Spontaneous bacteremia and spontaneous bacterial peritonitis in cirrhosis: two infections but similar outcomes?

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Bacterial infections are an important reason for progressive liver failure, development of liver-related complications, end-organ damage and death in patients with cirrhosis [1]. Infections remain the most common reason for readmissions and increased health-care costs in these patients [1]. Almost, 25–35% of cirrhotics have infections either at admission or develop during hospitalization. Cirrhotics have a defective innate and adaptive immune system with a parallel state of persistent inflammation referred to as the cirrhosis-associated immune dysfunction syndrome (CAIDS) [2]. A myriad of defects such as reduced expression of monocyte HLA-DR expression, decreased ability to produce tumor necrosis factor (TNF α), reduced number of immune active cells such as neutrophils, helper and cytotoxic T-cells, plasmacytoid, and myeloid dendritic cells, reduced phagocytic activity of neutrophils as well as a genetic predisposition with microsatellite polymorphisms in the Toll-like receptor and nucleotide-binding oligomerization domain-containing protein (NOD2) increase the risk of infections in these patients. For the same reason, infections with multidrug-resistant organisms are also more common and associated with increased fatality in cirrhotics compared to the general population [2, 3]. Amongst all infections, spontaneous bacterial peritonitis (SBP) and urinary tract infections are the most frequent followed by skin and soft tissue infections, pneumonia, and bacteremia. SBP is the most common infection causing renal impairment in cirrhotics [2, 3]. However, the incidence and outcome of renal dysfunction have not been particularly addressed for infections other than SBP.

In this issue of *Hepatology International*, Marciano and colleagues did a study comparing the incidence and outcomes of acute kidney injury and mortality in patients with spontaneous bacteremia (SB) and SBP in a tertiary hospital

at Argentina [4]. Patients with SB did not have evidence of infection at any other body site and patients with an index episode of SB and SBP were included for analysis. These patients were subsequently followed for 90 days from the day of infection diagnosis or until liver transplant or death. The antibiotic protocol was based on the acquisition of infection (community, health-care, nosocomial) with use of colistin in high-risk patients (colonization with carbapenemase-producing Enterobacteriaceae, prior carbapenem use or antibiotic exposure). Intravenous albumin was administered to patients with SBP based on standard guidelines. Acute kidney injury (AKI) was defined as an increase in serum creatinine ≥ 0.3 mg/dL or $\geq 50\%$ in two measurements 48 h apart. Additionally, a peak value of serum creatinine of 1.5 mg/dL was considered essential for defining AKI in the included patients. Seventy-one patients with SB were enrolled while only 55 randomly selected patients with SBP were included in the study. The cause of cirrhosis in majority of these patients was either alcohol or chronic viral hepatitis. Systemic inflammatory response syndrome was documented in only 56% and the median MELD score was 20 (IQR 16–26). A comparable cumulative incidence of AKI and mortality both on day 28 and day 90 was noted in patients with SB and SBP despite significant difference in the baseline MELD score and predominance of multidrug-resistant infections in patients with SBP compared to those with SB. The authors nicely adjusted for these factors in the multivariate analysis. Further, in patients with SB, age and MELD score were identified as risk factors for AKI and serum sodium and MELD predicted mortality.

Marciano and colleagues should be complemented of carefully studying a select group of patients with SB with respect to development of AKI and outcomes and comparing this to SBP which is the most frequently studied infection in cirrhotic. Bacterial infections remain the main drivers for renal dysfunction in patients with cirrhosis [3]. In fact, development of renal dysfunction is one of the most powerful predictor of death in patients with SBP and

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develops despite resolution of infection in almost one-third of these patients [1–3]. Current guidelines clearly recommend the use of intravenous albumin in prevention of renal failure in patients with SBP, which reduces the incidence of renal impairment from 33 to 10% [5]. However, the same has not been established for infections other than SBP. Considering a similar outcome of AKI, it would have been worthwhile to study the role of intravenous albumin in prevention of AKI in patients with SB. Previous studies in patients with SBP have suggested an excessive systemic inflammatory response syndrome (SIRS) of the host and hemodynamic alterations particularly circulatory dysfunction as important predictors of AKI [6]. Interestingly, authors did not find the presence of SIRS to predict AKI development in either SB or SBP and details of circulatory dysfunction were not analysed in the current study. In a previous study by Fernandez et al. [7] evaluating AKI in the context of non-SBP infections, degree of liver impairment, severity of AKI as well as the type of infection were recognized as important predictors of death. Further, they observed marked differences in the prevalence of AKI in different infections with use of different definitions for AKI. In the current study, the authors used a peak serum creatinine of 1.5 mg/dL to define AKI; therefore, it is quite likely that patients with milder degree of renal impairment would have been missed. Further the details of type of AKI (prerenal, hepatorenal or acute tubular necrosis) and outcomes (resolution or progression) were not analysed in the current investigation. Intriguingly, apart from severe liver disease the adequacy of initial antibiotic therapy as well as presence of multidrug-resistant organisms (MDR) were not found to be predictors of either AKI or mortality in patients with SB. It is quite possible that patients who had multidrug-resistant (MDR) organisms also had more severe liver disease. In a previous study by Alexopoulou et al. in patients with SBP, severity of liver disease as suggested by higher MELD score, a health-care acquisition and prior fluoroquinolone prophylaxis were reported to be the independent predictors of MDR isolates in SBP [8]. In the same context, with the recent change in epidemiology towards a more fearful spectre of MDR infections as a new therapeutic challenge in patients with cirrhosis, there has been an increase in the use of drugs such as colistin as empirical therapy which clearly have nephrotoxicity as a major dose-limiting adverse effect when administered to patients with severe sepsis or septic shock [9]. It would have been interesting to evaluate the impact of colistin on AKI outcomes in patients with SB and SBP. The authors did not analyse the incidence and outcomes of AKI with use of colistin as an empirical therapy in their study.

The main limitations of the study by Marciano et al. remain the retrospective study design, an extremely small sample size and selection of patients with SBP as a random

sample for analysis. Even though the authors did show an acceptable power of the study, the number of patients enrolled is too small to assess the impact of relevant factors both on the risk of AKI development and mortality. Furthermore, details on severity of sepsis and hemodynamic impairment, presence of gastrointestinal bleeding, hepatic encephalopathy, and intensive care unit admission which are factors known to impact AKI and its outcomes in patients with SBP have been ignored. The authors have not provided information on infection resolution as well as the course, severity and type of AKI and the cause of death which would have added more weight to the interesting observations of their study.

In summary, the work by Marciano and colleagues shows similar short and midterm rates of AKI and mortality in patients with SB when compared to patients with SBP; however, this interesting observation would require validation in future studies with larger sample size. The role of albumin is another intriguing piece in the puzzle of non-SBP AKI [10, 11]. It would be worthwhile to investigate whether albumin may have beneficial effects specifically in the subset of patients with SB-related AKI. Further, considering a paradigm shift in MDR isolates with growing bacterial resistance against the conventional antibiotics, novel strategies beyond antibiotics targeting the dysregulated immune system are an unmet need in cirrhotics to prevent renal dysfunction, end-organ damage and death.

Compliance with ethical standards

Conflict of interest Rakhi Maiwall have declared no conflict of interest.

Research involving human participants and animals This article does not contain any studies with human or animal subjects.

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