Editorial

The role of Gram-positive and drug-resistant bacteria in bacterial infections in cirrhosis

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Bacterial infections are a frequent complication of cirrhosis, with a 5-fold higher incidence than that reported in the general population (1,2). Infections in cirrhosis are life-threatening as they increased mortality fourfold; Short-term mortality is 30% at one month and about 60% at 12 months (2). Despite advances in the understanding of the pathogenetic mechanisms and management, bacterial infections are associated with the development of complications leading to hospitalization of cirrhotic patients in common wards or in intensive care units (ICUs) (2). Types of bacterial infections in cirrhosis are spontaneous bacterial peritonitis (SBP), pneumonia, urinary tract infections, skin or soft tissue infections and spontaneous or secondary bacteremia (1,3). SBP and spontaneous bacteremia are characteristic for patients with decompensated liver cirrhosis and are originated from the intestinal tract (endogenous infections) (3). The pathogenetic process leading to the development of SBP or spontaneous bacteremia is the traverse of viable microorganisms from the intestinal tract through the gut wall to the mesenteric lymph nodes, passing to the systemic circulation (development of spontaneous bacteremia) and entrance to the peritoneal fluid through the liver (development of SBP). This mechanism was first depicted in 1979 and was named bacterial translocation (4). The components that enhance bacterial translocation in cirrhosis are disturbed bacterial overgrowth, increased gut permeability and impaired gut-associated-lymphatic tissue (5).

Gram-negative usually Enterobacteriaceae SBP are the most prevalent bacteria causing SBP (6). Since 1990, a change in epidemiology of type of bacteria associated with infections in cirrhosis was reported. Initially, quinolone-resistant bacteria were observed due to wide use of this family of antibiotics for SBP prophylaxis (7). This phenomenon was followed by a growing rate of infections with Gram-positive bacteria (cocci) (8-10). In a Spanish study of 405 patients with cirrhosis, Gram-positive bacteria were isolated in 53% patients overall and in 59% of nosocomial infections (1). Infections by Gram-positive bacteria were associated with hospital environment and interventional techniques such as ligation of esophageal varices, insertion of central catheters and chemoembolization (1,9). The emergence of vancomycin-resistant enterococci (VRE) strains was firstly observed in US hospitals and Liver Centers and was attributed to the avoparcin enrichment of the animal food and the transmission to humans through food chain (11). It was reported that VRE distribution varied globally from less than 1% in Finland, France, Iceland and Sweden to 40–50% in Latin America or Ireland and >70% in USA (11). Recently, Piano *et al.* in a worldwide multicenter study including 1,302 patients with cirrhosis and bacterial or fungal infections found that the global prevalence of Gram-positive bacteria was 38% and differed in geographical areas, being higher in Europe (43%) and lower in Asia (28%) (12).

The most important shift in epidemiology is the growing incidence of bacterial infections induced by multi-drug-resistant organisms (MDRO). The MDRO are classified as multidrug-resistant (MDR), extensively-drug-resistant (XDR) or pandrug-resistant (13). Even though extended-spectrum-b-lactamase-producing

(ESBL) Enterobacteriaceae have been described since the 80's decade, ESBL-related infections were not at that time detected in cirrhosis. Hence, third-generation cephalosporins were recommended as the empirical treatment of choice for decades (14). In the beginning of 2000, an increasing prevalence of a strain of *E.coli* that produced a different class of ESBL and the pandemic spread of *E.coli* ST131, which was also isolated from cirrhotic patients was described (11). The extensive use of carbapenems that are the preferred drug for ESBL-producing Enterobacteriaceae resulted in the emergence and selection of the carbapenem-resistant Enterobacteriaceae (XDR strains) and especially the carbapenem-resistant *K. pneumonia*, which disseminated globally (15). In Spain, an increasing rate of MDRO was reported from <10% over 1998–2000 (1) to 23% over 2010–2011 period (3). In an Italian tertiary Center, the MDRO accounted for 51% of the isolates during 2008–2013 (16) and in Greece, during two study periods 2008–2011 (10) and 2012–2014 (17), the MDR/XDR rate accounted for about 30%. Recently, Piano *et al.* demonstrated that the frequency of MDR and XDR worldwide were 35% and 8%, respectively, and the highest frequency was encountered in Asia (50% and 16%, respectively) (12).

Risk factors for infections from MDRO were advanced liver disease, use of systemic antibiotics for at least five days during the previous three month-period, undergoing invasive procedures or exposure to health-care environment during the previous 30-day-period (12,16) and use of antibiotic prophylaxis (16).

Infections due to MDRO are associated with high rates of treatment failure, acute renal disease, acute-on chronic liver failure (ACLF), sever sepsis or septic shock and increase short-term mortality due to failure of antibiotic strategies (15,18). The remarkable role of XDR (but not MDR) in adversely affecting outcome was previously reported (17). More recently, a large multicenter study stressed that type of infection such as SBP and pneumonia and infections induced by XDR bacteria were more often associated with development of ACLF (19).

Empirical therapy with antibiotics should be initiated as soon as infection was suspected in order to treat the usually isolated pathogens and maximize the probability of survival. Due to increasing frequency of Gram positive and MDRO, third-generation cephalosporins are inappropriate for the management of 18–49% of the SBP cases and this is more evident in health-care associated (HCA) and nosocomial infections (11). Hence, EASL in 2014 (20) and 2018 (21) modified the therapeutic strategies for bacterial infections in cirrhosis and recommended that the selection of the optimal initial antibiotic treatment should be based on local epidemiological data about antibiotic resistance and mode of acquisition of infection [nosocomial/HCA or community-acquired (CA)]. Moreover, severity of infection namely sepsis or septic shock with or without ACLF should be considered in severely ill patients where accurate, empirical treatment is life-saving (15).

Third-generation cephalosporins or piperacillin/tazobactam are the treatment of choice in CA infections and carbapenems alone or in combination with daptomycin, vancomycin or linezolide are recommended for HCA or nococomial SBP especially in areas where MDRO are highly endemic and/or in case of sepsis (21). It is worth noting that carbapenem-resistant strains of Enterobacteriacaea are not susceptible to carbapenems and in that case limited-spectrum albeit more toxic antibiotics are needed (20).

Khoury *et al.* (22) in a retrospective study from a single tertiary Center illustrated a high rate of Gram-positive bacteria in SBP patient. Remarkably, the incidence of Gram-positive bacteria was increasing year over year during the 5-year study. Gram-positive infections were associated with systemic antibiotic use during the previous 30 days and a lower Sequential Organ Failure Assessment score. Only 4 MDR were observed {*E. Coli* ESBL [1], VRE *E. faecium* [2] and *S. aureus* MRSA [1]}. Authors showed that 44.4% and 66.7% of isolated bacteria were susceptible to fluoroquinolones and sulfamethoxazole/trimethoprime, respectively and 88.9% to ceftriaxone. All Staphylococcus and Streptococcus spp were susceptible to vancomycin and only two E. faecium isolates were VRE but susceptible to linezolide. Even if the frequency of MDRO in SBP was low in their institution, the majority was isolated from patients with hospital-acquired infection.

This study emphasizes the importance of treatment individualization according to local epidemiological data and the type of acquisition of infection (HCA/nosocomial or CA) and confirms that there are regional differences of microbiological and resistance patterns in bacterial infections in cirrhosis.

In conclusion, it is of great importance for the clinicians to know the local/regional bacterial epidemiology and antimicrobial susceptibility pattern in order to make a more rational use of antibiotics. A more complex approach including antibiotic combinations and de-escalation of therapy when culture is available, is the optimal approach in order to restrict overuse and select the optimal antibiotic treatment.

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