Position Paper

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Bacterial infections in cirrhosis: A position statement based on the EASL Special Conference 2013

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We are dedicating this paper to Drs. Joan Cordoba and Andrew Burroughs in recognition of their excellent work as Doctors and Scientists. They will be remembered by many as a good friends and colleagues. Joan, Andrew may you rest in peace.

Summary

Bacterial infections are very common and represent one of the most important reasons of progression of liver failure, development of liver-related complications, and mortality in patients with cirrhosis. In fact, bacterial infections may be a triggering factor for the occurrence of gastrointestinal bleeding, hypervolemic hyponatremia, hepatic encephalopathy, kidney failure, and development of acute-on-chronic liver failure. Moreover, infections are a very common cause of repeated hospitalizations, impaired health-related quality of life, and increased healthcare costs in cirrhosis. Bacterial infections develop as a consequence of immune dysfunction that occurs progressively during the course of cirrhosis. In a significant proportion of patients, infections are caused by gram-negative bacteria from intestinal origin, yet gram-positive bacteria are a frequent cause of infection, particularly in hospitalized patients. In recent years, infections caused by multidrug-resistant bacteria are becoming an important clinical problem in many countries.

The reduction of the negative clinical impact of infections in patients with cirrhosis may be achieved by a combination of prophylactic measures, such as administration of antibiotics, to reduce the occurrence of infections in high-risk groups together with early identification and management of infection once it has developed. Investigation on the mechanisms of altered gut microflora, translocation of bacteria, and immune dysfunction may help develop more effective and safe methods of prevention compared to those that are currently available. Moreover, research on biomarkers of early infection may be useful in early diagnosis and treatment of infections.

The current manuscript reports an in-depth review and a position statement on bacterial infections in cirrhosis.

Keywords: Cirrhosis; Bacterial infection; Multiresistant bacteria; Diagnosis.
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Introduction

Bacterial infections are very common in patients with cirrhosis and currently represent one of the most common causes of admission to hospital in these patients and a major challenge for physicians caring for patients with liver diseases. Despite the recent improvements in the knowledge of pathogenesis, prevention, and management, bacterial infections still represent a major cause of morbidity and mortality among patients with cirrhosis. On this background, the European Association for the Study of the Liver (EASL) decided to hold a Special Conference on Bacterial Infections in cirrhosis in May 2013 in Barcelona. The conference gathered a large number of clinical and basic scientists as well as clinicians with special interest on the topic who had presentations and extensive discussions on the main areas of the field. The current manuscript represents a position statement that summarizes the different areas that were discussed during the Conference and includes expert opinions on important aspects of the management of bacterial infections in cirrhosis.

Key Points

- The incidence and severity of infection in cirrhosis is greater than in the population without cirrhosis
- Infection with multiresistant organisms is common in cirrhosis and its occurrence is associated with higher mortality rates than in patients without cirrhosis
- The end-organ damaging effect of bacterial infection is greater in patients with cirrhosis due to altered sensitivity, which often culminates in acute-on-chronic liver failure
- Delays in the diagnosis and start of treatment results in higher mortality particularly in hypotensive patients with cirrhosis
- In patients with spontaneous bacterial peritonitis, the addition of albumin to antibiotics reduces mortality
- Primary prophylaxis of spontaneous bacterial peritonitis with norfloxacin is indicated in patients with variceal bleeding, severely decompensated cirrhosis, and those with ascites protein concentration of <15 g/L
- In patients with variceal bleeding, intravenous administration of 3rd generation cephalasporins improves survival
- Administration of norfloxacin to prevent recurrence of spontaneous bacterial peritonitis reduces mortality in cirrhosis
- Research into the mechanisms associated with increased risk of infection in cirrhosis, better use of current therapeutic strategies, development of rapid and accurate diagnostic tools, and development of new strategies to modulate the gut-liver interaction are urgently needed

Clinical aspects of bacterial infections in cirrhosis and the problem of multiresistant bacteria

Patients with cirrhosis have increased risk of developing bacterial infections [1,2]. Infections are present at admission or develop during hospitalization in 25–35% of patients [3,4], an incidence that is 4–5 fold higher than that observed in the general population. Spontaneous bacterial peritonitis (SBP) and urinary tract infections are the most frequent infections followed by pneumonia, skin and soft tissue infections, and bacteremia. Clinical factors associated with an increased risk of infection are poor liver function, variceal bleeding, low ascitic fluid protein levels, prior SBP and hospitalization [1,2]. Severity of infection is also higher in patients with cirrhosis who are more likely to die from sepsis than individuals without cirrhosis. Bacterial infection increases 3.75 fold the probability of death of patients with decompensated cirrhosis, reaching 30% at 1 month and 63% at 1-year (Fig. 1) [5,6].

Enterobacteriaceae and non-enterococcal streptococci cause the majority of spontaneous infections in cirrhosis. As a consequence, β-lactams and quinolones have been widely used in their treatment and prevention [1,2]. This feature and the increasing level of invasiveness to which patients with cirrhosis are currently submitted have induced important changes in the epidemiology of bacterial infections in cirrhosis. Spontaneous and secondary infections caused by non-classical pathogens or multidrug resistant (MR) bacteria are nowadays increasingly reported in this population [1,4].

Infections by multiresistant bacteria in the general population and cirrhosis

MR bacteria are pathogens resistant to 3 or more of the main antibiotic families, including β-lactams [7]. The main MR bacteria are extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL), non-fermentable gram-negative bacilli such as *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia* or *Acinetobacter baumanii*, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-susceptible or resistant enterococci (VSE, VRE). Infections caused by these bacteria have increased in the general population mainly due to the dispersion of the so-called high-risk clones not only in the hospitals but also in the community. These clones are specific bacteria able to acquire several resistance mechanisms and virulence determinants. Moreover, they efficiently colonize different human niches, including the gastrointestinal tract [8].

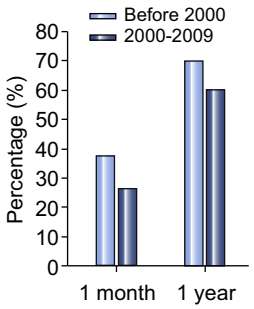

Fig. 1. Mortality rate caused by bacterial infections in cirrhosis in the last decades. 1-month and 1-year mortality rates were higher before than after 2000, although differences were not statistically significant. Modified from [6].

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