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Bacterial resistance in cirrhotic patients: An emerging reality

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Bacterial infections are frequent and represent a relevant issue in cirrhotic patients. Susceptibility to bacterial infections is increased in cirrhotic patients for multiple reasons. These patients show immunological dysfunctions, due to the so called "immune paralysis", and an impairment in the reticuloendothelial system function resulting in a reduced ability of the liver to contrast the bacterial load from the intestine [1]. Moreover, they are predisposed to an increase in the rate and severity of "gut bacterial translocation" (GBT), defined as the migration of viable microorganisms and microbial products from the gut to mesenteric lymph nodes and other extra intestinal sites. GBT appears to be related mainly to three pathophysiological mechanisms: intestinal bacterial overgrowth, due to decreased small bowel motility, increased intestinal permeability, proportional to the degree of portal hypertension, and impaired local and systemic immunity [2]. All these factors are particularly evident in decompensated patients and GBT is reported to occur in 30–40% of patients with ascites.

Infections are particularly harmful in advanced liver disease. Decompensated cirrhotic patients suffering from a bacterial infection are more prone to develop a systemic inflammatory response syndrome [3]. In fact, hepatic dysfunction brings to a decreased cytokine clearance capacity leading to a "storm of pro-inflammatory mediators" (interleukin-1, interleukin-6, tumor necrosis factor alpha), which causes the conversion of a response normally useful against bacteria into a damaging inflammation. This may induce an increased demand of acute-phase-reaction proteins and an "exhaustion" of the hepatocytes reserve function and further aggravation of the splanchnic vasodilatation [4,5]. In cirrhotic patients sepsis may induce complications such as renal failure and hepatic encephalopathy. In addition, the accelerated deterioration of liver function may lead to the so called "acute on chronic liver failure". Severe sepsis may also cause the development of "multiple organ failure" defined by at least two of the following: renal failure, acute lung injury or acute respiratory distress syndrome, coagulopathy, brain failure, sepsis-induced adrenal insufficiency and shock [6].

Bacterial infections and sepsis are one of the main causes of death in hospitalized patients with chronic liver disease and seem to increase the 1-year mortality also in those discharged after the resolution of the infectious episode [7].

According to the hypothesis that the main mechanism in the onset of infection is the GBT, the pathogens more frequently isolated in cirrhotic patients are Gram-negative ones. Gram-positive bacteria are also found mainly in nosocomial infections, due to the large number of diagnostic and therapeutic invasive procedures which are needed in hospitalized patient [8].

A relevant issue emerging in recent years is the change in the epidemiological pattern of infections observed in cirrhotic patients. In the course of their illness, cirrhotic patients are frequently in need of day hospital care, recurrent hospitalization, or admission in intensive care units. The classification of infections in Community Acquired (CA) and Nosocomial (NA) has been recently recognized to be inadequate in the general population, and the term Health Care Related (HCR) infections, has been introduced to define a new epidemiological category [9]. According to the proposal of Friedman and co-workers, an infection is defined HCR if the diagnosis is made within 48 h of hospitalization in a patient with a recent contact with the Health Care system (i.e. when the patient has attended a hospital or a hemodialysis clinic, or has received intravenous chemotherapy during the 30 days before infection; or was hospitalized for at least 2 days, or had undergone surgery during the 3 months before infection; or has resided in a nursing home or a long-term care facility) [9]. HCR infections are associated with an increased prevalence of antibiotic resistant bacteria, have a worse prognosis and need to be treated according to different guidelines [10]. Recent data underline the need to separately consider this epidemiological group also in cirrhotic patients [11].

Antibiotic resistance in cirrhotic patients has been initially feared due to the chronic use of quinolones in secondary prophylaxis for spontaneous bacterial peritonitis (SBP). However, it has been clarified that quinolones-resistant strains are still sensitive to third generation cephalosporins (recommended first line therapy for SBP) [8,12]. A more relevant emerging problem in cirrhotic patients is the increased prevalence of multidrug resistant (MDR) bacteria, frequently isolated in the NA and HCR groups. The definition of MDR pathogen includes methicillin-resistant *Staphylococcus aureus* (MRSA), *Acinetobacter baumannii*, extended-spectrum beta-lactamases-producing Gram-negative strains (ESBL), and any bacterial isolate resistant to at least three classes of antimicrobial agents [13]. In our experience,

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consecutive positive isolates from cirrhotic patients admitted in our unit, which is a tertiary referral center, in the last year evidenced an increase in MDR pathogens mainly in HCR and NA infections (33% in CA, 50% in NA and 80% in HCR; $p = 0.0000$) [14].

The more important types of infection in cirrhosis are urinary tract infections, SBP, pneumonia and spontaneous bacteraemia [3,11,15]. SBP is the most common infection in some series and represents one of the most studied infections because of the severe prognosis and high rate of recurrence [8]. The outcome of PBS has improved significantly over the past 30 years thanks to an early diagnosis, and, especially, to the use of a more appropriate antibiotic therapy as suggested in current guidelines [16].

The paper of Ariza and co-workers [17] provides interesting data about the prevalence of third generation cephalosporin resistance (MR-Cef) in cirrhotic patients with a diagnosis of SBP. The study is retrospective and analyzes 246 consecutive episodes of culture-positive SBP occurring in 200 cirrhotic patients in a single Spanish center between 2001 and 2009. As the current guidelines suggest the use of third generation cephalosporins for the first line empirical treatment of SBP, the authors evaluated the appropriateness of this regimen and the predictors of failure. The impact on mortality was also investigated. Some studies have already drawn their attention on the reduced efficacy of this therapy in recent years [18,19].

The rate of MR-Cef was low in the group with CA infections (7.1%), intermediate in the HCR (21.1%), and high in the NA (40.9%), confirming the link between bacterial resistance and the epidemiology of infections. Previous use of cephalosporins, upper gastrointestinal bleeding, nosocomial acquisition and diabetes were found to be independent predictors of MR-Cef. Furthermore, the authors found a close association between the days of contact with the health care system and the likelihood of MR-Cef. A further important message coming from the study of Ariza and co-workers is that, besides the other factors related to the host condition, an inadequate empirical treatment of the infection was an independent predictor of 30-day mortality.

Some shortcomings of the study need to be underlined. Due to the retrospective design, the therapy was not properly standardized in all patients; in particular, ceftriaxone was utilized at a dose of 1 g/24 h for 5–10 days while the dosage recommended in guidelines is cefotaxime 4 g/day [13,20] corresponding to at least 2 g/day of ceftriaxone. Therefore, some patients could have been undertreated, causing a recurrence of SBP with MR-Cef strains. It is also interesting to note that 39 patients, all in severe clinical conditions, based on the physician decision, received piperacillin–tazobactam or imipenem as first line empirical therapy, determining a sort of "violation of the clinical protocol". All these patients were classified as suffering from an HCR or a NA infection and, in 36%, the cultures eventually resulted in MR-Cef strains. In the statistical evaluation, the authors had to face this bias by excluding some of these patients from the analysis of mortality.

This study underlines the need of prospective studies in cirrhotic patients with bacterial infections, taking care of the different epidemiological conditions of bacterial acquisition. Different antibiotic protocols need to be compared for their efficacy and costs in different patients' settings to define, based on the evidence, which is the most appropriate empiric antibiotic therapy according to their risk factors. Therapeutic trials need also to be extended to culture-negative SBP which frequently occurs in cirrhotic patients, and to infections located at different sites. Patients with long and multiple contact with the healthcare system are at high risk of infections sustained by multi-drug resistant strains and a change in the policy for the first line empirical antibiotic therapies in these patients is warranted.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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