the ml.min cut point.

Ruebner et al studied a cohort comprising 4997 liver recipients. Group 1 comprised 3005 recipients with GFR always > 30 ml.min. Group 2 comprised 1455 recipients with GFR fluctuating above and below 30. Group 3 comprised 156 recipients with GFR always < 30 ml.min.

276 subjects (6%) underwent SLK transplantation. The percentage was 1% in group 1 (30 patients); 7% in group 2 (98 patients); 45% (45 patients) in group 3.

Focusing on LTA recipients the rate of death by 3 years were 21%, group 1; 25% group 2; 37%, group 3;. Compared to group 1, the HR associated with death for group 2 was 1.36 (CI 1.15 to 1.60); for group 3 was 1.35 ( 0.80 to 2.28, ns).

Focusing on LTA recipients the rate of ESRD by 3 years were 5%, group 1; 6% group 2; 31%, group 3. Lower pre transplant GFR was strongly associated with a significant increased risk of ESRD ( HR 7.23 for group 3 vs group 1; HR 1.66 for group 2 vs group 1). Diabetes (HR 2.65), black race ( HR 1,63) and male gender ( HR 1.51) were also independently associated with reaching ESRD after liver transplant.

Severity and duration of pre transplant renal dysfunction were strongly associated with an increased risk of post transplant ESRD. The risk was most pronounced in recipients with sustained GFR < 30 for the 90 days before transplantation. These findings validate the recommend-dation to consider SLK for this group.

The post-transplant mortality rate far outstrips the rate of ESRD for patients in group 1 ( by 3 years, ESRD: 5%; death 21%) and most patients in group 2 ( by 3 years, ESRD: 31% but quite heterogeneous; death 37%). The overriding goal in managing these patients on the waiting list shoul be to obtain the optimal liver to minimize mortality risk (10. Ruebner, 2012).

**LTA or combined liver kidney transplant (CLKT) in cirrhotic patients with renal failure.**

Using the UNOS database, this study was undertaken to compare outcomes of cirrhotic patients with renal failure who received either a liver transplant alone (LTA) or combined liver kidney transplant.

4275 cirrhotic patients with renal failure (serum creatinine of 2.5 mg% or higher) underwent OLT. LTA was performed in 2774 patients; 1501 patients underwent CLKT. The 1501 patients were grouped according to the cause of renal failure: HRS, 369 cases; known cause other than HRS, 839 patients; unknown cause 393 patients.

Overall patient survival rates of LTA patients ( one, three and five years: 79.5%; 69.5%; 62.9%) were significantly lower than those of CLHT ( one, three and five years: 84.5%; 74.8%; 67.4%). Liver allograft and patient's survival were superior in CLKT patients compared with LTA patients irrespective of dialysis status before transplantation.

There was a significant proportion of patients with renal dysfunction (defined as serum creatinine > 2.5 mg%) after transplantation among those patients who received LTA compared with patients who underwent CLKT at 6 months through 3 years after transplantation (4. Fong, 2012 )

**Liver transplantation in ACLF patients**

- Published results

Finkenstedt et al studied 144 patients fulfilling the criteria for ACLF. 26 patients (18%) were already on the wait list at the time of decompensation. 68 patients (47%) were evaluated for LT when the acute decompensation arrived; 50 cases were not evaluated.

From the 68 patients evaluated for LT 45 were listed. Reasons for not listing the other 23: psychiatric complications (6); uncontrolled sepsis (6); death during evaluation (5); cardiopulmonary contraindications (2); improved liver function (2); patient refusal (1); neurological contraindication (1).

In this cohort less than half of the patients (71 cases out of 144) could be listed for LT. Only 33 patients underwent LT. The majority (28) underwent transplantation during their first hospitalization after a median waiting time of 24 (5 a 115) days. 5 patients were transplanted between 130 and 320 days after inclusion. It means that more than 50% of the listed

ACLF patients died on the waiting list, whereas only 16% of the patients listed for other indications did.

28 (85%) of the 33 transplant patients were alive after a mean follow up period of 20 months. Comparing the outcome of theses patients after LT with the outcomes of a cohort of 356 patients transplanted during the same study period for other indications, it can be seen that the overall mortality rates did not differ between the two groups ( 15% for ACLF Pts, 16% for the controls, 3. Finkenstedt, 2013)

- The CANONIC study again

Patients with ACLF who do not improve with supportive measures are potential candidates for liver transplantation but in spite of the very high short term mortality the possibility of LT has rarely been addressed for these patients. These patients are at high risk for acquiring bacterial and fungal infections or developing sepsis, which may preclude them from transplantation. Clinical deterioration can evolve rapidly. The time period for evaluating and assessing them for LT is short. In fact the data from the CANONIC study show that at 90 days only 38 (13.8%) out of 275 ACLF patients underwent liver transplantation. One year after enrolment 53 (20%) had been transplanted (5. Jalan, 2014).

- The SOFT score

The selection of a candidate for liver transplantation depends on the probability of dying without transplantation but also on the probability of surviving after the procedure. MELD proved to be a useful tool for selecting the cirrhotic patients on the basis of anticipated survival without the replacement of the liver. In the context of ACLF, MELD should be replaced by the prognostic formula designed by the CLIF-Consortium.

It is clear that recipient factors alone are not predictive of survival following liver transplantation. Rana e al developed the Survival Outcomes following Liver Transplantation (SOFT) score to predict recipient post transplant survival at 3 months. SOFT score combines the recipient wait list score in addition to certain donor factors. Using SOFT score the 3-month survival of recipients with less than 5 points is 97%; 6-15 points was 94%; 16 to 35 points was 84%; 36 to 40 points 62%; more than 40 points, 38% (9. Rana,2008). These observations support the concept of futility in liver. The CLIF Consortium has not yet produced any relevant observation in this context.

**Conclusions**

Acute-on-chronic-liver failure is associated with a dismal prognosis. A liver transplantation would be required to improve the prognosis of these patients. Some cases need a combined liver-kidney transplant.

The clinical condition of most patients precludes the possibility of liver transplantation. Guidelines to define the futility in this context are urgently needed.

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