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ORIGINAL ARTICLE

Comparative outcomes of Piperacillin-Tazobactam versus Ceftriaxone in managing spontaneous bacterial peritonitis in cirrhotic patients: An observational study

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ABSTRACT

Background: Spontaneous bacterial peritonitis (SBP), a serious complication of liver cirrhosis, demands prompt antibiotic treatment, but rising resistance to ceftriaxone has spurred interest in alternative therapies.
Objective: To compare the treatment outcomes of Piperacillin-Tazobactam versus ceftriaxone in spontaneous bacterial peritonitis among cirrhotic patients.
Methods: This comparative observational study was conducted from 1st January to 1st July 2023 at the Services Institute of Medical Sciences, Lahore, Pakistan. A total of 218 cirrhotic patients, 18-60 years of age, diagnosed with SBP based on an ascitic fluid polymorphonuclear (PMN) count >250/μL, were enrolled using non-probability consecutive sampling. On the physician's discretion, patients receiving Piperacillin-Tazobactam (4.5 g IV every 8 hours) were allocated to Group A (n=109) and those receiving Ceftriaxone (2 g/day) were allocated to Group B (n=109). Treatment response was observed on day five by assessing clinical improvement and repeat ascitic fluid analysis. A Chi-square test was conducted using SPSS version 22 for statistical analysis.
Results: The mean age of the study population was 35.7 ± 6.5 years, with 61.93% male patients. A higher proportion of patients treated with Piperacillin-Tazobactam (75.2%) showed resolution of SBP by day 5 compared to those receiving Ceftriaxone (62.4%). Although there was a difference in the response to the treatments (χ^2=3.61, p=0.0574), it was statistically not significant. Across stratified subgroups, age, gender, symptom duration, Child-Pugh score, and PMN count for the Piperacillin-Tazobactam (group A) showed higher, though statistically insignificant, treatment response rates compared to Ceftriaxone (group B).
Conclusion: Piperacillin-Tazobactam showed a higher, though statistically insignificant, resolution rate of SBP compared to Ceftriaxone. This trend was consistent across age groups, gender, symptom duration, Chil-Pugh score, and PMN count, suggesting a potential clinical advantage.

Key Words: Spontaneous Bacterial Peritonitis, Piperacillin-Tazobactam, Ceftriaxone, Cirrhosis.

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INTRODUCTION

Chronic liver disease is among the leading causes of morbidity and mortality worldwide. In 2010, it was estimated that there were approximately 1 million deaths due to liver cirrhosis globally.[1,2] Another study reported that liver cirrhosis accounted for 31 Disability Adjusted Life Years (DALYs) per 1,000 population by 2010.[3] Deaths in cirrhotic patients often occur due to complications such as variceal bleeding, portosystemic encephalopathy, hepatorenal syndrome, and hepatopulmonary syndrome. One of the critical consequences of portal hypertension is

ascites, which may lead to spontaneous bacterial peritonitis (SBP). SBP is an ascitic fluid infection without an evident intra-abdominal surgically treatable source.[4,5] The prevalence of SBP in hospital settings ranges from 8% to 36%[6], and in-hospital mortality for the first episode of SBP varies between 10% and 50%, depending on various risk factors.[6,7] To reduce the high mortality associated with SBP, several antibiotics have been prescribed. Cefotaxime, administered as 2 g every 8 hours (6 g/day), is considered a standard regimen for the treatment of SBP.[8,9] However, recent studies have reported increasing bacterial resistance to cefotaxime.[10] In one study, resistance to cefotaxime was noted in 62.5% of gram-positive and 85.7% of gram-negative bacteria.[10] Another commonly used antibiotic for SBP is ceftriaxone, a broad-spectrum third-generation cephalosporin, which has shown some favourable results. However, recent studies have reported growing resistance to ceftriaxone as well, likely due to its widespread and sometimes inappropriate use. In one extensive study, the response rate to ceftriaxone in SBP[11] patients was only 57%.[12] This highlights the need for an alternative antibiotic with better efficacy. Piperacillin-Tazobactam, a combination of an extended-spectrum penicillin and a β-lactamase inhibitor, offers broad antimicrobial coverage and has shown promising outcomes in SBP. In one study conducted in Denmark, the response rate to Piperacillin-Tazobactam in SBP treatment was reported as 73%.[12]

The rationale for this study is rooted in the increasing resistance to Ceftriaxone, making it essential to evaluate and compare other antibiotics with broader microbial coverage and better clinical outcomes. Furthermore, no local studies compared the efficacy of ceftriaxone and Piperacillin-Tazobactam in treating SBP. Therefore, this study was undertaken to address this knowledge gap. The present study was conducted to compare the treatment outcomes of Piperacillin-Tazobactam versus ceftriaxone in spontaneous bacterial peritonitis among cirrhotic patients.

METHODS

This was a comparative observational study conducted in the Department of Gastroenterology, Services Hospital, Lahore, Pakistan, over six months from 1st January to 1st July 2023, after ethical approval. The sample size was calculated using anticipated response rates of 70% for Piperacillin-Tazobactam and 62.8% for ceftriaxone, with an alpha error of 5% and 80% power.[13] A total of 218 patients diagnosed with SBP were included following their written informed consent. Participants were enrolled through non-probability consecutive sampling. On the physician's discretion, patients receiving Piperacillin-Tazobactam (4.5 g IV every 8 hours) were allocated to Group A (n=109) and those receiving Ceftriaxone (2 g/day) were allocated to Group B (n=109).

Patients between 18-60 years of age with a confirmed diagnosis of cirrhosis and SBP, defined by an ascitic fluid PMN count >250/μL, were included in the study. Patients were excluded if they had received antibiotics within the past 8 weeks, had hepatocellular carcinoma, chronic kidney disease (serum creatinine>1.3 mg/dL), were pregnant or lactating, or had known hypersensitivity to Cephalosporins or Piperacillin-Tazobactam. Clinical and laboratory parameters were recorded at baseline and monitored over a five-day treatment course. Laboratory report of the ascitic fluid examination done on day 5 was collected it was to assess treatment response, defined as a PMN count <250/μL. Additional clinical indicators such as abdominal pain, fever, urine output, and systemic signs of infection were recorded from the patient's medical record. Any adverse reactions or complications related to therapy were documented.

Ethical Approval

The study was conducted from 1st January to 1st July 2023 at the Services Institute of Medical Sciences, Lahore, Pakistan. Approval to conduct the study was obtained from the Institutional Review Board (IRB/1047/SIMS) of Services Institute of Medical Sciences, Lahore, Pakistan, prior to data collection.

Statistical Analysis

Data were analyzed using SPSS version 22. Quantitative variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. The chi-square test was used to compare treatment response between groups. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

A total of 218 patients were enrolled in this study. The mean age was 35.7±6.5 years, with 64.22% of patients falling within the 3160 years age group. Of the total participants, 135 (61.93%) were male and 83 (38.07%) were female. Most patients (95.29%) had a baseline PMN count >500/µL, with a mean PMN count of 655.6 ± 72.5/µL (Table 1).

Table 1: Baseline demographic characteristics

Variables	**mean ± SD**
Age (years)	35.7±6.5
	n (%)
Gender	
Male	135 (61.93%)
Female	83 (38.07%)
Age Groups	
18-30 (years)	78 (35.78%)
31-60 (years)	140 (64.22%)

Stratified treatment response to Piperacillin-Tazobactam and Ceftriaxone across various patient subgroups in this comparative observational study is shown in Table 2. A higher proportion of patients treated with Piperacillin-Tazobactam (75.2%) showed resolution of SBP by day 5 compared to those receiving Ceftriaxone (62.4%). Although there was a difference in the response to the treatments (χ^2=3.61, p=0.0574), it did not meet the conventional threshold for statistical significance.

Age-stratified analysis revealed that patients aged 18–30 years showed a higher response rate to Piperacillin-Tazobactam (78.4%) compared to Ceftriaxone (61.5%). A similar pattern was observed in the 30–60 years age group (73.6% vs. 62.9%). However, neither of these differences reached statistical significance (p > 0.05). In gender-based analysis, males demonstrated a higher response to Piperacillin-Tazobactam (68.0%) than to Ceftriaxone (52.5%; χ^2=3.26, p=0.0712), whereas response rates among females were comparable between the two treatment groups (Table 2).

Further subgroup analysis based on duration of symptoms, Child-Pugh scores, and PMN counts consistently showed a higher proportion of treatment responders in the Piperacillin-Tazobactam group across all clinical variables. However, none of these comparisons yielded statistically significant results (Table 2).

These observational findings suggest a potential clinical advantage of Piperacillin-Tazobactam over Ceftriaxone in the management of SBP, although causality cannot be established due to the non-randomized nature of the study.

Table 2: Stratified treatment response by patient subgroups

Variable	**Groups**	**Responded n (%)**	**Not Responded n (%)**	**χ^2/p value**
Drug	Piperacillin-Tazobactam	82(75.2%)	27(24.8%)	3.61/0.057
	Ceftriaxone	68(62.4%)	41(37.6%)	
Age Group	Piperacillin-Tazobactam	29(78.4%)	08(21.6%)	1.82/0.178
(18-30years)	Ceftriaxone	24(61.5%)	15(38.5%)	
Age Group	Piperacillin-Tazobactam	53(73.6%)	19(26.4%)	1.43/0.232
(30-60years)	Ceftriaxone	44(62.9%)	26(37.1%)	
Gender (Male)	Piperacillin-Tazobactam	51(68.0%)	24(32.0%)	3.26/0.071
	Ceftriaxone	42(52.5%)	38(47.5%)	
Gender (Female)	Piperacillin-Tazobactam	31(91.2%)	03(8.80%)	0.00/0.971
	Ceftriaxone	46(93.9%)	03(6.10%)	
Symptom Duration	Piperacillin-Tazobactam	33(75.0%)	11(25.0%)	1.00/0.318
(≤ 3 Days)	Ceftriaxone	27(62.8%)	16(37.2%)	
Symptom Duration	Piperacillin-Tazobactam	49(75.4%)	16(24.6%)	1.62/0.204
(≥ 3 Days)	Ceftriaxone	44(63.8%)	25(36.2%)	
Child-Pugh Score	Piperacillin-Tazobactam	30(75.0%)	10(25.0%)	0.92/0.338
Less than or equal to 9	Ceftriaxone	29(63.0%)	17(37.0%)	
Child-Pugh Score	Piperacillin-Tazobactam	52(75.4%)	17(24.6%)	2.19/0.139
Less than or equal to 9	Ceftriaxone	39(61.9%)	24(38.1%)	
PMN Count	Piperacillin-Tazobactam	04(66.7%)	02(33.3%)	0.09/0.764
Less than or equal to 500/ µL	Ceftriaxone	03(42.9%)	04(57.1%)	
PMN Count	Piperacillin-Tazobactam	78(75.7%)	25(24.3%)	2.95/0.086
Less than or equal to 500/ µL	Ceftriaxone	65(63.7%)	37(36.3%)	

PMN=polymorphonuclear; Chi-square test was applied. p<0.05 was statistically significant.

DISCUSSION

In the present study, we compared the treatment response of cirrhotic patients with SBP receiving either Piperacillin-Tazobactam or Ceftriaxone. Although Piperacillin-Tazobactam demonstrated a higher treatment response compared to Ceftriaxone, the difference was not statistically significant. Nonetheless, the findings suggest a potential clinical advantage of Piperacillin-Tazobactam, particularly in settings with emerging antimicrobial resistance.

SBP remains a serious and potentially fatal complication of cirrhosis, necessitating timely and appropriate empirical antibiotic therapy. While third-generation cephalosporins (TGCs) like ceftriaxone have long served as the standard treatment, the rising prevalence of multidrug-resistant organisms (MDROs) has brought their continued efficacy into question.

This finding resonates with the work of Kim et al., who, in a large cohort study, reported improved outcomes with carbapenems over third-generation cephalosporins TGCs in critically ill SBP patients with higher (Chronic Liver Failure-Sequential Organ Failure Assessment) CLIF-SOFA scores, although no overall mortality benefit was observed in the general SBP population.[14] These results suggest that empirical antibiotic selection should be tailored to disease severity, with broader-spectrum agents preferred in high-risk scenarios. Similarly, Liu et al. found that over 15% of SBP cases in patients with acute decompensated cirrhosis were caused by Extended-spectrum beta-lactamase-producing gram-negative bacteria, advocating for the use of Piperacillin/tazobactam and carbapenems in both community-acquired and nosocomial infections.[15] This supports the utility of Piperacillin-Tazobactam as a frontline option in resistance-prone settings like ours.

While our findings align with this trend toward broader-spectrum coverage, they are balanced by contrasting evidence from Sheikh et al., who observed higher efficacy of Ceftriaxone (89.9%) compared to Ciprofloxacin (79.8%) in SBP resolution, although Ciprofloxacin was associated with fewer complications.[16] These data reinforce ceftriaxone's continued role in SBP management, especially in low-resistance contexts, but highlight the need for caution where antimicrobial resistance is prevalent. Furthermore, Yim et al. demonstrated that Cefotaxime, Ceftriaxone, and Ciprofloxacin had comparable efficacy when adjusted using a response-guided approach. Their results validate the 2021 AASLD practice guidance and emphasize the importance of early clinical reassessment and antibiotic modification in SBP.[17]

Adding further nuance, Santoiemma et al. reported antimicrobial resistance to first-line agents—including both ceftriaxone and piperacillin/tazobactam—in over 21% of SBP cases. This resistance was associated with higher ICU transfers and a trend toward worse outcomes, particularly among patients who had previously received prophylactic antibiotics.[18] Their findings underscore the necessity of local antibiogram awareness and emphasize personalized, data-driven antibiotic stewardship.

In a recent two-cohort study comparing Piperacillin-Tazobactam alone versus in combination with Linezolid (LZD), the addition of LZD significantly reduced treatment failure rates (16% vs. 48%, $p = 0.001$), though 30-day survival remained comparable between groups ($p = 0.87$). While our study did not evaluate combination regimens, we observed a higher response rate with TZP (75.22%) compared to Ceftriaxone (62.39%), supporting the role of Piperacillin-Tazobactam as a more effective monotherapy than ceftriaxone in empirical SBP management, particularly in settings with emerging resistance.[19] Resistance trends reported in recent studies show considerable rates of non-responsiveness to first-line agents, with Piperacillin-Tazobactam resistance observed in 26.7% of all SBP cases and up to 44.4% in nosocomial episodes, while Ceftriaxone resistance reached 31.7% overall. In contrast, our study population—largely community-acquired—demonstrated a significantly higher response to Piperacillin-Tazobactam compared to ceftriaxone (62.39%), suggesting that local resistance patterns and infection setting play a crucial role in empirical therapy outcomes[19]. In a recent culture-based analysis, Ceftriaxone and Piperacillin-Tazobactam showed low sensitivity rates of 31.4% and 25.7%, respectively, against SBP-causing organisms such as E. coli and Staph aureus.[20] Despite this, our study observed a higher clinical response with Piperacillin-Tazobactam (75.22%) compared to ceftriaxone (62.39%), possibly reflecting differences in patient population, empirical use versus culture-

based tailoring, or local microbial ecology. This underscores the importance of ongoing antimicrobial surveillance to guide empirical therapy.[21]

Taken together, these recent studies support the core conclusion of our investigation: while third-generation cephalosporins retain some utility, piperacillin/tazobactam offers a stronger empirical alternative in settings where MDROs are prevalent. To optimize outcomes, empirical treatment of SBP should be based on individual risk factors, regional resistance profiles, and real-time response to therapy.

CONCLUSION

This observational study demonstrated a higher treatment response with Piperacillin-Tazobactam compared to Ceftriaxone in managing spontaneous bacterial peritonitis (SBP) in cirrhotic patients. Although the difference did not reach statistical significance, the observed trend suggests that Piperacillin-Tazobactam may offer clinical benefits, especially in settings with increasing antimicrobial resistance. These findings highlight the need for ongoing local resistance surveillance and thoughtful empirical antibiotic selection. Future large-scale, controlled studies are essential to validate these associations and guide evidence-based SBP management.

Limitations of study and future recommendations

This study was limited by its observational design, which restricts the ability to infer causality. Additionally, the lack of randomization and potential selection bias may have influenced treatment allocation. The sample size, while adequate for preliminary comparisons, may not have been sufficient to detect smaller but clinically significant differences. Furthermore, microbiological culture data were not consistently available to correlate clinical response with pathogen-specific resistance patterns.

Future research should focus on larger, multicenter, randomized controlled trials to validate these findings and further explore the impact of local antimicrobial resistance profiles on empirical treatment outcomes. Continuous antimicrobial surveillance and personalized treatment approaches are essential to optimize SBP management in cirrhotic patients.

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AUTHOR'S CONTRIBUTIONS:

- **AH:** Conception of study, study design, data acquisition & analysis
- **MUS**: Data acquisition & analysis, manuscript drafting, critical review
- **AT:** Interpretation of data, critical review, manuscript drafting, critical review
- **HGM:** Conception of study, study design, critical review
- **HS:** Data collection, data acquisition & analysis, manuscript drafting
- **WAS:** Data acquisition & analysis**,** manuscript drafting, critical review

All authors approved the final version to be published and agreed to be accountable for all aspects of the work, ensuring that any questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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