EVIDENCE-BASED GI
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Cephalosporins and Ciprofloxacin Still Appropriate First-Line Treatment for Spontaneous Bacterial Peritonitis

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LIVER

This article reviews Yim HJ, Kim TH, Suh SJ, et al. Response-Guided Therapy with Cefotaxime, Ceftriaxone, or Ciprofloxacin for Spontaneous Bacterial Peritonitis: A Validation Study of 2021 AASLD Practice Guideline for SBP. Am J Gastroenterol 2023; 118: 654-63.

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STRUCTURED ABSTRACT

Question: Are standard American Association for the Study of Liver Disease (AASLD) guideline-recommended antibiotics, cefotoxime, ceftriaxone, and ciprofloxacin, still effective for the treatment of spontaneous bacterial peritonitis (SBP) despite the rise in multidrug resistant organisms?

Design: Multicenter, unblinded randomized controlled trial (RCT).

Setting: Nine tertiary hospitals in South Korea between 2007-2018.

Patients: Included patients were: (a) age 16-75 years old; (c) clinical diagnosis of cirrhosis with ascites; and (c) ascitic polymorphonuclear (PMN) cell count $\geq$ 250/mm^3. Multiple exclusion criteria were used to exclude patients with secondary peritonitis as cause of elevated PMN count.

Interventions/Exposure: Two grams of Cefotaxime intravenously (IV) every 8 hours vs ceftriaxone 2 grams IV every 24 hours vs 200 mg

ciprofloxacin IV every 12 hours for 5 days with 1:1:1 randomization.

Repeat paracentesis was performed 48 hours after starting antibiotics. If ascitic PMN count had not decreased by >25%, then the patient was switched to broader-spectrum antibiotics. Twenty percent albumin could be infused at admission and at 48 hours after admission to prevent acute kidney injury at the discretion of the investigator.

Outcome: The primary endpoint was resolution of SBP at 120 hours (5 days) defined by: a decrease in ascitic PMN cell count < 250/mm^3; normalized leukocytosis in peripheral blood count; no bacterial growth in blood or ascitic fluid cultures; and resolution of any symptoms/signs of SBP, including abdominal pain and fever.

Data Analysis: Intention-to-treat (ITT) analysis for patients who received at least 1 dose of antibiotic and per-protocol (PP) analysis for patients who completed assigned antibiotic course were performed. Categorical variables were compared using chi-square test or Fisher exact test, as appropriate, and continuous variables were assessed with analysis of variance (ANOVA).

Funding: Korea Healthcare Technology R&D Project, Ministry of Health and Welfare, Republic of Korea, and a research grant from Korea University.

Results: Among 261 randomized patients, mean age was 56 years (51-63); 76% male; etiology of cirrhosis was 43% alcohol, 40% chronic hepatitis B infection, 11% chronic hepatitis C infection; mean Child-Pugh score 10 (9-12) and mean MELD score was 20 (16-24). For the primary endpoint, there was no significant difference in resolution of SBP at 120 hours for cefotaxime vs ceftriaxone vs ciprofloxacin, respectively: 67.8% vs 77.0% vs 73.6% (P= 0.39) in the ITT analysis. Per-protocol analysis results were 80.6% vs 85.5% vs 85.9%, respectively (P= 0.65) (Figure 1). After the 48-hour paracentesis, broad spectrum antibiotics were started because PMN count had not decreased by at least 25% in a minority of patients initially treated with cefotaxime vs ceftriaxone vs ciprofloxacin, respectively (10.3% vs 5.7% vs 12.6% [P= 0.21]). *Escherichia coli* was the most frequently isolated bacteria in culture (34.1%) and 21.4% of these isolates were resistant to third-generation cephalosporins. There were no significant differences in other secondary outcomes.

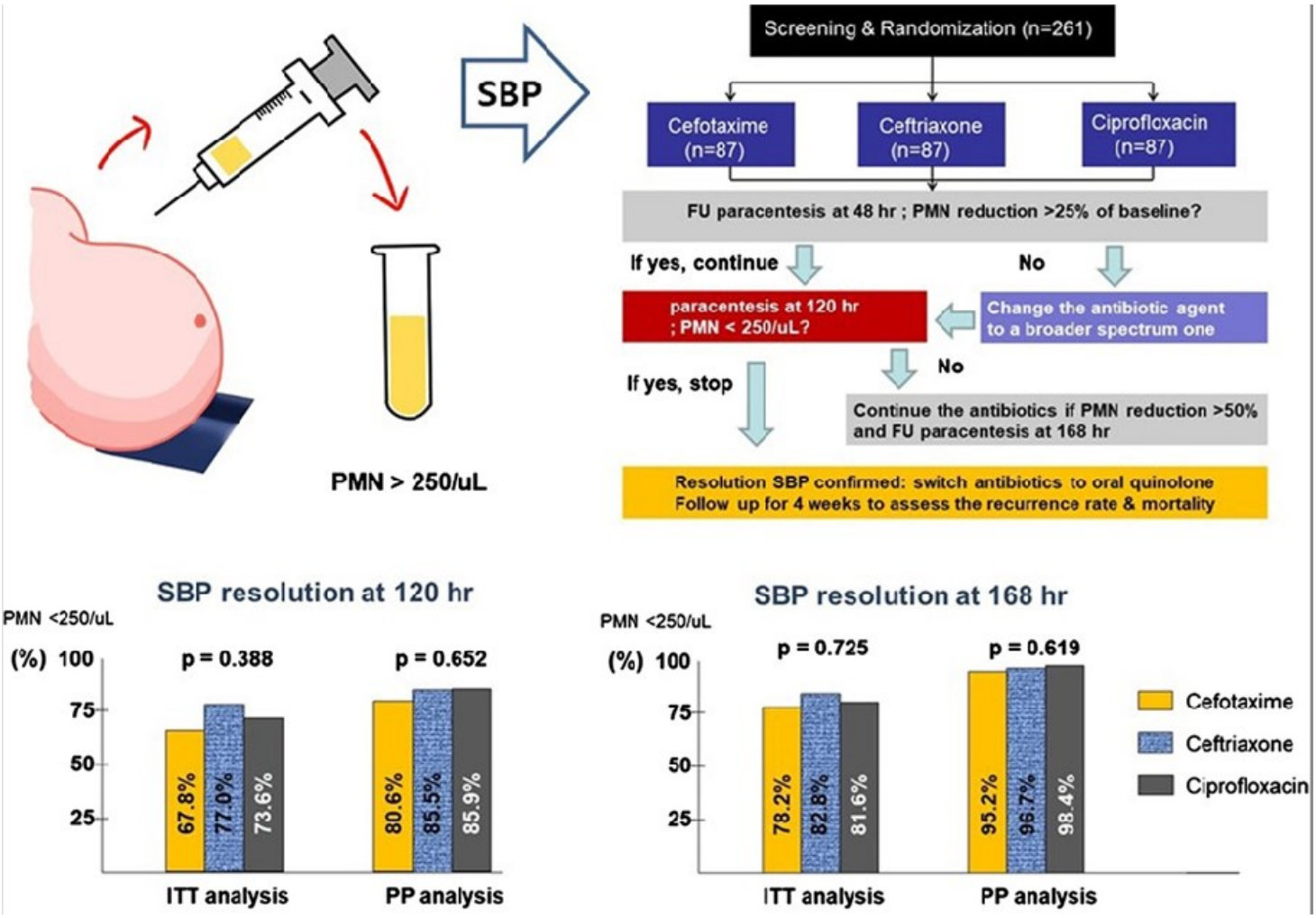

Figure 1. Visual abstract
FU, follow-up; ITT, intention-to-treat; PMN, polymorphonuclear; PP, per-protocol; SBP, spontaneous bacterial peritonitis.

COMMENTARY

Why Is This Important?

The 2021 AASLD guidelines[1] recommend that SBP should initially be treated with a third-generation cephalosporin, such as ceftriaxone, followed by repeat paracentesis in 48 hours. If ascitic PMN count has not decreased by 25%, then broader-spectrum antibiotics, such as piperacillin/tazobactam plus carbopenams, can be initiated.

SBP resolution rates of 90% had previously been reported with third-generation cephalosporins, but lower rates have been reported recently due to multi-drug resistant species of *E. coli* and *Klebsiella pneumoniae*. This has led to more routine use of broader-spectrum antibiotics, like piperacillin/tazobactam, as first-line treatment. However, increased use of these antibiotics may represent poor

antibiotic stewardship and lead to more antimicrobial resistance.[2]

This RCT is an important contribution because it validates current AASLD guidelines. The investigators should be commended for their excellent study design and diligence to address this important issue.

Key Study Findings

There was no significant difference in resolution of SBP at 120 hours for cefotaxime vs ceftriaxone vs ciprofloxacin, respectively: 67.8% vs 77.0% vs 73.6% (P= 0.39) in the ITT analysis.

Per-protocol analysis results were 80.6% vs 85.5% vs 85.9%, respectively (P= 0.65).

Caution

This is a South Korean study which took 11 years to enroll the study population. Unknown factors may confound the results and minimize its applicability to US settings. However, unless your setting has substantially higher rates of third generation cephalosporin-resistant *E. coli* and *Klebsiella* spp these results should apply to your SBP patients.

My Practice

Although I'm a general gastroenterologist, I treat SBP patients frequently on our inpatient service. Usually, our internal medicine staff have already started a patient on antibiotics before I see the patient. They usually prescribe broad-spectrum antibiotics, such as piperacillin-tazobactam— which the AASLD guideline recommends avoiding as first-line therapy and saving for patients that are likely to have multidrug-resistant (MDR) organisms.

I'm reassured by the 85% SBP resolution rates reported with ceftriaxone in this trial, which reinforces my current teaching to house staff to start ceftriaxone as first-line treatment for SBP, unless the patient was recently hospitalized and is at higher risk for MDR organisms. This represents good antibiotic stewardship. I will check with my infectious disease colleagues and our infection control teams to assess the frequency of MDR *E. coli* and *Klebsiella sp.* in our setting. If it's substantially higher than 20%, then I may reassess my practice after consultation with my hepatology and infectious disease colleagues. This study is also a good reminder to follow AASLD

guidelines[1] to repeat paracentesis at 48 hours and confirm that patients are responding to antibiotic therapy with at least 25% decrease in PMN count.

For Future Research

Better tools, including molecular diagnostic tools, are needed to quickly identify MDR organisms and guide selection of appropriate antibiotic therapy.[1]

Conflict of Interest

Dr. Schoenfeld reports no conflicts of interest.

REFERENCES

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2. Avadhanam M, Kulkarni AV. Conventional Antibiotics for Spontaneous Bacterial Peritonitis: Are They Still Effective. Am J Gastroenterol 2023; 118: 613-14.