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TOPIC HIGHLIGHT

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New determinants of prognosis in bacterial infections in cirrhosis

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Abstract

Despite major advances in the knowledge and management of liver diseases achieved in recent decades, decompensation of cirrhosis still carries a high burden of morbidity and mortality. Bacterial infections are one of the main causes of decompensation. It is very important for clinical management to be aware of the population with the highest risk of poor outcome. This review deals with the new determinants of prognosis in patients with cirrhosis and bacterial infections reported recently. Emergence of multiresistant bacteria has led to an increasing failure rate of the standard empirical antibiotic therapy recommended by international guidelines. Moreover, it has been recently reported that endothelial dysfunction is associated with the degree of liver dysfunction and, in infected patients, with the degree of sepsis. It has also been reported that relative adrenal insufficiency is frequent in the non-critically ill cirrhotic population and it is associated with a higher risk of developing infection, severe sepsis, hepatorenal syndrome and death. We advise a change in the standard empirical antibiotic therapy in patients with high risk for multiresistant infections and also to take into account endothelial and adrenal dysfunction in prognostic models in hospitalized patients with decompensated cirrhosis.

Key words: Bacterial infections; Liver cirrhosis; Drug resistance; Bacterial; Endothelial dysfunction; Relative adrenal insufficiency

Core tip: Despite major advances in the management of cirrhosis, it still carries high morbidity and mortality. Bacterial infection is one of the major causes of decompensation. This review deals with the new determinants of prognosis in patients with cirrhosis and bacterial infection reported recently. It summarizes the existing evidence for emergence of multiresistant bacteria, endothelial dysfunction, and relative adrenal insufficiency; and resultant changes in medical practice are given.

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INTRODUCTION

Decompensation of liver cirrhosis carries a huge burden of morbidity and mortality in society. In the past 30 years there has been major progress in the knowledge and management of liver disease; despite this, there are approximately 29 million people in the European Union who still suffer from a chronic liver condition. Available data suggest that about 0.1% of the European popula-

tion is affected by cirrhosis, corresponding to 14-26 new cases per 100000 inhabitants per year or an estimated 170000 deaths per year[1,2].

Bacterial infection is a major cause of decompensation. Patients with cirrhosis are at an increased risk of developing bacterial infections, sepsis, severe sepsis and death[3]. Thus, infection is present at admission or develops during hospitalization in about 25%-30% of patients[4,5]. Bacterial infection is not only more frequent but also more severe in cirrhosis, causing a four-fold increase in the probability of death, reaching 38% at 1 mo[6]. Infection can accentuate circulatory dysfunction leading to the development of hepatorenal syndrome (HRS) and can also induce an excessive pro-inflammatory response that could contribute to the development of sepsis-related organ failure (acute-on-chronic liver failure) and septic shock[7]. Therefore, it is important to identify determinants of poor prognosis in patients with bacterial infections and cirrhosis in order to be alert to the group of patients with highest risk of death and, if possible, reverse the deleterious effect of these determinants by modifying the standard clinical practice performed in this major disease.

This review aims to summarize the recently reported data regarding recent changes in the epidemiology of bacterial infections in cirrhosis, endothelial dysfunction, and relative adrenal insufficiency; all of which are the new determinants of prognosis in patients with cirrhosis and bacterial infections reported recently.

EMERGENCE OF MULTIRESISTANT BACTERIA IN CIRRHOSIS

The discovery of antibiotics in the early to mid-20th century remains one of the most significant achievements to date, but inherent with its use is the development of antimicrobial resistance. In consequence, epidemiology of bacterial infections is continuously changing and the emergence of multiresistant (MR) bacteria in the general and cirrhotic population has risen as a new determinant of prognosis.

In the 1980s, epidemiological surveillance showed that most infections were community acquired and approximately 70% to 80% of the isolated organisms were gram-negative bacilli (GNB)[4]. Since the 1990s, practice in hepatology has involved invasive procedures (*i.e.*, variceal ligation, transjugular intrahepatic portosystemic shunt, and arterial chemoembolization or percutaneous ablation of hepatocellular carcinoma) and also severely ill patients have been treated in Intensive Care Units. Consequently, in the 2000s some important changes were reported: 39% of infections were of nosocomial origin and gram positive cocci (GPC) was the most frequently isolated bacteria in the nosocomial setting. GPC were also isolated more frequently in the admissions which required invasive procedures or treatment in the Intensive Care Unit. Another important change observed was the emergence of SBP caused by quinolone-resistant GNB in patients under long-term norfloxacin prophylaxis. At that time, only 1.2% of infections caused by *Enterobacteriaceae* were resistant to third generation cephalosporines (TGC)[4]. On that account, international clinical guidelines recommend the use of TGC to treat the most common infections in cirrhosis as they are active against *Enterobacteriaceae* and streptococci, but not against enterococci, and they also have a good security profile[8-10].

Types of multiresistance patterns around the world

The employment of TGC for two decades has led to the emergence of MR bacteria, as evidenced by various reports from very different geographical areas[5,11-22]. MR bacteria are resistant to at least three of the main antibiotic families including β-lactamics[23]. The most common MR bacteria are extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL), non-fermentable GNB such as *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia* or *Acinetobacter baumanii*, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-susceptible *Enterococcus* (VSE) and vancomycin-resistant *Enterococcus* (VRE).

The emergence of MR bacteria is present worldwide, but in a heterogeneous manner. Thus, different geographical areas have different epidemiological patterns of multiresistance; for example, ESBL-producing *Enterobacteriaceae* are predominant in South Europe and Asia[5,11-19], while MRSA and VRE are frequently isolated in centers of the United States[22]. Moreover, Carbapenemase-producing *K. pneumoniae* has only been reported in some centers in Italy[24]. Table 1 summarizes the prevalence and risk factors for the development of MR bacteria across the world.

Risk factors and clinical impact of multiresistance bacterial infections

The main risk factors for the development of infections caused by MR bacteria are: nosocomial origin of infection [hazard ratio (HR): 4.43], long-term norfloxacin prophylaxis (HR: 2.69), recent infection by an MR bacteria (HR: 2.45), and recent use of β-lactams (HR: 2.39)[5]. Other reports suggest that infections that develop in the setting of recent contact with the health-care environment (health-care associated), like dialysis centers, are also at risk of developing MR bacteria infections[16].

The emergence of MR bacteria has a major impact on the clinical evolution of infected patients with cirrhosis, through impairment of the efficacy of standard empirical antibiotic therapy. In an in-depth prospective study regarding this topic, the final resolution of infection was still high in community-acquired infections (83%), but low in healthcare associated infections (73%), and extremely low in nosocomial infections (40%)[5]. Final resolution was significantly lower in infections caused by multiresistant strains (70% *vs* 92%, $P < 0.0001$), particularly in SBP and pneumonia (50% and 55%, respectively). In consequence, septic shock was more frequently observed in MR infections (26% *vs* 10%, $P < 0.0001$) and hospital mortality in MR infections duplicate that observed in infections caused by susceptible bacteria (25% *vs* 12%, $P =$

Table 1 Prevalence, clinical impact and risk factors of multiresistant bacterial infections around the world

Ref.	Infections	Prevalence of MR bacteria	Risk factors	Clinical impact
Song *et al*[14], 2006 South Korea	SBP	29% ESBL-producing *Enterobacteriaceae*: 14% in community-acquired, 67% in nosocomial episodes	No data	No impact
Angeloni *et al*[61], 2008 Italy	SBP	8% ESBL-producing *Enterobacteriaceae*	Healthcare-associated infections	Higher initial treatment failure No impact on mortality
Umgelter *et al*[20], 2009 Germany	SBP	10% VSE, 1% *Pseudomonas aeruginosa*	No data	Higher initial treatment failure Higher hospital mortality
Piroth *et al*[19], 2009 France	SBP and bacterioascites	8% MRSA 5% VSE 4% ESBL-producing *Enterobacteriaceae*	No data	No data
Cheong *et al*[13], 2009 South Korea	SBP	15% ESBL-producing *Enterobacteriaceae*	Previous exposition to β-lactams Nosocomial infection	Independent predictor of 30-d mortality
Song *et al*[12], 2009 South Korea	SBP	4%-7.5% ESBL-producing *Enterobacteriaceae*	Recent hospital stay Previous SBP Antibiotic treatment in the last month	Higher initial treatment failure Higher hospital and 30-d mortality
Merli *et al*[16], 2010 Italy	All	20% ESBL-producing *Enterobacteriaceae* 7% MRSA	Antibiotic treatment in the last month HCA infection	Higher hospital mortality
Ariza *et al*[17], 2012 Spain	SBP	6% ESBL-producing *Enterobacteriaceae* 2% *Pseudomonas aeruginosa* 2% *Acinetobacter baumannii* 1% VSE	Nosocomial infection Previous exposition to β-lactams Diabetes mellitus Upper gastrointestinal bleeding	Independent predictor of mortality at 30 d
Fernández *et al*[5], 2012 Spain	All	8%-9% ESBL-producing *Enterobacteriaceae* 3% *Pseudomonas aeruginosa* 3%-4% MRSA 3%-7% VSE	Nosocomial infection Long-term norfloxacin prophylaxis Treatment with β-lactams in the last 3 mo MR bacteria in the last 6 mo	Lower infection resolution Higher risk of septic shock Higher hospital mortality
Novovic *et al*[21], 2012 Denmark	SBP	1% ESBL-producing *Enterobacteriaceae* 12% VSE-VRE	No data	Higher hospital mortality
Tandon *et al*[22], 2012 United States	All	9% VRE 6.5% ESBL-producing *Enterobacteriaceae* 5% MRSA	Systemic antibiotics in the past 30 d Nosocomial infection	No data

ESBL: Extended-spectrum β-lactamase-producing *Enterobacteriaceae* (bacteria with chromosomal β-lactamases are also included); MRSA: Methicillin-resistant *Staphylococcus aureus*; VSE: Vancomycin-susceptible enterococci; VRE: Vancomycin-resistant enterococci; SBP: Spontaneous bacterial peritonitis.

0.001)[5].

New recommendations of empirical antibiotic therapy

According to this new epidemiological data it has been recommended to change the empirical antibiotic therapy (*i.e.*, third generation cephalosporins) employed in nosocomial infections. Marked epidemiological differences observed among countries and centers suggest that local epidemiology should be evaluated regularly and new guidelines should be tailored according to the specific local epidemiological pattern of multiresistance[25].

In general, our recommendation for nosocomial infections is that in areas with a high prevalence of ESBL-producing *Enterobacteriaceae*, carbapenems should be used. It is also important to tailor the antibiotics according to the severity of infection: in severe sepsis and septic shock it is important to cover all possible bacteria, therefore glycopeptides should be added[5]. In areas with high prevalence of VSE and MRSA, a glycopeptide should be used. In the United States and other regions with a high rate of infections caused by VRE, glycopeptides should be replaced by linezolid or daptomycin. In areas with low prevalence of MR bacteria but high prevalence of *Enterococcus faecalis*, piperacillin-tazobactam should be used.

In healthcare associated infections our recommendation is to treat as nosocomial infections those patients under long-term norfloxacin prophylaxis or those with an MR bacteria infection in the previous six months because these two factors identify a subgroup of patients with high risk of MR bacteria infection (Figure 1).

In summary, recent data demonstrate that currently recommended empirical antibiotic therapy is not appropriate for the treatment of nosocomial and some healthcare associated infections in cirrhosis because of the high prevalence of MR bacteria in these settings. New antibiotic strategies for these infections should be tailored according to the local epidemiological patterns of multiresistance and early de-escalation of antibiotics according to the microbiological results is also mandatory to slow down the development of new resistances.

CIRCULATORY AND ENDOTHELIAL DYSFUNCTION

It is well known that a clinically important characteristic of cirrhotic patients is systemic circulatory dysfunction which is characterized by arterial splanchnic vasodilation which progresses in parallel with the degree of liver impairment and portal hypertension. This situation is due to a local release of vasoactive substances, especially nitric oxide[26-28] but also prostaglandines, P substance, carbon monoxide, calcitonin gene-related peptide and endocannabinoids[29-33]. In the initial phase of the disease, the

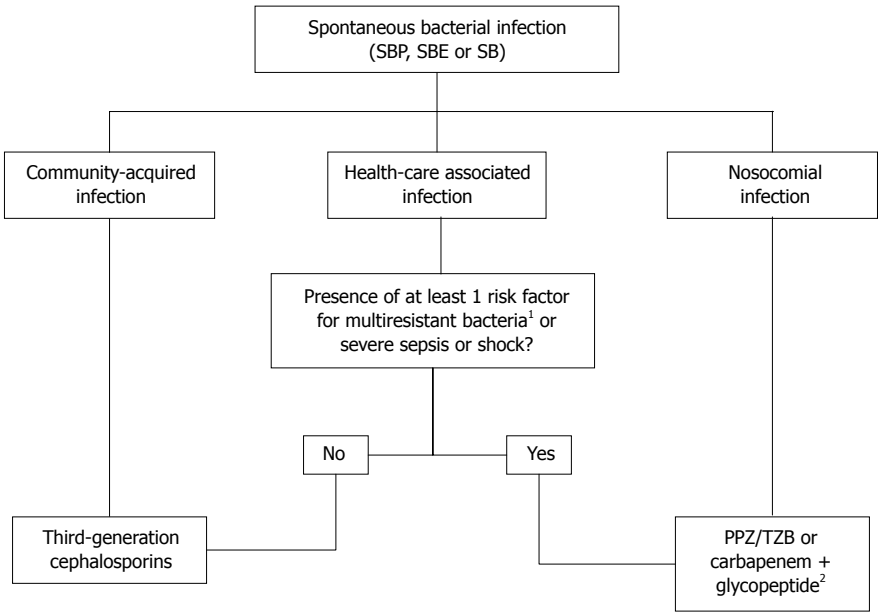

Figure 1 Proposed algorithm for the empirical treatment of infections in cirrhosis. [1]Risk factors for multiresistant bacteria in Health care associated infections are long-term norphloxacin prophylaxis or previous infection by multiresistant (MR) bacteria within 6 mo; [2]Piperaziline/tazobactam in areas of low MR bacteria but high *Enterococcus faecalis* prevalence. Meropenem and glycopeptides in areas with high prevalence of extended-spectrum β-lactamase-producing *Enterobacteriaceae* and methicillin-resistant *Staphylococcus aureus*. SBP: Spontaneous bacterial peritonitis; SBE: Spontaneous bacterial empyema; SB: Spontaneous bacteremia; PPZ/TZB: Piperaziline/tazobactam.

reduction of effective arterial volume is compensated for by an increase in cardiac output. Nevertheless, while liver dysfunction progresses patients develop cirrhotic cardiomyopathy characterized by diastolic dysfunction which can affect inotropic function during stress[34]. Therefore, patients develop arterial hypotension and compensating activity of vasoactive systems (sympathetic and renin-angiotensin-aldosterone) with sodium and water retention and ascites production[26]. When circulatory dysfunction continues to progress, vasopressin is activated which leads to dilutional hyponatremia and hepatorenal syndrome[35].

Bacterial infection is a main cause of circulatory dysfunction. Infection in cirrhosis is characterized by a more intense inflammatory response than that observed in non-cirrhotic population. Accordingly, cirrhotic patients with SBP present very high levels of cytokines[36] which exacerbate circulatory dysfunction[37]. Thus, infection in a patient with baseline circulatory dysfunction can have devastating effects. Up to 30% of patients develop progressive circulatory dysfunction with acute renal failure, cardiac impairment, hepatic encephalopathy, type-1 hepatorenal syndrome and death[38]. On that account, expansion of effective arterial volume with intravenous albumin reduces renal failure and improves survival in SBP[39].

Moreover, advanced cirrhosis is characterized by an increased intestinal permeability and bacterial translocation which results in severe infections like spontaneous bacterial peritonitis, spontaneous bacteremia, and spontaneous empyema[40,41]. Increased intestinal permeability is caused by many factors including structural changes in intestinal mucosa due to circulatory dysfunction[42,43], hypomotility secondary to sympathetic nervous system hyperactivity, and oxidative damage produced by high levels of nitric oxide and proinflammatory cytokines[44,45]. Translocation of not only viable bacteria, but also bacterial products like DNA, have been associated with a higher inflammatory response and worse prognosis, due to the development of acute-on-chronic liver failure[46,47].

Endothelial dysfunction

There are well recognized markers of endothelial dysfunction; these involve mainly the von Willebrand factor (vWF), but also P-selectin and isoprostanes. It has been reported that serum levels of vWF increase according to the degree of liver dysfunction and portal hypertension. Endothelial dysfunction, and higher levels of vWF have been associated with a higher incidence of decompensations related to portal hypertension and mortality[48,49]. In one study it has been suggested that vWF is released in the hepatosplanchnic vascular bed[49]. Furthermore, regarding infection in cirrhosis, it has been reported that the degree of endothelial dysfunction increases according to the degree of sepsis, vWF serum levels increased progressively among non infected patients, infected patients without sepsis, infected patients with sepsis and, showing the highest levels of vWF, patients with septic shock[50] (Figure 2).

The high mortality associated with endothelial dysfunction could be explained beyond its association with circulatory dysfunction. The increasing levels of vWF in parallel with increasing degrees of sepsis would reflect increasing endothelial activation produced by increasing levels of cytokines. Moreover, cytokines and inflammation activate coagulation cascade and lead to hemostatic abnormalities leading to poor organ perfusion reaching, in some cases, the extreme degree of disseminated intra-

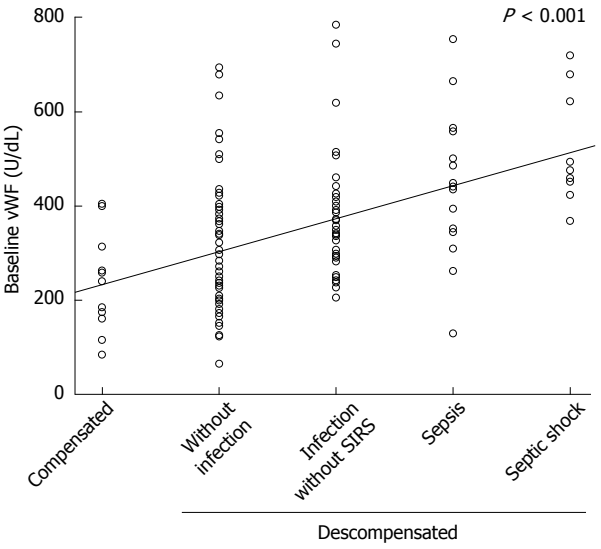

Figure 2 Correlation between von Willebrand factor and degree of sepsis. SIRS: Systemic inflammatory response syndrome. (thanks *Hepatology* journal for permission to reproduce the figure).

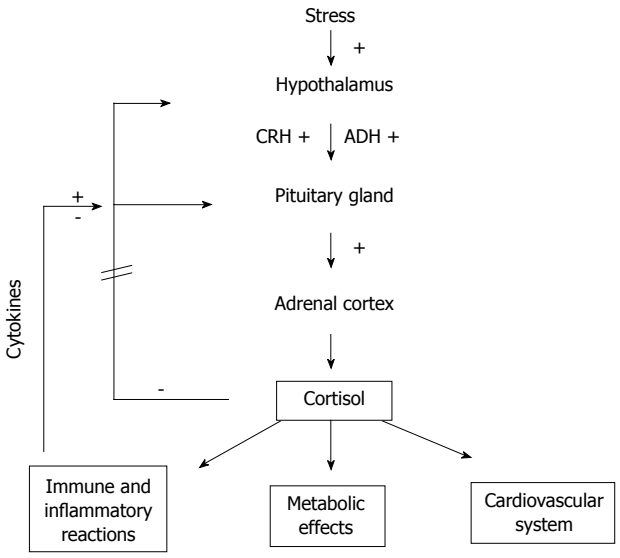

Figure 3 Hypothalamic-pituitary-adrenal axis in the critical illness. CRH: Corticotrophin releasing hormone; ADH: Antidiuretic hormone; ACTH: Adrenocorticotropic hormone. Original work of the authors.

vascular coagulation and multiple organ failure.

In summary, endothelial dysfunction is clearly associated with poor prognosis and vWF should be taken into account in predictive models in hospitalized patients.

ADRENAL DYSFUNCTION

A normal adrenal function is essential to surviving critical illness. Cortisol maintains vascular tone, endothelial integrity, vascular permeability and total corporal water distribution[51]. In consequence, an inappropriate adrenal response, *i.e.*, relative adrenal insufficiency (RAI), during a critical illness like severe sepsis or septic shock has important clinical consequences. These patients secrete cortisol and corticotrophin at the initial stage of the disease, but less than needed to overcome stress. Activation of the axis is triggered by cytokines and other factors that promote the release of corticotrophin releasing hormone (CRH) and vasopressin in the hypothalamus[51,52]. These hormones stimulate pituitary secretion of corticotrophin (ACTH) which induces adrenal production of cortisol. In addition, the levels of cortisol binding protein decrease fast, leading to higher levels of free cortisol, which is the active component of cortisol[53]. Furthermore, negative feedback of cortisol upon CRH and ACTH is inactive, thus maintained activation on the hypothalamic-pituitary-adrenal axis can be exerted[51]. Finally, there is an increase in the number and sensibility of cortisol receptors[51,52]. In this sense, during critical illness there is an integrated multilevel response that optimizes the cortisol effect in peripheral tissues, and cytokines and bacterial products are also able to modify the response of hypothalamic-pituitary-adrenal axis at each level[51] (Figure 3).

There is a high prevalence of RAI in patients with cirrhosis and septic shock and it is associated with liver and renal failure, refractory septic shock and hospital mortality[54-56]. Two recent studies confirmed a high prevalence of RAI in septic shock[57] and in digestive bleeding[58]. However, there are contradictory results on the beneficial effects on outcome produced by the administration of steroids at stress doses[55-59]; large-scale randomized controlled trials are required to clarify this point.

It has recently been reported that RAI is not only common in critically ill patients with cirrhosis but also in non-critically ill patients hospitalized by decompensation of cirrhosis. RAI prevalence in this setting is 26%, and it is associated with a higher degree of circulatory dysfunction evidenced through lower mean arterial pressure (76 ± 12 mmHg *vs* 83 ± 14 mmHg, $P = 0.009$), higher serum levels of noradrenaline (544 ± 334 pg/mL *vs* 402 ± 316 pg/mL, $P = 0.02$), plasma renin activity (7.1 ± 9.9 ng/mLh *vs* 3.4 ± 5.6 ng/mLh, $P = 0.03$), and lower serum sodium levels (131 ± 7 mEq/L *vs* 135 ± 5 mEq/L, $P = 0.007$). Furthermore, patients with RAI presented a tendency to a higher inflammatory state with a higher prevalence of systemic inflammatory response syndrome (SIRS) (60% *vs* 41%, $P = 0.08$) and higher plasmatic levels of tumoral necrosis factor alpha (54 ± 115 pg/mL *vs* 27 ± 24 pg/mL) and interleukine-6 (916 ± 2532 pg/mL *vs* 244 ± 439 pg/mL). Patients with RAI showed a higher probability of developing infections (41% *vs* 21%, $P = 0.008$), severe sepsis (27% *vs* 9%, $P = 0.003$), type-1 hepatorenal syndrome (16% *vs* 3%, $P = 0.002$), and death (22% *vs* 7%, $P = 0.01$) (Figures 4 and 5)[60].

The higher incidence of infections observed in patients with RAI is explained by the presence of an important circulatory dysfunction which leads to bacterial translocation. The higher degree of inflammation would contribute to mucosal barrier damage and bacterial translocation and also to the development of renal failure and hepatorenal syndrome by worsening circulatory dysfunction, as already described. The addition of a baseline low vascular tone and a functional deficit of cortisol which leads to a further decrease in vascular tone would con-

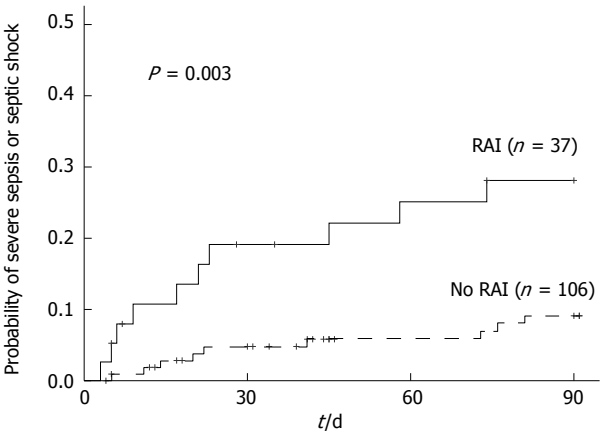

Figure 4 Probability of development of severe sepsis and septic shock in patients with and without relative adrenal insufficiency. Probability of developing new episodes of severe sepsis or septic shock in patients with relative adrenal insufficiency (RAI) (continuous line) or with normal adrenal function (doted line) during 3 mo follow-up. Probability was significantly higher in patients with RAI. (thanks *Hepatology* journal for permission to reproduce the figure).

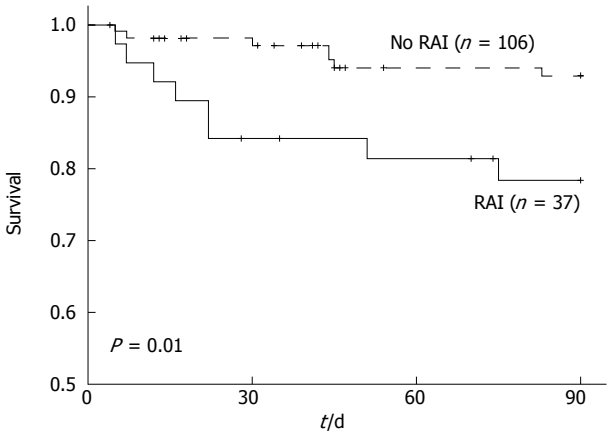

Figure 5 Probability of survival at 3 mo in patients with and without relative adrenal insufficiency. Probability of survival at 3 mo in patients with relative adrenal insufficiency (RAI) (continuous line) or with normal adrenal function (doted line). Probability was significantly higher in patients with RAI. (thanks *Hepatology* journal for permission to reproduce the figure).

tribute to the development of severe sepsis and septic shock[60].

Circulatory dysfunction and inflammation are causes of RAI through vasodilation and reduction in adrenal blood flow which diminishes adrenal function; high levels of proinflammatory cytokines also directly inhibit cortisol synthesis by the adrenal glands.

To sum up, RAI has a negative impact on prognosis in critically-ill and non critically-ill cirrhotic patients and large-scale randomized controlled trials should be performed, aimed at evaluating cortisol supplementation during critical illness and antibiotic prophylaxis during admission in the non-critically ill population.

CONCLUSION

New determinants of prognosis in patients with liver cirrhosis and bacterial infections have been identified in recent years. Recent changes in epidemiology and new findings in pathophysiology have been reported. On one hand, it has been reported worldwide emergence of multiresistant bacteria which leads to changes in the current recommended empirical antibiotic therapy in those patients with risk factors for MR bacteria infection, with the warning of tailoring it according to local patterns of multiresistance and de-escalating as soon as possible to diminish the impact of wide-spectrum antibiotics on the appearance of new resistant strains.

On the other hand, it has been reported an association between endothelial dysfunction and higher portal pressure and more episodes of decompensation of cirrhosis. Moreover, it is well known that relative adrenal insufficiency is related with refractory shock and mortality in critically-ill cirrhotic patients, and, in addition, it has been recently reported that relative adrenal insufficiency is related with a high risk of developing infections, septic shock and mortality in the non critically-ill cirrhotic population. Thus, endothelial dysfunction and relative adrenal insufficiency are clearly associated with poor prognosis and should be taken into account in prognostic models in hospitalized patients with decompensation of cirrhosis. Trials focused on whether steroid administration in patients with septic shock and RAI improves survival, and evaluation of antibiotic prophylaxis in the non critically-ill population with RAI would be interesting fields of research.

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