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INVITED COMMENTARY

Spontaneous Bacterial Peritonitis: The Bug Matters

Sunny Sandhu[1,2] · **Binu V. John**[1,2]

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Bacterial infections contribute to the morbidity and mortality of patients with cirrhosis, with infection rates up to 34% in hospitalized patients [1]. Spontaneous bacterial peritonitis (SBP) is defined as bacterial infection of the ascitic fluid in the absence of a proven or suspected intra-abdominal source of infection. Despite improvement in treatments, SBP remains associated with a mortality as high as 20%, as well as high recurrence rates after initial infection [2]. Its pathogenesis involves bacterial translocation, likely through specialized epithelial M cells located in the intestinal Peyer's patches overlying specialized subepithelial mesenteric lymphatic tissue, with bacteria entering the lymphatic circulation and ultimately, the bloodstream in the setting of impaired host defenses and compromised immune function [3].

The diagnosis of SBP is confirmed by an ascitic fluid absolute polymorphonuclear (PMN) count of > 250 cells/mm^3. Due to the widely variable presentations of SBP, including a high number of asymptomatic patients, diagnosis can be difficult. Clinicians must therefore maintain a low threshold for prompt diagnosis. Patients with cirrhosis and ascites hospitalized for any reason should have a diagnostic paracentesis performed during hospitalization, even in the absence of overt signs of infection. Ascitic fluid should also be simultaneously sent for culture, with direct inoculation of ascitic fluid into culture bottles at the bedside [4, 5]. Since SBP is associated with bacteremia, simultaneous blood cultures should also be obtained.

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✉ Binu V. John
Binu.John@miami.edu

[1] Division of Gastroenterology and Hepatology, University of Miami Miller School of Medicine, Miami VA Medical System, Miami, FL 33125, USA

[2] Division of Digestive Health and Liver Diseases, University of Miami Miller School of Medicine, Miami, FL, USA

SBP is usually a monomicrobial infection caused by enteric-type bacteria including *Escherichia coli*, *Klebsiella pneumoniæ*, and *Enterococcus fæcalis*. Therefore, empiric treatment of SBP even in the absence of culture-confirmed organisms has traditionally been recommended with third-generation cephalosporins, such as cefotaxime or ceftriaxone [6]. Nevertheless, the recent literature has reported an emerging global increase in both gram positive and multidrug resistant organism (MDRO) infections in patients with cirrhosis, in total contributing to approximately one third of all infections [6, 7]. Therefore, initial empiric treatment in those with risk factors for MDROs (such as recent antibiotic use, hospitalization, or critically illness), warrants the consideration of treatment with broad-spectrum antibiotics such as piperacillin/tazobactam and vancomycin. Since empiric carbapenem treatment decreases in-hospital mortality in patients who are critically ill, it should be considered in such cases [8].

In regards to SBP prophylaxis, there are indications for both primary and secondary prophylaxis. Primary prophylaxis decreases not only the incidence of SBP, but also delays the development of hepatorenal syndrome and improves overall survival in a subset of patients with cirrhosis. Thus, antibiotic prophylaxis is currently recommended in patients with cirrhosis along with low-protein ascites (defined as ascites protein < 1.5 g/dL) along with advanced liver disease (Child–Pugh Score ≥ 9 and with serum total bilirubin level ≥ 3 mg/dL) or impaired renal function (serum creatinine ≥ 1.2 mg/dL, blood urea nitrogen ≥ 25 mg/dL, or serum sodium ≤ 130 mEq/L) [9]. Patients with cirrhosis and upper gastrointestinal hemorrhage should also receive short-term antibiotic prophylaxis with IV ceftriaxone for 5–7 days, and patients with prior SBP should receive long-term secondary prophylaxis [3, 10].

Despite multiple studies examining outcomes of patients with SBP, limited data exists addressing the outcomes of SBP due to specific microorganisms. Though the presence of MDRO is an independent predictor of mortality in patients with SBP, little is known regarding outcomes due to individual culprit organisms other than

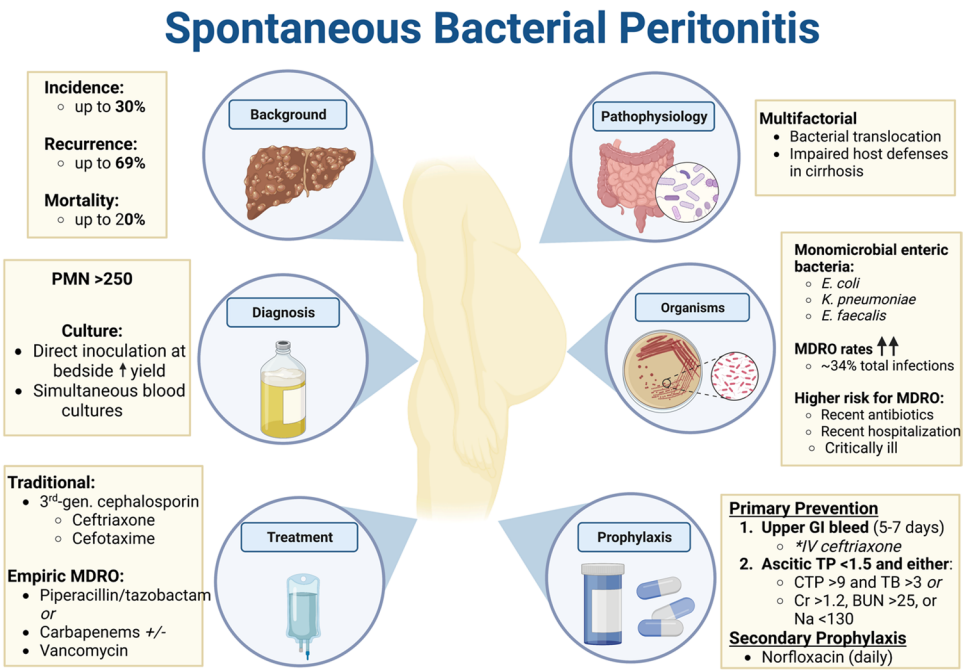

Fig. 1 Pathophysiology, diagnosis, and treatment of spontaneous bacterial peritonitis

MDRO [11]. In this issue of *Digestive Diseases and Sciences*, Furey et. al describe a retrospective study examining the outcomes of 267 participants with cirrhosis and SBP between 2016 and 2021, reporting outcomes stratified by the causative organism isolated from cultures [12]. The primary outcome was morbid complications of SBP progression, defined as death or liver transplantation within 1 month of paracentesis.

Since the causative organism in 88/267 cases was identified by culture, this study is one of the largest published reports of culture-positive SBP patients. The most common organisms identified were *E. coli* (33%), *Streptococcus* spp. (15%), *Klebsiella* spp. (13%), *Enterococcus* spp. (13%), *Staphylococcus* spp. (9%), and others (18%). This data agree with published epidemiologic data in regard to the specific pathogens that are typically implicated in SBP. It also highlights ongoing difficulties with obtaining positive cultures from ascitic fluid, since only 33% of patients in this study had a successful culture of the causative organism.

Interestingly, of those successfully cultured, a 41% of organisms were MDR, defined as resistance to at least 3 antimicrobial drug classes. Of those that were MDR, 50% were extensively drug-resistant (defined as an organism only sensitive to one or two antimicrobial classes). These frequencies are significantly higher than the incidences of MDRO reported from Europe, which was < 15% of participants with SBP [7]. When the authors stratified outcomes by organism type, they found that overall SBP progression within 1 month occurred in 91% for *Klebsiella* spp., 59% for *E. coli*, and 16% for *Streptococcus* spp. When also adjusted for confounders such as MELD-Na and MDRO status, the risk of SBP progression trended higher for *Klebsiella* (adjusted Hazard Ratio [aHR] 2.07, 95% CI 0.98–4.24; p-value = 0.06) compared with the other organisms. Interestingly, SBP associated with *Streptococcus* actually trended toward a decreased risk for SBP progression (aHR 0.28, 95% CI 0.06–1.21; p-value = 0.09) that did not meet statistical significance.

The findings of an association of specific pathogens with clinical outcomes of SBP are novel. The pathophysiology of poor outcomes related to *Klebsiella* may be due to a combination of altered gut microbiota as well as a potential component of underlying pathogenic and virulence factors related to this genus. Although some genetic studies have shown increasing hypervirulence factors such as regulator of mucoid phenotype A (*rmpA*), K2A, and mucoviscosity-associated gene A (*magA*), larger genetic studies may help to identify these organisms with antibiotic resistant genes, potentially useful information for informing successful treatment approaches in the future [13].

We congratulate the authors of this study, which contributes meaningful data to the literature from a relatively higher number of culture-positive SBP patients. Although this study was one of the largest studying patients with culture-positive SBP, the authors mentioned in their limitations that only 88 total patients were studied and that a larger multicenter study done may help support and further investigate these findings. If MDRO are truly becoming more prevalent on a national level throughout the United States, these findings may support a lower threshold for initiation of broad-spectrum antibiotics. Furthermore, confirmation of these data might suggest more aggressive treatment and

monitoring of patients infected with the species associated with inferior outcomes. Future studies are warranted to help elucidate the role of various organisms and the role of their associated pathogenic and virulence factors in the outcomes of patients with SBP.

Acknowledgments Figure 1 created with BioRender.com.

Declarations

Conflict of interest None of the authors have personal or financial conflicts of interests to declare concerning this publication.

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