Acute-on-Chronic Liver Failure: Recent Concepts

Richard Moreau[*,†,‡,§,‖], Rajiv Jalan[‖,¶], Vicente Arroyo[‖,#]

*Inserm, U1149, Centre de Recherche sur l'Inflammation (CRI), Clichy and Paris[†]UMRS1149, Université Paris Diderot-Paris 7, Paris[‡]Département Hospitalo-Universitaire (DHU) UNITY, Service d'Hépatologie, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy[§]Laboratoire d'Excellence Inflamex, PRES Sorbonne Paris Cité, Paris, France[‖]EASL–CLIF Consortium, Hospital Clinic, Centro de Investigacion Biomedica en Red Enfermedades Hepaticas y Digestivas (CIBERehd), Barcelona, Spain[¶]Institute for Liver and Digestive Health, Royal Free Hospital, London, United Kingdom and[#]Liver Unit, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERehd, Barcelona, Spain

A proportion of patients hospitalized for an acute complication of cirrhosis are at high risk of short-term death. The term Acute-on-Chronic Liver Failure (ACLF) is used to characterize these patients. Until recently there was no evidence-based definition of ACLF. In 2013 a definition has been proposed based on results of a large prospective observational European study, called "European Association for the Study of the Liver (EASL)–Chronic Liver Failure (CLIF) Consortium Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC)" study. Results of this study led to elaborate new concepts about ACLF. First, it was found that ACLF is a syndrome that is distinct from mere decompensated cirrhosis. It was also shown that ACLF is a dynamic syndrome which can improve or conversely worsen. Patients who worsen die rapidly from multiorgan failures. The CANONIC study also found that identifiable precipitating events (e.g., bacterial infection, active alcoholism) are found in only 50% of cases of ACLF indicating that these events are dispensable for defining ACLF. In addition precipitating events may be initiators of ACLF but do not drive the outcome. An important concept derived from the CANONIC study is that ACLF is associated with systemic inflammation even in patients who do not have identifiable precipitating events. Finally it was found that ACLF may develop in patients without prior episodes of decompensation or in those with recent decompensation (<3 months). Moreover these patients with "early" ACLF were more severe than patients who developed ACLF after a long of history of decompensated cirrhosis. (J Clin Exp Hepatol 2014;5:81–85)

A proportion of patients admitted to the hospital for an acute complication of cirrhosis may rapidly die within one month. The term Acute-on-Chronic Liver Failure (ACLF) is universally used to characterize these patients.[1–3] However, until recently (see below) there were only definitions of ACLF based on expert opinions and remarkably definitions differed according of the origin of experts (Eastern vs. Western countries). In Asia, the following definition has been suggested: acute hepatic insult manifesting as jaundice (serum bilirubin level ≥5 mg/dL) and coagulopathy (international normalized ratio ≥1.5), complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease.[4] This definition is based on the dogma that liver failure is the primary and driving event of severity in patients with ACLF. The Asian definition has been already operative as it was used to enroll patients with direct liver injury (reactivation of hepatitis B[5,6] or severe alcoholic hepatitis[6]) in randomized interventional trials. In Europe and the United States of America experts proposed to define ACLF as an acute deterioration of liver function in patients with cirrhosis which is usually associated with a precipitating event and results in the failure of one or more organs and high short-term mortality.[1,2] There is now an evidence-based definition of ACLF; indeed results of a large prospective observational European study called "European Association for the Study of the Liver (EASL)–Chronic Liver Failure (CLIF) Consortium Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC)" study have been published in 2013 establishing diagnostic criteria for ACLF in 1343 hospitalized patients who had an acute decompensation (AD) of cirrhosis.[7] AD was defined as an acute development of large ascites, hepatic encephalopathy, gastrointestinal hemorrhage or bacterial infections, or any combination of these.[7] The study was performed under the umbrella of the EASL–CLIF Consortium and involved 29 Liver Units from 8 European countries which enrolled patients between February and

Keywords: organ failures, inflammation, cirrhosis
Received: 10.7.2014; *Accepted:* 7.9.2014; *Available online* 3.10.2014
Address for correspondence: Richard Moreau, Inserm, U1149, Centre de Recherche sur l'Inflammation (CRI), Faculté de Médecine Site Bichat, 16 Rue Henri Huchard, F-75890 Paris Cedex 18, France.
E-mail: richard.moreau@inserm.fr
Abbreviations: ACLF: acute-on-chronic liver failure; AD: acute decompensation; CANONIC: Consortium Acute-on-Chronic Liver Failure in Cirrhosis; CLIF: chronic liver failure; CRP: C-reactive protein; EASL: European Association for the Study of the Liver; INR: international normalized ratio; SOFA: sequential organ failure assessment; SBP: spontaneous bacterial peritonitis
http://dx.doi.org/10.1016/j.jceh.2014.09.003

September 2011. Here we will review the new concepts regarding ACLF that have been generated by the design and the results of the CANONIC study.

ASSESSMENT OF ORGAN FAILURES IN CIRRHOSIS REQUIRES SPECIFIC TOOLS

The Sequential Organ Failure Assessment (SOFA) scale which is widely used to diagnose organ failures in general intensive care units[8] has also been used for this purpose in patients with cirrhosis admitted to the ICU.[8–11] In these patients, the SOFA score was a better predictor of short-term prognosis than liver-specific scores (i.e., Child-Pugh score and MELD score).[9–11] However, components of the SOFA scale do not take into account some specific pathophysiological and clinical features of cirrhosis. This gave rise to the concept that the diagnosis of organ failures should be assessed by using tools specifically designed for patients with cirrhosis irrespective of their site of admission (ICU, ward). Thus the Committee in charge of the design of the CANONIC study decided to modify the SOFA scale and established a new scale called CLIF–SOFA that was subsequently used by all investigators of the study. Like the original scale,[8] the CLIF–SOFA scale assessed the function of six organ-systems (liver, kidneys, brain, coagulation, circulation, and lungs) but also took into account some specificities of cirrhosis.[7] Each organ-system received a subscore ranging from zero (normal) to four (most abnormal). A total CLIF–SOFA score ranging from zero to twenty-four was calculated; the total score assesses the overall severity. All variables included in the CLIF–SOFA scale were variables easy to obtain in every hospital. The definitions for organ failures based on the CLIF–SOFA scale were the following. Liver failure was defined by serum bilirubin levels of 12.0 mg/dL or more. Kidney failure was defined by serum creatinine levels of 2.0 mg/dL or more, or the use of renal-replacement therapy. Cerebral failure was defined by grade III or IV hepatic encephalopathy; unlike the original SOFA scale which used the coma Glasgow score, the CLIF–SOFA scale used the West Haven classification.[7] Coagulation failure was defined by an International Normalized Ratio (INR) of more than 2.5 and/or platelet count of 20×10^9/L or less. Platelet count was present in the original SOFA scale and was kept in the modified CLIF–SOFA scale because low platelet count is a surrogate marker for severity of cirrhosis in terms of portal hypertension and presence of disseminated intravascular coagulation. The original SOFA scale did not include the INR.[8] Circulatory failure was defined by the use of catecholamines, or terlipressin to maintain arterial pressure; the study protocol recommended using catecholamines to maintain systolic arterial pressure ≥90 mm Hg. The use of terlipressin, which is very specific for patients with cirrhosis, was not taken into account by the original SOFA scale.[8] Respiratory failure was defined by a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (FiO_2) of 200 or less or a pulse oximetric saturation (SpO_2) to FiO_2 ratio of 200 or less. The SpO_2 to FiO_2 ratio was not used in the original SOFA scale.

ACUTE-ON-CHRONIC LIVER FAILURE IS DISTINCT FROM MERE DECOMPENSATED CIRRHOSIS

Once results of the CANONIC study were prospectively collected, a first analysis was performed to obtain a definition of ACLF and ACLF grades. This analysis was done by examining the relationship between phenotypes measured at enrollment and short-term (28-day) transplant-free mortality. Of note it was prespecified in the study protocol that patients with ACLF should have a 28-day transplant-free mortality of at least 15%. The results of the CANONIC showed that ACLF is a new syndrome which is distinct from mere decompensated cirrhosis.[7]

The first group was composed of the majority of patients (77.5%); these did not have ACLF but had "mere" decompensated cirrhosis and were divided into three subgroups: 1) patients with no organ failure; 2) patients with a single "non-kidney" organ failure (i.e., single failure of the liver, coagulation, circulation or respiration) who had serum creatinine <1.5 mg/dL and no hepatic encephalopathy; and 3) patients with single cerebral failure who had serum creatinine <1.5 mg/dL. The 28-day mortality rate in this group was far below the threshold of 15% (i.e., 4.7%).

The second group included 11% of enrolled patients and was called ACLF grade 1. This group was divided into three subgroups: 1) patients with single kidney failure; 2) patients with single failure of the liver, coagulation, circulation or respiration, who had serum creatinine ranging from 1.5 to 1.9 mg/dL or mild-to-moderate hepatic encephalopathy or both; and 3) patients with single cerebral failure who had serum creatinine ranging from 1.5 to 1.9 mg/dL. The 28-day mortality rate in this group was very significant (22.1%).

The third group included 8% of enrolled patients and was called ACLF grade 2. This group included patients with two organ failures and was associated with high 28-day mortality (32%).

The last group included 3.5% of enrolled patients and was called ACLF grade 3. This group included patients with three organ failures or more and was associated with very high 28-day mortality (76.7%).

ACUTE-ON-CHRONIC LIVER FAILURE IS A DYNAMIC SYNDROME

In the CANONIC study, ACLF was present in 23% of patients on admission or developed in 11% of patients who did not have ACLF on admission.[7] Another lesson from this study was that multiorgan failure (i.e., ACLF grade

3) was the common final pathway leading to death. Thus ACLF does not seem to be a "fixed" syndrome. This hypothesis is also supported by the following findings of the CANONIC study.[12] First, the finding that patients without any organ failure on admission had a 28-day mortality of ~5% (see above) and not 0% is explained by the fact that some of these patients subsequently developed ACLF which progressed to ACLF grade 3 and death. Conversely, patients who did not have ACLF on admission and remained free of this syndrome during the following 28 days had a very low short-term mortality (1.9%). Second, 50% of patients with ACLF grade 1 at diagnosis improved and survived while one-third worsened to ACLF grade 3 and died. A large number of patients with ACLF grade 3 at diagnosis acquired new organ failures and died. However 16% of patients with ACLF grade 3 at diagnosis improved and reached a "no ACLF" status.

IDENTIFIABLE PRECIPITATING EVENTS ARE DISPENSABLE FOR DEFINING ACUTE-ON-CHRONIC LIVER FAILURE

Experts from Western countries suggested to include precipitating events in the definition of ACLF.[1] A major end point of the CANONIC study was to assess the prevalence of precipitating factors that have been long known to trigger AD. Bacterial infection was significantly more common in patients with ACLF than in those without.[7] Infections most commonly associated with ACLF were spontaneous bacterial peritonitis (SBP) and pneumonia.[7] The process of bacterial infection resulting in organ failure(s) is called severe sepsis or septic shock.[13] Of note bacterial infection was present as a precipitating event in only 33% of patients with ACLF (vs. 22% in patients without ACLF) indicating that ACLF cannot be reduced to severe sepsis.

In the CANONIC study another precipitating event of ACLF was active alcoholism during the last 3 months.[7] It was present in ~25% of patients with ACLF (vs. 15% in patients without ACLF). In the subgroup of active drinkers with ACLF there was evidence of severe alcoholic hepatitis.[7] Interestingly in patients with ACLF the prevalence of alcoholic cirrhosis was much higher (60%) than the prevalence of active alcoholism. Together these findings suggest that severe alcoholic hepatitis accounts for only part of cases of ACLF in patients with alcoholic cirrhosis.

There was a small proportion (8%) of patients in whom ACLF was related to other precipitating events such as TIPS insertion, acute toxic or viral hepatitis superimposed to cirrhosis, major surgery or large volume paracentesis without intravenous albumin administration.[7]

As a trigger, gastrointestinal hemorrhage tended to be less frequent in patients with ACLF than in those without (13% vs. 17%). This apparent paradox may be related to the significant improvement of the management of gastrointestinal hemorrhage in patients with cirrhosis.[14]

These results indicate that in a significant proportion of cases ACLF developed in the absence of any identifiable trigger. The proportion of ACLF of unknown origin admitted to the hospital was 45%.[7] Together these findings indicate that the existence of precipitating events is dispensable for defining ACLF.

PRECIPITATING EVENTS MAY INITIATE ACUTE-ON-CHRONIC LIVER FAILURE BUT DO NOT DRIVE ITS OUTCOME

The CANONIC study revealed that among patients with ACLF, mortality was similar in the presence or absence of precipitating events (Table 1).[7] These events were triggers for a proportion of cases of ACLF but once ACLF had developed the prognosis relied on other factors independent of the precipitating events.

ACUTE-ON-CHRONIC LIVER FAILURE IS ASSOCIATED WITH SYSTEMIC INFLAMMATION

In the CANONIC study white-cell count and plasma C-reactive protein (CRP) levels were higher in patients with ACLF than in those without (Table 2)[7] indicating that ACLF is associated with systemic inflammation. Furthermore, the higher the grade of ACLF the higher white-cell count and CRP levels suggesting that the number of failing organs is closely related to the intensity of inflammation. The higher prevalence of SBP and pneumonia in the

Table 1 Twenty-eight-day Mortality Rate in Patients with ACLF According to the Presence or Absence of Precipitating Events at Enrollment in the CANONIC Study.[d]

Characteristics	Patients with the characteristic (%)	Patients without the characteristic (%)	*P* value
One or more precipitating events[a]	34.0	34.2	0.97
More than one precipitating event[a]	36.8	33.6	0.70
Active alcoholism within the 3 months before hospital admission[b]	31.3	34.7	0.62
Bacterial infection at enrollment	36.7	33.0	0.54
Other precipitating events at enrollment[c]	40.0	33.6	0.52

[a]Excluding gastrointestinal hemorrhage.
[b]Active alcoholism was defined as more than 14 drinks per week in women and more than 21 drinks per week in men.
[c]Other precipitating events included therapeutic paracentesis without use of intravenous albumin, transjugular intrahepatic portosystemic shunting, major surgery, acute hepatitis, and alcoholic hepatitis.
[d]Adapted from Ref. 7.

Table 2 Leukocyte Count and Plasma C-reactive Protein Level at Enrollment and After Enrollment in the CANONIC Study from All Patients and the Specific Group of Patients Without Bacterial Infection.[e]

	No ACLF	ACLF (all grades)	*P* value
At enrollment (all patients)[a]			
Leukocyte count ($\times 10^9$/L)	6.8 ± 4.1	10.1 ± 0.4	<0.01
C-reactive protein (mg/L)	25.4 ± 31.9	39.4 ± 42.7	<0.01
At enrollment (patients without bacterial infection)[b]			
Leukocyte count ($\times 10^9$/L)	6.6 ± 3.8	9.4 ± 5.3	<0.01
C-reactive protein (mg/L)	20.9 ± 24.5	33.4 ± 38.5	<0.01
After enrollment (all patients)[c]			
Leukocyte count ($\times 10^9$/L)	5.9 ± 4.0	9.3 ± 5.7	<0.01
C-reactive protein (mg/L)	18.1 ± 17.7	36.2 ± 35.9	<0.01
After enrollment (patients without bacterial infection)[d]			
Leukocyte count ($\times 10^9$/L)	6.0 ± 3.9	9.0 ± 5.4	<0.01
C-reactive protein (mg/L)	16.2 ± 14.6	34.4 ± 37.7	<0.01

[a]Leukocyte count and plasma C-reactive protein levels were measured in 1037 and 762 patients without ACLF and in 302 and 249 patients with ACLF, respectively.
[b]Leukocyte count and plasma C-reactive protein level were measured in 759 and 550 patients without ACLF and in 176 and 142 patients with ACLF, respectively.
[c]Leukocyte count and plasma C-reactive protein level were measured in 216 and 183 patients without ACLF and in 112 and 85 patients with ACLF, respectively.
[d]Leukocyte count and plasma C-reactive protein level were measured in 158 and 130 patients without ACLF and in 82 and 64 patients with ACLF, respectively.
[e]Adapted from Ref. 7. Data are means ± SD.

ACLF group may explain this feature.[7] Indeed, it has been shown that a proportion of patients with cirrhosis and bacterial infection (in particular SBP) has an excessive systemic pro-inflammatory response, develop acute kidney injury and have a poor outcome.[15] However, the higher white-cell count and CRP levels were also observed in the subgroup of patients with ACLF unrelated to bacterial infection (Table 2).[7] Of note in patients with ACLF, higher white-cell count is an independent predictor of 28-day transplant-free mortality.[7] These findings are consistent with previous results showing that prognosis of kidney failure is worse in patients with systemic inflammatory response than in those without.[16]

ACUTE-ON-CHRONIC LIVER FAILURE IS NOT SPECIFIC FOR PATIENTS WITH PRIOR EPISODES OF DECOMPENSATION

The common sense would expect that most cases of ACLF are final events in a long-lasting history of decompensated cirrhosis. This expectation was not confirmed by the CANONIC study since it revealed that almost half of patients with ACLF did not have prior history of decompensation or has developed ACLF within few weeks (less than 3 months) after the first episode of decompensation.[7] Moreover, in the ACLF group, patients with no history of decompensated cirrhosis developed a more severe form of ACLF, higher levels of systemic inflammation and higher mortality than patients with previous episode of decompensation.[7]

ACUTE-ON-CHRONIC LIVER FAILURE SHOULD BE SOUGHT AT ENROLLMENT IN INTERVENTIONAL STUDIES

It should be emphasized that the CANONIC study showed that the prognosis of kidney failure depends on the context: mortality is ~20% in patients with isolated kidney failure and much higher when kidney failure is associated with another organ failure or more. These findings suggest that interventional studies in patients with cirrhosis and kidney failure (e.g., hepatorenal syndrome, HRS) should take into account the presence of other organ failure(s) at enrollment. This hypothesis is supported by the recent finding in patients with HRS that the CLIF–SOFA score at enrollment was the only predictor for renal response to standard medical therapy (i.e., a combination of terlipressin plus intravenous albumin): the higher the CLIF–SOFA scores the higher the risk to be renal non-responder to therapy.[17] Moreover it has long been known that survival is significantly shorter in renal non-responders than in responders to terlipressin.[18] Studies should be performed in patients with HRS to determine whether death occurs because of a lack of response to therapy or whether the non-response to therapy is due to premature death.

BEYOND THE CONSORTIUM ACUTE-ON-CHRONIC LIVER FAILURE IN CIRRHOSIS STUDY

A recently published study[19] used results obtained in the whole cohort of patients enrolled in the CANONIC study to develop a simplified organ function scoring system (called "CLIF-Consortium Organ Failure (CLIF-C OF)" score) for the diagnosis of ACLF. Then in the subgroup of patients with ACLF the CLIF-C OF score and two other independent predictors of mortality (age and white-cell count) were combined to develop a specific prognostic score for ACLF (called "CLIF-CONSORTIUM score for ACLF", CLIF-C ACLF score).[19] It was shown that CLIF-C ACLF score at ACLF diagnosis was superior to MELD and MELD-Na scores in predicting mortality suggesting that the CLIF-C ACLF sore is a clinically relevant scoring system that could be used sequentially to stratify the risk of mortality in ACLF patients. Studies are needed to evaluate the use of the CLIF-C ACLF sore for prioritization of sickest patients to liver transplantation.

There may be two categories of ACLF. First, in the setting of primary liver insult (e.g., alcohol or HBV reactivation) liver failure may be the driver of extra-hepatic organ failures. Second the liver and other organs may be victims of a common mechanism (e.g., SBP-induced sepsis). Future studies should be designed to address this hypothesis.

ACLF is associated with systemic inflammation. Thus organ failures may a consequence of an excessive response of the immune system of the host inflammation (a process called immunopathology). Interestingly, in the CANONIC cohort, patients with ACLF were younger than those without.[7] Younger age is associated with more vigorous immune responses.[20] Future studies are needed to investigate the pathophysiology of organ failures in patients with ACLF.

CONCLUSIONS

ACLF is a syndrome that is distinct from mere decompensated cirrhosis, based not only on the presence of organ failure(s) and high mortality rate but also on younger age, alcoholic etiology of cirrhosis, and higher level of systemic inflammation. ACLF may or may not be preceded by identifiable triggers and is a dynamic syndrome with various outcomes. ACLF may be particularly severe when it develops in patients without prior history of decompensated cirrhosis.

CONFLICTS OF INTEREST

RM has no relevant conflicts of interest.

RJ received research funding from Vital Therapies, has served on Scientific Advisory Board for Conatus Pharma, and received lecture fees from Gambro and has on-going research collaboration with Gambro, Grifols and is the Principal Investigator of an Industry sponsored study (Sequana Medical). He is also the inventor of a drug, L-ornithine phenylacetate which UCL has licensed to Ocera Therapeutics.

VA has received grant and research support from Grifols.

REFERENCES

1. Olson JC, Wendon JA, Kramer DJ, et al. Intensive care of the patient with cirrhosis. *Hepatology*. 2011;54:1864–1872.
2. Jalan R, Gines P, Olson JC, et al. Acute-on-chronic liver failure. *J Hepatol*. 2012;57:1336–1348.
3. Wlodzimirow KA, Eslami S, Abu-Hanna A, et al. A systematic review on prognostic indicators of acute on chronic liver failure and their predictive value for mortality. *Liver Int*. 2013;33:40–52.
4. Sarin SK, Kumar A, Almeida JA, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL). *Hepatol Int*. 2009;3:269–282.
5. Garg H, Sarin SK, Kumar M, et al. Tenofovir improves the outcome in patients with spontaneous reactivation of hepatitis B presenting as acute-on-chronic liver failure. *Hepatology*. 2011;53:774–780.
6. Garg V, Garg H, Khan A, et al. Granulocyte colony-stimulating factor mobilizes CD34(+) cells and improves survival of patients with acute-on-chronic liver failure. *Gastroenterology*. 2012;142:505–512.
7. Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology*. 2013;144:1426–1437.
8. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med*. 1996;22:707–710.
9. Wehler M, Kokoska J, Reulbach U, et al. Short-term prognosis in critically ill patients with cirrhosis assessed by prognostic scoring systems. *Hepatology*. 2001;34:255–261.
10. Das V, Boelle PY, Galbois A, et al. Cirrhotic patients in the medical intensive care unit: early prognosis and long-term survival. *Crit Care Med*. 2010;38:2108–2116.
11. Levesque E, Hoti E, Azoulay D, et al. Prospective evaluation of the prognostic scores for cirrhotic patients admitted to an intensive care unit. *J Hepatol*. 2012;56:95–102.
12. Moreau R, Arroyo V. Acute on chronic liver failure: a new clinical entity. *Clin Gastroenterol Hepatol*. 2014. in press.
13. Gustot T, Durand F, Lebrec D, Vincent JL, Moreau R. Severe sepsis in cirrhosis. *Hepatology*. 2009;50:2022–2033.
14. Garcia-Tsao G, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. *N Engl J Med*. 2010;362:823–832.
15. Navasa M, Follow A, Filella X, et al. Tumor necrosis factor and interleukin-6 in spontaneous bacterial peritonitis in cirrhosis: relationship with the development of renal impairment and mortality. *Hepatology*. 1998;27:1227–1232.
16. Thabut D, Massard J, Gangloff A, et al. Model for end-stage liver disease score and systemic inflammatory response are major prognostic factors in patients with cirrhosis and acute functional renal failure. *Hepatology*. 2007;46:1872–1882.
17. Rodríguez E, Elia C, Solà E, et al. Terlipressin and albumin for type-1 hepatorenal syndrome associated with sepsis. *J Hepatol*. 2014;60:955–961.
18. Moreau R, Durand F, Poynard T, et al. Terlipressin in patients with cirrhosis and type 1 hepatorenal syndrome. A retrospective multicenter study. *Gastroenterology*. 2002;122:923–930.
19. Jalan R, Saliba F, Pavesi M, et al. Development and validation of a prognostic score to predict mortality in patients with acute on chronic liver failure. *J Hepatol*. 2014. in press.
20. Medzhitov R, Schneider DS, Soares MP. Disease tolerance as a defense strategy. *Science*. 2012;335:936–941.