ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Nancy S. Reau, MD

Prophylaxis for Spontaneous Bacterial Peritonitis

Richard K. Sterling, MD, MSc
VCU Hepatology Professor of Medicine
Chief, Section of Hepatology
Chief Clinical Officer, Stravitz-Sanyal Institute for Liver Disease and Metabolic Health
Assistant Chair for Research, Department of Medicine
Virginia Commonwealth University
Richmond, Virginia

G&H What is spontaneous bacterial peritonitis, and what are its potential consequences?

RS Spontaneous bacterial peritonitis (SBP) is defined as an infection of ascitic fluid without an intra-abdominal source (such as a perforated bowel) usually in a patient with cirrhosis. SBP can present with or without abdominal pain, fever, increased white cell count, or worsening hepatic encephalopathy (HE) or acute kidney injury (AKI). In fact, up to one-third of patients with SBP can present with no abdominal symptoms or only with HE or AKI. SBP is diagnosed by either a positive culture of the ascitic fluid or having at least 250 polymorphonuclear cells in the fluid even if the culture is negative. Once identified, treatment includes intravenous antibiotics and albumin. If left untreated (or unrecognized), potential consequences from SBP can result in increased morbidity (including AKI and/or sepsis) and mortality.

G&H In which cirrhotic patients has primary and secondary prophylaxis for SBP traditionally been recommended, and what has this prophylaxis consisted of?

RS Primary prophylaxis measures in patients with decompensated cirrhosis include controlling the ascites with diuretics and a low-sodium diet, identifying and treating infection elsewhere (eg, in the blood, urinary tract) before it can spread to the ascitic fluid, giving intravenous antibiotics when patients have upper gastrointestinal bleeding, and minimizing the use of proton pump inhibitors. Current guidelines from the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) recommend considering primary prophylaxis for patients with ascites who have low total protein (<1.5 g/dL) or who also have severe liver or renal dysfunction. Because the risk of having another episode of SBP has been reported to be as high as 70% within the next year, especially in patients with low total protein ascites, increased bilirubin, or increased international normalized ratio, secondary prophylaxis has been recommended. Secondary prophylaxis consists of taking an oral antibiotic to cover the most likely organisms to prevent another episode of SBP.

G&H What are the potential harms or disadvantages of using prophylaxis for this condition?

RS With the widespread use of antibiotics for other infections (real or not), there has been an increase in antibiotic-resistant organisms. One concern of primary or secondary SBP prophylaxis is the development of resistant organisms that would not respond to current regimens, making treatment of SBP increasingly difficult. The emergence of drug-resistant organisms from overuse of antibiotics has become a major concern in the medical community.

G&H How strong is the evidence supporting the use of primary and secondary prophylaxis for SBP?

RS With the emergence of antibiotic resistance and the shift of causative organisms, there have been calls to re-examine the use of SBP prophylaxis. In a recent study by Bajaj and colleagues using the North American

Consortium for the Study of End-Stage Liver Disease, 154 patients were propensity score–matched with controls. Patients receiving primary prophylaxis were more likely to experience admission systemic inflammatory response syndrome (*P*=.02), with higher intensive care unit admissions (31% vs 21%; *P*=.05) and inpatient mortality (19% vs 9%; *P*=.01) than those receiving secondary prophylaxis. Compared with primary prophylaxis, patients receiving secondary prophylaxis experienced higher total (22% vs 10%; *P*=.004), readmission (16% vs 9%; *P*=.03), and nosocomial (6% vs 0.5%; *P*=.01) SBP rates with predominant Gram-negative organisms. At 90 days, patients receiving primary prophylaxis had a higher mortality (35% vs 22%; *P*=.02) and AKI incidence (48% vs 30%; *P*=.04) compared with those receiving secondary prophylaxis. As a result, the Veterans Affairs (VA) health system no longer recommends primary SBP prophylaxis.

> Using multivariate analysis controlling for race, ethnicity, and renal function, the risk of developing recurrent SBP was higher in patients who received prophylaxis compared with those who did not ....

In the past, the data seemed very strong for secondary prophylaxis. Several meta-analyses have shown a reduction in morbidity and mortality with secondary prophylaxis for SBP. However, like with primary prophylaxis, there have been calls recently to re-examine the use of secondary prophylaxis.

G&H Could you discuss the design and findings of the recent study you and your colleagues conducted that compared secondary SBP prophylaxis with no prophylaxis?

RS Results from this study were recently published in the *American Journal of Gastroenterology* by Silvey and colleagues from Virginia Commonwealth University. The aim of this study was to re-assess the risk-benefit ratio of secondary prophylaxis for SBP. Using validated International Classification of Diseases–9 and –10 codes, we analyzed data from 2 cohorts, the VA Corporate Data Warehouse and the non-VA national TriNetX database, of patients who survived their first episode of SBP from 2009 to 2019. We then compared the outcomes of patients who received secondary prophylaxis with those who did not. Among the 4673 VA patients and 6708 TriNetX patients, secondary prophylaxis was prescribed in 54% and 49%, respectively. Using multivariate analysis controlling for race, ethnicity, and renal function, the risk of developing recurrent SBP was higher in patients who received prophylaxis compared with those who did not (hazard ratio, 1.63; 95% CI, 1.36-1.91; *P*<.001 in the VA cohort and hazard ratio, 1.68; 95% CI, 1.33-1.80; *P*<.001 in the TriNetX cohort). Secondary prophylaxis was also associated with higher fluoroquinolone resistance (odds ratio, 4.32; 95% CI, 1.36-15.83; *P*=.03) in the VA cohort. Importantly, the results remained consistent at 6-month and 2-year time points. However, secondary prophylaxis was not associated with all-cause mortality. We concluded that because the rate of SBP recurrence actually increased by 63% to 68% with secondary prophylaxis, its use should be reconsidered.

G&H What might explain these findings?

RS It is first important to note that despite recommendations in both the AASLD and EASL guidelines, only approximately half of patients surviving their first episode of SBP received secondary prophylaxis. As we pointed out in our study, this may have been owing to both provider and health system challenges, patient adherence, health literacy, fear of side effects, and costs of the antibiotics. One reason the rate of secondary SBP was higher in patients receiving prophylaxis is the lower rate of susceptibility of the organisms to commonly used oral antibiotics. In the VA cohort, 84% were receiving a fluoroquinolone (92% were on ciprofloxacin) whereas 16% were receiving trimethoprim/sulfamethoxazole. Studies in patients on secondary SBP prophylaxis have shown higher rates of Gram-positive organisms, microbial virulence, and changes in the effectiveness of antibiotics. These changes may increase over time the longer secondary prophylaxis is used.

G&H What limitations should be kept in mind when viewing these study findings?

RS This study was limited by its retrospective design and database restrictions. Furthermore, while prior studies on the VA Corporate Data Warehouse have been validated, there may have been misclassification from miscoding

of diagnosis or antibiotic use, especially in the TriNetX database. However, because results were similar among the 2 cohorts, that may not have been a significant factor.

G&H Do these findings apply to all patients with portal hypertension and ascites?

RS It should be noted that these data should not be extrapolated to individuals with ascites without cirrhosis such as those with noncirrhotic portal hypertension. The risk of developing SBP is much lower in these patients.

> Given these data, I think the use of primary and secondary SBP prophylaxis should be re-examined.

Similarly, those with right heart failure or hepatic venous outflow obstruction (Budd-Chiari syndrome) who have high protein ascites are at low risk for SBP.

Additionally, some providers have questioned whether the decision to use SBP prophylaxis should be affected by whether the patient is a liver transplant candidate. However, my colleagues and I do not differ our approach in managing most complications of cirrhosis based on liver transplant candidacy unless the patient is moving toward palliative care or hospice.

G&H What are the next steps in research in this area?

RS Given these data, I think the use of primary and secondary SBP prophylaxis should be re-examined. Now that these recent retrospective studies in both primary and secondary prophylaxis have shown worse outcomes, prospective data on SBP prevention or recurrence with or without primary or secondary prophylaxis with antibiotic resistance testing are needed. Additionally, if providers are seeing increased resistant bacteria to currently used antibiotics, they need to know what other options are available, including changing the fecal microbiome or modulating the immune system.

Disclosures

Dr Sterling has no relevant conflicts of interest to disclose.

Suggested Reading

Badal BD, Silvey S, Dragilev L, et al. Primary prophylaxis for spontaneous bacterial peritonitis is linked to antibiotic resistance in the Veterans Health Administration. *Hepatology*. 2023;77(6):2030-2040.

Bajaj JS, Rodriguez MP, Fagan A, et al. Impact of bacterial infections and spontaneous bacterial peritonitis prophylaxis on phage-bacterial dynamics in cirrhosis. *Hepatology*. 2022;76(6):1723-1734.

Bajaj JS, Tandon P, O'Leary JG, et al. Outcomes in patients with cirrhosis on primary compared to secondary prophylaxis for spontaneous bacterial peritonitis. *Am J Gastroenterol*. 2019;114(4):599-606.

Biggins SW, Angeli P, Garcia-Tsao G, et al. Diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology*. 2021;74(2):1014-1048.

Faust N, Yamada A, Haider H, et al. Systemic review and network meta-analysis: prophylactic antibiotic therapy for spontaneous bacterial peritonitis. *World J Hepatol*. 2020;12(5):239-252.

Komolafe O, Roberts D, Freeman SC, et al. Antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with liver cirrhosis: a network meta-analysis. *Cochrane Database Syst Rev*. 2020;1(1):CD013125.

Silvey S, Patel N, O'Leary JG, et al. Secondary spontaneous bacterial peritonitis prophylaxis is associated with a higher rate of infections other than spontaneous bacterial peritonitis in 2 US-based national cirrhosis cohorts [published online March 10, 2025]. *Clin Transl Gastroenterol*. doi:10.14309/ctg.0000000000000837.

Silvey S, Patel NR, Tsai SY, et al. Higher rate of spontaneous bacterial peritonitis recurrence with secondary spontaneous bacterial peritonitis prophylaxis compared with no prophylaxis in 2 national cirrhosis cohorts. *Am J Gastroenterol*. 2025;120(5):1066-1075.