Evidence-Based Commentary: Antibiotics for Prophylaxis of Spontaneous Bacterial Peritonitis

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Introduction

Ascites is the major decompensating event in the natural history of cirrhosis.[1] Peritoneal infection is one of the most common sites of infection in cirrhosis.[2] Ascitic fluid infection without any evidence of a surgically treatable intra-abdominal source is termed as spontaneous bacterial peritonitis (SBP).[2] The diagnosis of SBP is established by demonstrating $\geq 250/mm^3$ polymorphonuclear cells on ascitic fluid analysis (performed with strict aseptic precautions) irrespective of the culture positivity in a cirrhosis patient presenting with or without symptoms of peritoneal infection, that is, fever, abdominal pain, tenderness, diarrhea, or ileus.[3] The prevalence of SBP is approximately 1.2 to 3.5% in outpatients and 10 to 27% in hospitalized patients with cirrhosis.[4] SBP is an indication for liver transplantation as the recurrence rate is as high as 70% at 1 year and is associated with high mortality.[5] Therefore, selective intestinal decontamination (SID) with antibiotics may reduce the incidence of SBP and positively impact the course of cirrhosis patients. In this commentary, we will discuss the indications, advantages, and disadvantages of prophylactic antibiotics to prevent SBP.

Why is Prophylaxis Required in Cirrhosis Patients?

Gram-negative bacilli (GNB) belonging to *Enterobacteriaceae* are the frequent cause of SBP, although recently, there has been a rise in Gram-positive cocci infections.[2] Common organisms causing SBP include *Escherichia coli*, *Klebsiella pneumoniae*, enterococci, and *Staphylococcus aureus*.[3] Cirrhosis-associated immune dysfunction, impaired intestinal permeability, and bacterial overgrowth increase the risk of bacterial translocation and endotoxemia.[6] Infections in cirrhosis can rapidly worsen liver disease and culminate in acute-on-chronic liver failure (ACLF) with multiorgan dysfunction. SID with antibiotics can reduce bacterial translocation, contain endotoxemia, reduce the incidence of infections, and improve outcomes.

Who Can Benefit the most from Antibiotic Prophylaxis?

The seminal study by Llach et al demonstrated that patients with ascitic fluid protein < 1 g/dL are at the increased risk of developing SBP.[7] Similarly, the recurrence of SBP was also dependent on the ascitic fluid protein.[5] Based on several studies, Fernández et al randomized patients with ascitic fluid protein < 1.5 g/dL with renal or hepatic failure to receive norfloxacin or placebo.[8] This was the first study to demonstrate a survival benefit. The incidence of SBP was 7% in the norfloxacin arm compared with 61% in the placebo arm. Similarly, the incidence of hepatorenal syndrome was 28% in the norfloxacin arm compared with 41% in the placebo arm. Norfloxacin was also reported to improve 3-month (94% vs. 62%) and 1-year (60% vs. 48%) survival compared with placebo. This study formed the basis to recommend primary prophylaxis with norfloxacin for patients with decompensated cirrhosis with low ascitic fluid protein (< 1.5 g/dL) with liver failure (defined as serum bilirubin ≥ 3.0 mg/dL with Child-Pugh score ≥ 9) or renal dysfunction (defined as blood urea nitrogen ≥ 25 mg/dL or serum creatinine ≥ 1.2 mg/dL or serum sodium ≤ 130 mmol/dL).[2,8] The same was upheld by the recent randomized controlled trial (RCT) by Moreau et al

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which demonstrated significant mortality benefit with norfloxacin in patients with ascitic fluid protein < 1.5 g/dL but not in patients with ascitic fluid protein > 1.5 g/dL.[9]

Approximately 30 to 40% of patients with variceal bleed have bacterial infections, increasing the risk of variceal rebleed and mortality.[10] Intravenous ceftriaxone and norfloxacin are equally effective in preventing infections in patients with variceal bleed. Secondary prophylaxis is indicated for patients with a history of SBP. There have been several studies evaluating the role of antibiotics in preventing SBP. Some of the landmark RCTs are discussed in ►**Supplementary Table S1** (available in the online version). A recent study also demonstrated the efficacy of norfloxacin in reducing bacterial infections in patients with ACLF.[11] SBP was less frequently noted in ACLF patients.[12] Although norfloxacin could not prolong the transplant-free survival in patients with ACLF, norfloxacin led to a reduction in the incidence of hepatic encephalopathy and contained the endotoxin rise. Furthermore, the trial highlighted the beneficial role of prophylactic norfloxacin in patients with alcohol-associated hepatitis receiving steroid therapy. Lastly, the dose of norfloxacin needs to be adjusted only in patients with estimated glomerular filtration rate < 30 mL/min/1.73 m^2 and those on dialysis.

What are the Other Drugs for Prevention of SBP?

Norfloxacin has low systemic bioavailability due to low solubility and low permeability. Furthermore, norfloxacin has been proven to prevent SBP and infections in patients with gastrointestinal hemorrhage. Thus making norfloxacin an ideal choice for SID.[11] Therefore, norfloxacin is the most commonly used drug. Food and Drug Administration discontinued norfloxacin as the company manufacturing norfloxacin discontinued the medication. There were no safety concerns regarding the drug. Several other drugs have equal efficacy as norfloxacin and are frequently used in countries where norfloxacin is unavailable.

Once-weekly rufloxacin, a long-acting quinolone, was assessed against daily norfloxacin. Norfloxacin was reported to be more effective than rufloxacin in preventing the recurrence of peritonitis due to *Enterobacteriaceae*.[13] Rufloxacin is a well-known effective drug for respiratory infections and is not recommended to prevent SBP. Administered once weekly, 750 mg of ciprofloxacin is as effective as norfloxacin in preventing SBP.[14] However, with an elimination half-life of 3 to 6 hours, the benefit of once-weekly ciprofloxacin to prevent SBP needs to be assessed in further studies.

Trimethoprim-sulfamethoxazole (TMP-SMX) is a safer alternative to norfloxacin and is a preferred choice when norfloxacin is unavailable or for patients who are intolerant to fluoroquinolones. Few studies comparing TMP-SMX and norfloxacin have demonstrated both to be equally effective in preventing SBP. However, skin rashes, cytopenias, and deterioration in renal function with TMP-SMX require frequent monitoring (►**Supplementary Table S1**, available in the online version).

Rifaximin, a nonabsorbable gut sterilizer, has excellent efficacy in preventing the recurrence of hepatic encephalopathy.[15] Four RCTs have evaluated the role of rifaximin in the primary and secondary prevention of SBP (►**Supplementary Table S2**, available in the online version). A meta-analysis including 13 studies and 1,703 patients concluded that rifaximin has a protective role in prophylaxis for SBP; however, the quality of the evidence was very low.[16] A recent high-quality randomized study reported rifaximin to be more effective in preventing recurrence (secondary prophylaxis) of SBP but not occurrence (primary prophylaxis).[17] Although rifaximin and norfloxacin have similar immunomodulatory effects in patients with cirrhosis, the cost of twice-daily dosing of rifaximin is a major limiting factor.[18] Future studies should compare norfloxacin and rifaximin with respect to preventing extraperitoneal infection, fungal peritonitis, infection by multidrug-resistant organisms (MDROs), change in endotoxin levels, and/or prevention of encephalopathy. In the absence of any such added benefit, in the author's opinion, the utility of rifaximin in SBP prophylaxis (especially primary prophylaxis) remains limited and cannot be recommended till further evidence.

Several meta-analyses have assessed the role of antibiotic prophylaxis in preventing SBP and improving survival[16,19–24] (►**Table 1**). The latest meta-analysis by Mücke et al demonstrated that norfloxacin prophylaxis led to a decrease in the incidence of SBP. However, the efficacy of norfloxacin in preventing death decreased over a period.[21] The authors attributed this to the rise in MDROs in recent years. Nevertheless, SID with antibiotics remains the cornerstone of management for patients with cirrhosis.

How to Manage Recurrent SBP?

Antibiotic prophylaxis is less effective in patients harboring MDROs at baseline. MDROs are a common cause of recurrent SBP and are associated with higher mortality. Bedside ascitic fluid culture in (both aerobic and anaerobic) blood culture bottles before initiating antibiotics is more valuable in SBP as it can guide the therapy. Broad-spectrum antibiotics (piperacillin-tazobactam in countries where MDROs prevalence is low and carbapenems where MDROs prevalence is high) are the preferred drug of choice. Further studies are required to assess a suitable prophylactic antibiotic for patients harboring MDROs.

Can any Vaccination Prevent SBP?

Streptococcus pneumoniae-related SBP patients are more likely to be community-acquired infections, frequently present with concurrent bacteremia, and have a higher risk of variceal bleed.[25] Pneumococcal vaccination may reduce the incidence of SBP due to Streptococcus pneumonia. Universal vaccination strategies should be followed in all patients with cirrhosis to improve the outcomes.[4]

What are the Disadvantages of Prophylactic Antibiotics in Cirrhosis Population?

Despite the several advantages of once-daily norfloxacin, the drug is associated with few drawbacks. Norfloxacin prophylaxis increases the risk of quinolone-resistant GNB infections

Table 1 Major meta-analysis comparing different regimens in the past 5 years

Author, year	Inclusion	Number of studies and patients	Primary prophylaxis	Secondary prophylaxis	Conclusions/comments
Soni et al 2020[20]	Randomized studies evaluating the role of antibiotics in adult cirrhotic patients with ascites for primary or secondary prophylaxis of SBP	10 and 973 patients for primary prophylaxis; nine studies and 737 patients in secondary prophylaxis	NFX daily; rifaximin daily, and NFX and rifaximin alternate months were effective	Rifaximin daily was effective	Rifaximin effective both for primary and secondary prevention of SBP. Included only one study on rifaximin. Needs large RCTs
Komolafe et al 2020[19]	Randomized clinical trials in adults with cirrhosis undergoing prophylactic treatment to prevent spontaneous bacterial peritonitis	23 trials, 2,587 participants	Any adverse events per participant were fewer with NFX and TMP-SMX versus no active intervention. There were fewer other decompensation events with rifaximin versus no active intervention and NFX plus neomycin		The authors highlighted the need to assess the effect of antibiotics on health-related quality of life and decompensation events. Similar to other Cochrane reviews, the current review failed to demonstrate any benefit with antibiotics, contrary to several other studies, and pointed to a high risk of bias from the included studies
Mücke et al 2020[21]	Randomized controlled trials of patients with liver cirrhosis that assessed SBP occurrence/recurrence during antibiotic prophylaxis with the common antibiotic agents	12 trials, 1,626 patients	NFX reduced the incidence rate of SBP and death	NFX was not superior to other antibiotics	On meta-regression, NFX was most effective at bilirubin levels between 3 and 5 mg/d. The authors raised the concern of MDROs as the cause of decreasing efficacy of NFX over time
Facciorusso et al 2019[22]	Randomized controlled trials comparing antibiotic treatments (NFX, ciprofloxacin, TMP-SMX, and rifaximin) with each other or placebo	10 studies	Moderate quality evidence supported use of NFX and ciprofloxacin in primary prophylaxis. Low-quality evidence suggests superiority of rifaximin. No difference among various antibiotics		NFX could reduce mortality and the incidence of SBP but not other site infections. Ciprofloxacin has unclear mortality benefit

(*Continued*)

Table 1 (*Continued*)

Author, year	Inclusion	Number of studies and patients	Primary prophylaxis	Secondary prophylaxis	Conclusions/comments
Menshawy et al 2019[23]	Studies involving use of rifaximin for prophylaxis	Six studies involving 973 patients	Rifaximin plus NFX had less incidence of SBP and hepatic encephalopathy than the only NFX-based regimen group. No significant difference between rifaximin and NFX in terms of frequency of SBP and success rate of primary prevention of SBP		Rifaximin is as effective as NFX based on a limited number of studies
Kamal et al 2017[16]	Comparative studies evaluating the effect of rifaximin on the occurrence of SBP and HRS	13 studies (4 RCTs and 9 observational studies), 1,703 patients	Rifaximin is effective on subgroup analysis, including four studies in reducing the occurrence of SBP	Rifaximin effective in reducing recurrence based on two studies	Rifaximin also reduced the incidence of hepatorenal syndrome. The study included observational studies, and the quality of evidence was very low
Goel et al 2017[24]	Studies on the association between rifaximin and SBP	5 studies, 555 patients	Rifaximin failed to reduce the occurrence of SBP compared with systemic antibiotics on sensitivity analysis	Rifaximin reduced the recurrence of SBP compared with systemic antibiotics on sensitivity analysis	The number of studies included was low to recommend rifaximin for prophylaxis over NFX

Abbreviations: HRS, hepatorenal syndrome; MDRO, multidrug-resistant organism; NFX, Norfloxacin; RCT, randomized controlled trial; SBP, spontaneous bacterial peritonitis; TMP-SMX, trimethoprim-sulfamethoxazole.

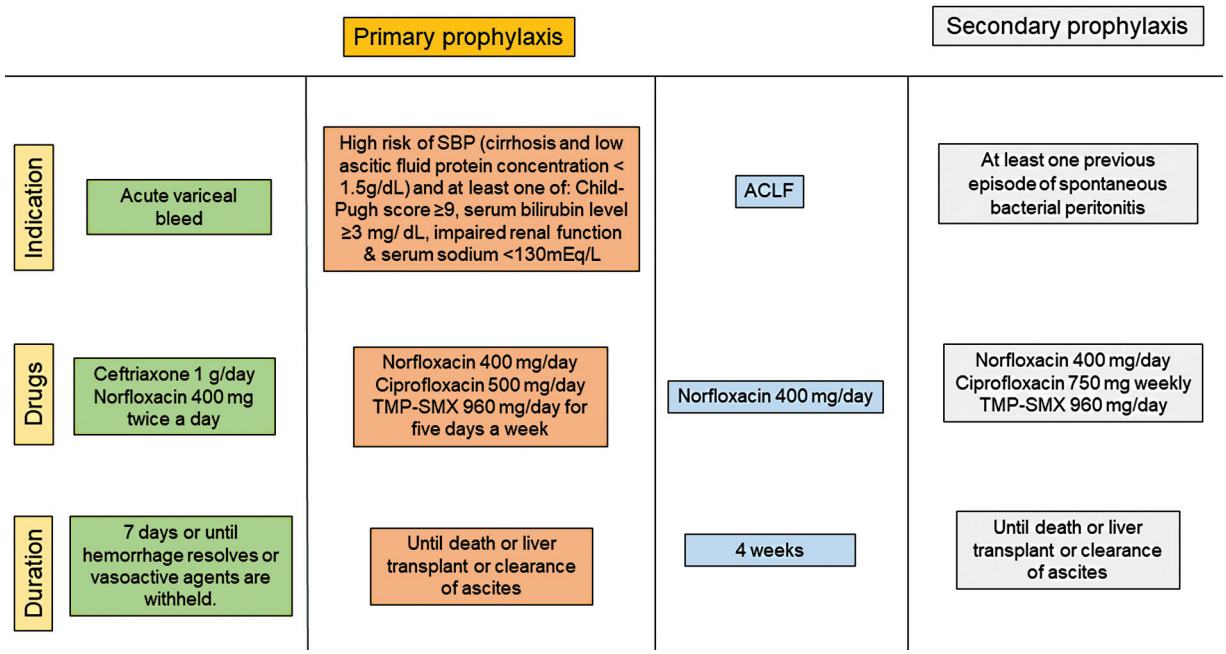

Fig. 1 Prophylactic antibiotic indications and duration of therapy for patients with cirrhosis. ACLF, acute-on-chronic liver failure; TMP-SMX, trimethoprim-sulfamethoxazole.

and infections by Gram-positive organisms.[26] Few reports have suggested an increased risk of *Clostridium difficile* infection with norfloxacin prophylaxis.[27] A recent study also reported an increased risk of *Candida albicans* infection in patients receiving prophylactic norfloxacin.[11] The burden of MDROs is rapidly growing. The incidence of MDROs among patients with cirrhosis ranges between 20 and 34% globally and 70% in India.[28] Although initial studies reported an increased risk of MDROs with prophylactic norfloxacin, some major studies have contradicted and suggested that even long-term norfloxacin prophylaxis is safe in patients with cirrhosis without the added risk of MDROs.[9,28] Lastly, tuberculosis is highly prevalent in Asia and fluoroquinolones are well-known second-line antitubercular drugs. Empirical treatment with fluoroquinolones may lead to development of resistant tuberculosis. Therefore, we strongly suggest excluding tuberculosis before prophylactic fluoroquinolone initiation.[29]

How to Reduce the Incidence of MDROs?

Some measures to reduce the burden of MDROs include avoiding unnecessary: hospital admissions, prolonged hospital stay, invasive procedures, antibiotic treatment (as an over-the-counter drug), and prolonged proton-pump inhibitor therapy. Universal precautions, including hand hygiene, must be adhered to while caring for these immunocompromised patients. Cirrhosis patients should be frequently screened for MDROs through nasal and rectal swabs. Strict local antibiotic policies and antibiotic stewardship are required to reduce the incidence of MDROs. Nonantibiotic methods to minimize the burden of infections are necessary. Beta-blockers,[30] simvastatin,[31] and immunonutrition[32] are some of the known nonantibiotic interventions to reduce the incidence of infections.[33] Recent studies have reported fecal (intestinal) microbiota transplantation to be safe and effective in modifying the gut antibiotic resistance genes and may be the future strategy to prevent MDROs.[34]

Conclusion

Infections, especially SBP, are the leading cause of morbidity and mortality in patients with cirrhosis. Prophylactic antibiotics can reduce the incidence of infections and prolong survival in carefully selected patients. Appropriate antibiotic prescription is low for primary and secondary SBP prevention. Clinicians need to be aware of such indications for antibiotic prophylaxis to improve the outcomes for patients with cirrhosis (►**Fig. 1**). Norfloxacin is the preferred antibiotic due to lack of safety concerns and more patient acceptability. Rifaximin appears to be a promising agent in the prevention of SBP.

Ethical Statement
None.

Author Contributions
I.F.: Initial draft and tables. AVK: Critical revision and figures. Both authors approved final version.

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