

# ACUTE-ON-CHRONIC LIVER FAILURE: APPLYING THE PIRO CONCEPT

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## ABSTRACT

Acute-on-chronic liver failure (ACLF), a clinical syndrome associated with a dismal prognosis, occurs acutely in previously stable cirrhotic patients. An important feature of this syndrome is the potential for reversibility if it is recognised early and supportive measures are instituted before multi-organ failure ensues. In response, there have been recent efforts to better define and understand the pathophysiological basis of the condition so as to aid early diagnosis and management. The PIRO concept is conceptually useful as it indicates a distinction between the insult and the response. Interventions that target inflammation may adversely impact on the ability to control the infection, and interventions that target infection may not be useful if pathophysiological process is being driven through inflammation. A classification based on the PIRO concept may allow the categorisation of patients into distinct pathophysiological and prognostic groups and allow a multidimensional definition of ACLF.

**Keywords:** Acute-on-chronic liver failure, cirrhosis, liver.

## INTRODUCTION

An early and proper diagnosis of acute-on-chronic liver failure (ACLF), together with the identification of indicators associated with disease severity, is critical for outcome prediction and therapy. Although this clinical entity is well recognised, it remains poorly defined due to the extreme heterogeneity in the mode of presentation. In order to clinically describe the group of patients referred to as ACLF, we adopted the definition that these patients would have an acute deterioration in liver function over a short period (up to four weeks), associated with a precipitating event in patients with well-compensated liver disease, characterised by organ failure.<sup>1,2</sup> The high prevalence of ACLF and mortality rates associated with it, remains an important healthcare issue as according to reported literature, short-term mortality rates vary from 46% to 89%.<sup>3</sup> In recent years, knowledge regarding the pathophysiology of ACLF has largely increased with the aim of improving the survival rates of these patients.

The pathophysiology of ACLF can be explained using the PIRO concept, which was initially developed for use in the sepsis setting.<sup>4</sup> Using this concept in ACLF, 'P' stands for *predisposition*: predisposing factors that make a cirrhotic individual more likely to develop ACLF and organ failure. 'I' represents the acute *insult or precipitating event*. 'R' stands for the *inflammatory/immune response*, which occurs as a consequence of the acute insult. 'O' signifies *organ dysfunction*, which is the final sequelae of the inflammatory response generated following the acute insult.<sup>5</sup> These could represent the four most important factors determining outcome.

## PIRO SYSTEM

### Predisposition (P)

In a large prospective study of ACLF patients conducted over six years,<sup>2</sup> it was clearly highlighted that the following factors predispose to the development of organ failure (OF) in cirrhotic patients with an acute deterioration:

- Male gender
- Higher bilirubin level
- Lower albumin level
- Higher Child-Pugh (CP) score
- Higher Model of End Stage Liver Disease (MELD) score
- Hospital admission in the preceding six months with hepatic decompensation.

Regarding factors that predict survival following the development of organ failure, the researchers found that patients who survived had the following characteristics: lower serum bilirubin, serum creatinine levels, Child-Pugh score and MELD scores, as well as a shorter prothrombin time, activated partial thromboplastin time, and higher albumin levels.

Although patients that survived following the development of organ failure had lower Child-Pugh score and MELD scores compared to the non-survivors, these scores may not accurately predict survival in ACLF. The literature suggests that once extrahepatic organ failure has developed, then organ failure scores such as the Sequential Organ Failure Assessment (SOFA)<sup>6</sup> or the Acute Physiology, Age, and Chronic Health Evaluation (APACHE)<sup>7</sup> may be more useful in predicting outcome and survival.<sup>4,8</sup>

### Precipitating Events/Acute Insult (I)

In the majority of patients, ACLF usually develops following an identifiable precipitating event. Since patients with ACLF have previously stable disease on the background of either well-compensated or decompensated disease, and thus have a variable functional mass at the time of insult, the precipitants in ACLF are widely variable.<sup>9</sup> These precipitants may directly affect the liver or may be a consequence of an extrahepatic insult (**Table 1**).

The most common precipitating event in ACLF is infection.<sup>2,9,10</sup> According to the literature, it accounts for up to 47% of all precipitating events.<sup>2</sup> In addition to bacterial infections, such as spontaneous bacterial peritonitis and urinary tract infections, viral infections are also recognised precipitants of ACLF. For example, acute hepatitis A infection superimposed in a patient with chronic hepatitis B cirrhosis is associated with a higher risk of ACLF, and thus a high mortality rate.<sup>11</sup> Cirrhotic patients who develop acute hepatitis B and E infection also have a high risk of developing ACLF, and of death.<sup>12-13</sup>

Hepatic precipitants of ACLF	Extra-hepatic precipitants of ACLF
Alcoholic Hepatitis	Infection
Acute Viral Hepatitis (A,B,E)	Variceal Haemorrhage
Drug Induced Liver Injury	Surgery
Portal Vein Trombosis	Trauma
Ischemic Hepatitis	

**Table 1. Common precipitating events in acute-on-chronic liver failure (ACLF)**

Variceal haemorrhage accounts for approximately 20% to 30% of all precipitating events. Alcoholic binge drinking is a contributory factor in between 50-70% of cases studied in the UK, but significantly lower in the patients in the CANONIC study where alcohol binge, as a precipitating event, was observed in about 20% of patients.<sup>14</sup> It is worth mentioning that in any given patient, there may be more than one insult leading to ACLF, and in a proportion of patients, there are no identifiable precipitants.

### Inflammatory Response (R)

Following the initial insult, there is an altered host response to injury, resulting in an excessive systemic inflammatory response. This induces tissue damage and subsequent organ failure. Deregulated inflammation is considered a hallmark of ACLF and the mechanism by which this arises is multifactorial.<sup>2,10</sup> A hyperdynamic circulation is a common aspect in patients with systemic inflammatory response syndrome. In fact, in these patients with enhanced cytokine production, there are severe disturbances of the cardiovascular system: the circulation becomes hyperdynamic, cardiac output increases, and both blood pressure and systemic vascular resistance decrease.<sup>15</sup>

In addition to the precipitating insult (which may be infectious or non-infectious), there is abundant evidence in the literature to suggest that cirrhotic patients have increased bacterial translocation, secondary to increased intestinal permeability and changes in intestinal microflora.

Despite the insults, ACLF patients are unable to

generate an adequate immune response due to a dysfunctional innate immune system.<sup>3,5,8</sup> Firstly, in patients with ACLF, the Kupffer cells (resident macrophages of the liver and main effectors of innate immune system) are bypassed due to the presence of multiple intra and extrahepatic shunts, leading to failure to effectively clear endotoxins. In addition, the reduced protein synthesis that occurs in cirrhosis results in defective complement production. This means that the opsonisation capacity of the Kupffer cells is reduced and thus, bacterial phagocytosis is impaired.<sup>3</sup> Another contributing factor to an altered host response in ACLF is a phenomenon known as “immune paralysis”, akin to that seen in sepsis, and associated with a high mortality. It has been demonstrated that in ACLF patients, there is reduced TNF- $\alpha$  production following stimulation with lipopolysaccharide. There is also a reduced expression of HLA-DR (an antigen-presenting receptor complex) on peripheral monocytes.<sup>16</sup>

The consequence of the immune dysfunction is that the initiating insult overwhelms the host immune system, leading to an exaggerated release of proinflammatory cytokines into the systemic circulation. This results in systematic inflammatory response syndrome (SIRS).<sup>3,8,17</sup> SIRS is defined as the clinical expression of an abnormal generalised inflammatory reaction in organs distant from the initiating insult.<sup>17</sup> It is reported that up to 42% of ACLF patients who develop organ dysfunction have evidence of SIRS despite the absence of infection in these patients.<sup>2</sup> In addition, the presence of SIRS is associated with more severe encephalopathy, an increased incidence of bacterial infection, and renal failure.<sup>18</sup> SIRS also occurs more frequently in non-survivors of ACLF compared with survivors.<sup>2</sup>

Innate immune dysfunction also results in macro-circulatory dysfunction. It is known that patients with ACLF have a hyperdynamic circulation and a high cardiac output. There is also peripheral vasodilatation and a low systemic vascular resistance, resulting in a reduced effective arterial volume and a decrease in mean arterial blood pressure. The consequence of these circulatory changes is end-organ hypoperfusion. This, in combination with a SIRS response, may result in organ failure, multi-organ failure and ultimately death.<sup>8</sup>

## Organ Dysfunction (O)

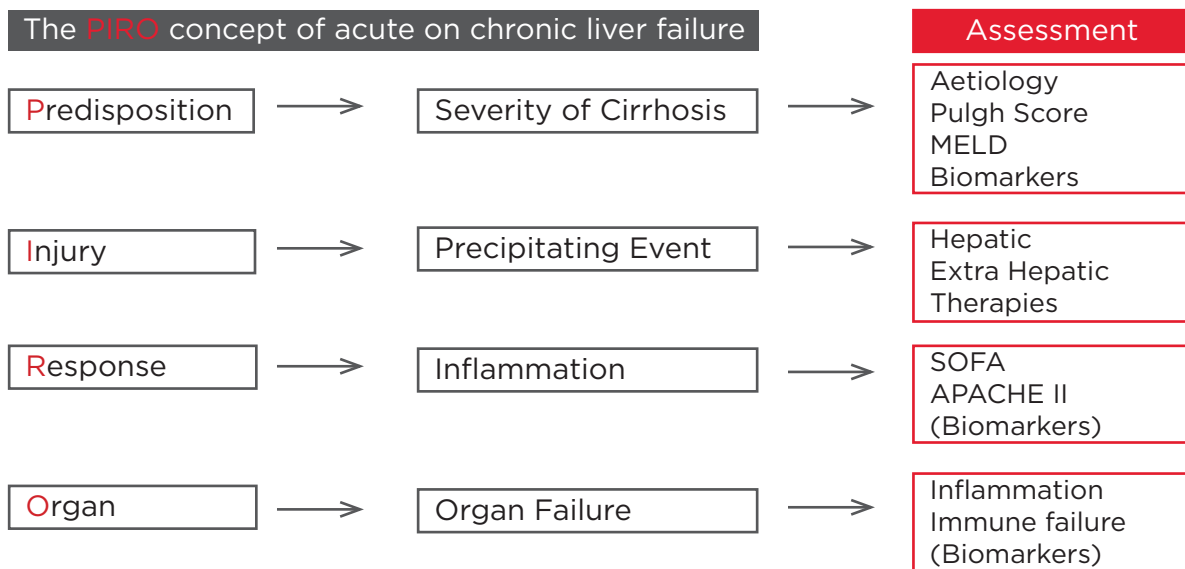
Organ failure plays a central role in the clinical course of ACLF, occurring in one third of patients. Following the development of organ failure, there

is an estimated mortality rate of 55% and 65% in the Intensive Care Unit (ICU)<sup>19,20</sup> and in hospital, respectively.<sup>21</sup> In addition to the liver, the organs commonly affected include the kidneys, brain, circulatory system and adrenal glands.

**Liver:** The hallmark of the liver manifestation of ACLF is hyperbilirubinaemia and coagulopathy. Hyperbilirubinaemia arises as a result of reduced detoxification function of the liver. In addition, the reduction in the liver’s synthetic function leads to a decrease in the production of coagulation factors, and as a consequence, coagulopathy results. Hyperbilirubinaemia and coagulation failure have been identified as independent predictors of mortality in ACLF.<sup>2,5,22,23</sup> Histopathologically, it appears that the presence of cholestasis is associated with increased risk of infection, and balloon degeneration may be associated with a poorer outcome. The mechanism of hepatocyte cell-death in this syndrome remains unclear and requires further studies.

**Kidney:** Renal function is almost universally altered in patients with ACLF.<sup>24</sup> The most common causes of kidney failure are prerenal azotemia, hepatorenal syndrome, and acute tubular necrosis.<sup>25</sup> SIRS is present in approximately 40% of patients with functional renal failure. In addition, the presence of SIRS in patients with functional renal failure was associated with an in-hospital mortality rate of 68%.<sup>26</sup> Further evidence that SIRS plays an important role in kidney failure associated with ACLF, is derived from studies which have shown that the use of anti-inflammatory agents, such as pentoxifylline, improves renal function or significantly decreases the risk of developing renal failure in patients with alcoholic hepatitis.<sup>27,28</sup>

Hepatorenal syndrome (HRS) is the development of functional renal failure in patients with advanced liver disease. Type 1 HRS, which occurs in an acute setting, is a rapidly progressive decline in renal function associated with a mortality rate of 80% at two weeks.<sup>29</sup> Our current understanding is that HRS develops as a result of the haemodynamic dysregulation associated with portal hypertension. In this setting, splanchnic vasodilatation leads to decreased effective arterial volume, resulting in severe renal vasoconstriction and hypoperfusion. Activation of the sympathetic nervous system through a hepatorenal reflex arc is also thought to play a role. In addition, there is altered renal blood flow autoregulation in patients with HRS. However, attempts to restore this circulatory dysfunction with the use of splanchnic vasoconstrictors (terlipressin)



**Figure 1. The PIRO concept of acute-on-chronic liver failure.** In patients with ACLF, it is useful to think about the PIRO concept in determining pathogenesis and prognosis. Predisposition is indicated by the severity of the underlying illness. Injury by the nature and severity of the precipitating event. Response by host response to injury, which determines the severity of inflammation and risk of infection. Organs by the extent of organ failure.<sup>2</sup>

and volume expanders (albumin) only improves renal function in about 40%-50% of patients.<sup>30</sup> These observations indicate that other pathophysiological mechanisms may be responsible for the development of HRS. Indeed, recent studies have demonstrated histopathological evidence of renal tubular cell-death associated with apoptosis, increased renal tubular expression of toll-like receptor-4, increased urinary markers of acute kidney injury such as neutrophil gelatinase-associated lipocalin (NGAL), and more recently, urinary toll-like receptor-4 providing possible novel biomarkers and approaches to therapy.<sup>31</sup>

**Brain:** Hepatic encephalopathy (HE) may be due either to a precipitating factor or as a consequence of ACLF. It is a feature in up to 75% of patients with ACLF.<sup>10</sup> Brain oedema is central to the development of HE in ACLF. Hyperammonemia occurs in ACLF because of a reduction in the liver's detoxifying abilities. This high level of ammonia then diffuses into the brain. Once in the brain, it combines with glutamate to form glutamine. An increase in brain glutamine levels results in astrocyte swelling. Hyponatremia, another common finding in ACLF patients, exacerbates astrocyte swelling due to differences in osmolality between the intracellular and the extracellular compartment,<sup>32,33</sup> and systemic inflammation also plays a role in astrocyte swelling and cerebral oedema. Patients with evidence of infection or SIRS are more likely to develop severe encephalopathy.<sup>34</sup> It is likely that a synergy exists

between hyperammonemia and inflammation. The high level of ammonia may prime the brain to the deleterious effect of superimposed inflammation by induction of microglial cells, which have a huge repertoire for cytokine production. This explains why measures which reduce the ammonia levels or levels of endotoxemia reduce the occurrence of HE.<sup>5, 35-37</sup>

**Adrenals:** Adrenal insufficiency occurs in 68% of patients with cirrhosis and septic shock. Although the mechanism responsible for this is not clear, it may be related to reduction in adrenal blood flow, which occurs as a consequence of circulatory changes in ACLF. In addition, high levels of pro-inflammatory cytokines, seen in ACLF, inhibit cortisol synthesis. Adrenal insufficiency may contribute to the development of multi-organ failure in ACLF.<sup>38</sup>

## CONCLUSIONS

ACLF is a devastating condition associated with a high mortality rate. Despite this, treatment options are limited and mainly supportive. The shortage of cadaveric livers means that liver transplant, the definitive treatment option, is not available to most patients with ACLF. There is an urgent need to better define the condition as well as further understand the patho-physiological basis of the condition. The PIRO system is conceptually useful as it indicates a distinction between the insult and the response, thus providing a framework for a better pathophysiological understanding of this syndrome.



## REFERENCES

1. Sen S, Williams R, Jalan R. The pathophysiological basis of acute-on-chronic liver failure. *Liver*. 2002;22:5-13.
2. Jalan R, Stadlbauer V, Sen S, Cheshire L, Chang YM, Mookerjee RP. Role of predisposition, injury, response and organ failure in the prognosis of patients with acute-on-chronic liver failure: a prospective cohort study. *Crit Care*. 2012;16:227.
3. Verbeke L, Nevens F, Laleman W. Bench-to-beside review: acute-on-chronic liver failure - linking the gut, liver and systemic circulation. *Crit Care*. 2011;15:233.
4. Angus DC, Burgner D, Wunderink R, Mira JP, Gerlach H, Wiedermann CJ, Vincent JL. The PIRO concept: P is for predisposition. *Crit Care*. 2003;7:248-51.
5. Jalan R, Gines P, Olson JC, Mookerjee RP, Moreau R, Garcia-Tsao G, Arroyo V, et al. Acute-on chronic liver failure. *J Hepatol*. 2012;57:1336-48.
6. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22:707-10.
7. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13:818-29.
8. Laleman W, Verbeke L, Meersseman P, Wauters J, van Pelt J, Cassiman D, Wilmer A, et al. Acute-on-chronic liver failure: current concepts on definition, pathogenesis, clinical manifestations and potential therapeutic interventions. *Expert Rev Gastroenterol Hepatol*. 2011;5:523-37.
9. Olson JC, Kamath PS. Acute-on-chronic liver failure: what are the implications? *Curr Gastroenterol Rep*. 2012;14:63-6.
10. Katoonizadeh A, Laleman W, Verslype C, Wilmer A, Maleux G, Roskams T, Nevens F. Early features of acute-on-chronic alcoholic liver failure: a prospective cohort study. *Gut*. 2010;59:1561-9.
11. Keeffe EB. Is hepatitis A more severe in patients with chronic hepatitis B and other chronic liver diseases? *Am J Gastroenterol*. 1995;90:201-05.
12. Garg H, Sarin SK, Kumar M, Garg V, Sharma BC, Kumar A. Tenofovir improves the outcome in patients with spontaneous reactivation of hepatitis B presenting as acute-on-chronic liver failure. *Hepatology*. 2011;53:774-80.
13. Kumar Acharya S, Kumar Sharma P, Singh R, Kumar Mohanty S, Madan K, Kumar Jha J, Kumar Panda S. Hepatitis E virus (HEV) infection in patients with cirrhosis is associated with rapid decompensation and death. *J Hepatol*. 2007;46:387-94.
14. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, Durand F, et al. Acute-on-Chronic Liver Failure is a Distinct Syndrome that Develops in Patients With Acute Decompensation of Cirrhosis. *Gastroenterology*. 2013.
15. Novelli G, Rossi M, Ferretti G, Pugliese F, Travaglia D, Guidi S, Novelli S, et al. Predictive parameters after molecular adsorbent recirculating system treatment integrated with model for end stage liver disease model in patients with acute-on-chronic liver failure. *Transplant Proc*. 2010;42:1182-7.
16. Wasmuth HE, Kunz D, Graf J, Stanzel S, Purucker EA, Koch A, Gartung C, et al. Hyperglycemia at admission to the intensive care unit is associated with elevated serum concentrations of interleukin-6 and reduced ex vivo secretion of tumor necrosis factor-alpha. *Crit Care Med*. 2004;32:1109-14.
17. Antoniadou CG, Berry PA, Wendon JA, Vergani D. The importance of immune dysfunction in determining outcome in acute liver failure. *J Hepatol*. 2008;49:845-61.
18. Leithead JA, Ferguson JW, Bates CM, Davidson JS, Lee A, Bathgate AJ, Hayes PC, et al. The systemic inflammatory response syndrome is predictive of renal dysfunction in patients with non-paracetamol-induced acute liver failure. *Gut*. 2009;58:443-49.
19. Juneja D, Gopal PB, Kapoor D, Raya R, Sathyanarayanan M, Malhotra P. Outcome of patients with liver cirrhosis admitted to a specialty liver intensive care unit in India. *J Crit Care*. 2009;24:387-93.
20. Shawcross DL, Austin MJ, Abeles RD, McPhail MJ, Yeoman AD, Taylor NJ, Portal AJ, et al. The impact of organ dysfunction in cirrhosis: survival at a cost? *J Hepatol*. 2012;56:1054-62.
21. Cavallazzi R, Awe OO, Vasu TS, Hirani A, Vaid U, Leiby BE, Kraft WK, et al. Model for End-Stage Liver Disease score for predicting outcome in critically ill medical patients with liver cirrhosis. *J Crit Care*. 2012;27:421-426.
22. Singh N, Gayowski T, Wagener MM, Marino IR. Outcome of patients with cirrhosis requiring intensive care unit support: prospective assessment of predictors of mortality. *J Gastroenterol*. 1998;33:73-9.
23. Zimmerman JE, Wagner DP, Seneff MG, Becker RB, Sun X, Knaus WA. Intensive care unit admissions with cirrhosis: risk-stratifying patient groups and predicting individual survival. *Hepatology*. 1996;23:1393-401.
24. Cardenas A, Gines P. Acute-on-chronic liver failure: the kidneys. *Curr Opin Crit Care*. 2011;17:184-9.
25. Hartleb M, Gutkowski K. Kidneys in chronic liver diseases. *World J Gastroenterol*. 2012;18:3035-49.
26. Thabut D, Massard J, Gangloff A, Carbonell N, Francoz C, Nguyen-Khac E, Duhamel C, 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;46:1872-82.
27. Akriviadis E, Botla R, Briggs W, Han S, Reynolds T, Shakil O. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. *Gastroenterology*. 2000;119:1637-48.
28. Mookerjee RP, Sen S, Davies NA, Hodges SJ, Williams R, Jalan R. Tumour necrosis factor alpha is an important mediator of portal and systemic haemodynamic derangements in alcoholic hepatitis. *Gut*. 2003;52:1182-7.
29. Gines A, Escorsell A, Gines P, Salo J, Jimenez W, Inglada L, Navasa M, et al. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. *Gastroenterology*. 1993;105:229-36.
30. Fabrizi F, Dixit V, Martin P. Meta-analysis: terlipressin therapy for the hepatorenal syndrome. *Aliment Pharmacol Ther*. 2006;24:935-44.
31. Shah N, Dhar D, El Zahraa Mohammed F, Habtesion A, Davies NA, Jover-Cobos M, Macnaughtan J, et al. Prevention of acute kidney injury in a rodent model of cirrhosis following selective gut decontamination is associated with reduced renal TLR4 expression. *J Hepatol*. 2012;56:1047-53.
32. Cordoba J, Garcia-Martinez R, Simon-Talero M. Hyponatremic and hepatic encephalopathies: similarities, differences and coexistence. *Metab Brain Dis*. 2010;25:73-80.
33. Garcia-Martinez R, Cordoba J. Acute-on-chronic liver failure: the brain. *Curr Opin Crit Care*. 2011;17:177-83.
34. Shawcross DL, Sharifi Y, Canavan JB, Yeoman AD, Abeles RD, Taylor NJ, Auzinger G, et al. Infection and systemic inflammation, not ammonia, are associated with Grade 3/4 hepatic encephalopathy, but not mortality in cirrhosis. *J Hepatol*. 2011;54:640-9.
35. Bass NM, Mullen KD, Sanyal A, Poordad

- F, Neff G, Leevy CB, Sigal S, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med.* 2010;362:1071-81.
36. Wright G, Davies NA, Shawcross DL, Hodges SJ, Zwingmann C, Brooks HF, Mani AR, et al. Endotoxemia produces coma and brain swelling in bile duct ligated rats. *Hepatology.* 2007;45:1517-26.
37. Wright G, Vairappan B, Stadlbauer V, Mookerjee RP, Davies NA, Jalan R. Reduction in hyperammonaemia by ornithine phenylacetate prevents lipopolysaccharide-induced brain edema and coma in cirrhotic rats. *Liver Int.* 2012;32:410-9.
38. Fernandez J, Escorsell A, Zabalza M, Felipe V, Navasa M, Mas A, Lacy AM, et al. Adrenal insufficiency in patients with cirrhosis and septic shock: Effect of treatment with hydrocortisone on survival. *Hepatology.* 2006;44:1288-95.