ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Antibiotic Prophylaxis in Patients With Cirrhosis



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G&H How strong is the evidence supporting prophylactic antibiotic use for upper gastrointestinal bleeding in patients with cirrhosis?

AD-R Based on multiple studies that have been performed, it has been taken for granted that antibiotic prophylaxis in any patient with cirrhosis who presents with gastrointestinal (GI) bleeding is beneficial. There are several outcomes that should be considered. The most common is whether the patient develops an infection during their hospital admission or, subsequently, if the patient is readmitted soon afterward for an infection. It is known that patients with cirrhosis who present with bleeding are at increased risk of infection because of decreased host defenses, greater gut permeability, and increased bacterial translocation. However, the most important outcome to consider is mortality. Are the antibiotics preventing patients from dying of an infection or its consequences following control of their upper GI bleeding? Good data are not available to answer this question. Although studies have been conducted, there is a lack of large well-designed, randomized controlled trials that address the full range of clinical scenarios in this population. There are too many nuances among cirrhotic patients seen in routine clinical practice. The risk of an infection prior to GI bleeding is not the same in a patient with compensated cirrhosis, a patient with decompensated cirrhosis, or a patient who has serious complications of portal hypertension, such as refractory ascites or recurrent hepatic encephalopathy, as the manifestation of decompensation.

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There is also variation in multidrug-resistant organisms (MDROs) across the geographic areas where studies have been performed. Plus, studies have used different antibiotics and treated for various durations. It should also be noted that clinicians are seeing more infections in patients with cirrhosis. At a minimum, 1 in 3 patients who come to the hospital develop an infection, and more infections are also being seen in the outpatient setting in patients with cirrhosis. As infections increase, particularly with MDROs, it is important to ask whether giving a patient an antibiotic prevents something clinically meaningful or, on the contrary, is increasing the risk for a MDRO that will be difficult to treat and might contribute to the patient's death. Thus, too much variability exists to claim there is solid evidence supporting the use of prophylactic antibiotics for GI bleeding in cirrhotic patients in current routine practice.

G&H When have prophylactic antibiotics traditionally been used in cirrhotic patients?

AD-R There are 3 scenarios. One, as already discussed, is upper GI bleeding. Another involves patients with ascites

and low protein in their ascitic fluid, who were found in early studies to be at higher risk of spontaneous bacterial peritonitis (SBP). Some of these patients are given primary prophylaxis. The third scenario involves patients who have already had an episode of SBP. Antibiotics are given to prevent a subsequent episode, which is known as secondary SBP prophylaxis.

For secondary prophylaxis in particular, there is better evidence that giving antibiotics significantly reduces the risk of a second episode of SBP. However, there is a lack of large well-designed, randomized controlled trials to confidently conclude that secondary prophylaxis prolongs a patient's life.

Both the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver recommend primary prophylaxis when ascitic fluid protein is low (<1.5 g/dL), but say it should be reserved for patients with severe liver disease and/or metabolic abnormalities. This includes patients with a Child-Pugh score of 9 or more, a bilirubin of 3 mg/dL or more, acute kidney injury, or hyponatremia. In practice, however, prophylaxis is given to nearly everyone with low-protein ascites, often without checking for coexisting severe liver failure or metabolic and electrolyte disturbances. Clinicians should be careful about this practice because one size does not fit all, and they need to mind antibiotic stewardship. As mentioned, the risks are very different for patients who are early in their decompensation journey vs those who are late. In fact, similarly to what was discussed for upper GI bleeding, evidence is limited, particularly for primary prophylaxis. On the flip side, emerging data show that patients receiving outpatient antibiotic prophylaxis have a higher risk of infections with MDROs and do not benefit in terms of recurrence. Some studies show that the risk of recurrent SBP is the same regardless of whether antibiotics are given, and prophylaxis may cause episodes of SBP that are more difficult to treat or infections other than SBP, findings that further muddy the picture.

Newer studies have shown that it does not matter whether patients with Child-Pugh A cirrhosis, for example, are given antibiotics.

G&H Which antibiotics are preferred for patients with cirrhosis?

AD-R In the case of upper GI bleeding, the recommendation is a third-generation cephalosporin. Ceftriaxone is usually given, but any third-generation cephalosporin is acceptable. Because these patients are in the hospital, the antibiotic is given intravenously for a duration of 3 to 7 days. In the past, fluoroquinolones such as ciprofloxacin were used, but studies have shown more fluoroquinolone-resistant strains in these patients, so now only third-generation cephalosporins are recommended. This is consistent with the Baveno VIII consensus document, which was published recently.

As for primary or secondary SBP prophylaxis in patients with ascites, an oral fluoroquinolone or trimethoprim-sulfamethoxazole is usually given in the outpatient setting.

G&H What is the optimal duration of prophylactic antibiotics for cirrhotic patients?

AD-R For upper GI bleeding, clinical practice is to never give antibiotic prophylaxis for more than 7 days and to essentially stop when the patient is sent home. If a patient is discharged on day 3, for example, cephalosporin is stopped and is not given anymore. If a patient is discharged on day 7, they have received the full course of antibiotics. Some studies show that a 3-day course is not inferior to a 5- or 7-day course, so as little as 3 days might be enough.

For primary or secondary SBP prophylaxis, it is important to note that antibiotics are given long term (eg, until transplant), which emphasizes the need for antibiotic stewardship and raises concerns for MDRO selection.

G&H How does the approach change in patients with less advanced liver disease?

AD-R Newer studies have shown that it does not matter whether patients with Child-Pugh A cirrhosis, for example, are given antibiotics. That is why the recent Baveno VIII guidelines say that for these patients, a shorter course of antibiotics can be given or antibiotics can even be omitted. A research agenda has been proposed to generate data to support or refute the use of antibiotics in this population, as it is probable that compensated patients do not need antibiotics at all. Although some research has already suggested this, confirmatory randomized trials are needed.

G&H Could you discuss the current recommendations for nonvariceal bleeding as opposed to variceal bleeding?

AD-R The pathophysiology of an infection that complicates nonvariceal and variceal bleeding in a patient with cirrhosis and portal hypertension is likely similar. In both instances, the bleeding increases gut permeability and stasis favors bacterial overgrowth, both of which promote bacterial translocation in the setting of cirrhosis-associated immune dysfunction. Because of the similarity, the risks are assumed to be the same and all bleeders are thus treated the same prophylactically. Nevertheless, what is happening in the splanchnic circulation, and how sick the patient is, are not the same if the patient has an ulcer as opposed to a decompensated variceal bleed. Particularly for patients with nonportal hypertensive bleeding, I do not think prophylaxis is needed unless they are decompensated. Evidence is insufficient to prove this, however, because most antibiotic prophylaxis studies have consisted of patients with variceal bleeding. In a recent meta-analysis in *JAMA Internal Medicine*, which summarized the literature well, most of the participants were variceal bleeders (91%). In summary, although in practice clinicians extrapolate variceal bleeding findings to nonvariceal bleeding, whether nonvariceal bleeders need this type of prophylaxis is still to be definitively determined and will likely depend more on how sick they are in terms of their liver disease and portal hypertension.

G&H How is real-world adherence to the current guidelines?

AD-R Real-world adherence is poor. One study from Japan found that it was only approximately 10%, whereas other studies suggest it can be as high as 60%, so adherence likely falls anywhere in between. Academic centers tend to have the best adherence. Because trainees are being educated at academic centers, there is a strong incentive to follow the best available evidence and, in consequence, health care professionals tend to be up-to-date with the literature. Adherence is lower in community hospitals that are not associated with an academic center, particularly those without a training program.

Publications have shown that quality improvement projects can significantly increase adherence to recommended practices. Additionally, admission or rounding checklists can help health care professionals be thorough about their care. Some of my colleagues and I put together a rounding checklist in the form of a mnemonic called HEPA-ROUNDS, with the P standing for prophylaxis—considering antibiotic prophylaxis. In the end, the pathophysiology of decompensated cirrhosis is so unique and these patients are so sick that it is important to have dedicated clinicians who are trained in their care. The more clinicians work from checklists or other tools, including dedicated mnemonics or electronic medical record automated pop-up alerts that help them remember what to do in each particular circumstance, the better adherence will be.

G&H What research is underway in this area, and what are the next steps?

AD-R The Veterans Administration (VA) is generating some interesting data on MDROs, and there are several studies underway with Dr Jasmohan S. Bajaj as one of the principal investigators. The findings have been reproduced outside the VA in other large databases, showing that patients who receive prophylaxis have more MDROs. The multinational CLEARED Consortium is looking at MDROs and how they might be associated with antibiotic prophylaxis.

Studies need to be repeated for upper GI bleeding as well as for SBP prophylaxis. Some were performed in the 1990s, but the MDRO landscape has changed and the antibiotics are different. Patients are also staying alive while being much sicker than before, particularly those on the transplant waiting list. Doctors go to the last resort to keep these patients eligible for transplantation. Such sick patients were not being treated in the 1990s, or probably even in the early 2000s, when many of these studies were performed. Therefore, new evidence is needed.

Disclosures

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Suggested Reading

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