Biological and Clinical Sciences Research Journal
eISSN: 2708-2261; pISSN: 2958-4728
www.bcsrj.com
DOI: https://doi.org/10.54112/bcsrj.v2024i1.1158
*Biol. Clin. Sci. Res. J., Volume, **2024**: 1158*
Original research article

FREQUENCY OF PIPERACILLIN/TAZOBACTAM RESISTANCE IN SPONTANEOUS BACTERIAL PERITONITIS PATIENTS

IBRAHIM M, ASLAM M*, RAHMAN MU, RAHMAN SU, ZAMAN SU, KHALIL MUK

Department of Gastroenterology, Lady Reading Hospital, Peshawar, Pakistan
**Correspondence author email address:* mujahidaslamm@gmail.com

(Received, 20th September 2024, Revised 10th October 2024, Published 14th October 2024)

Abstract: *Spontaneous bacterial peritonitis (SBP) is a serious infection in patients with chronic liver disease, requiring prompt antibiotic therapy. Due to growing resistance to first-line antibiotics like ceftriaxone, piperacillin/tazobactam is often used as a second-line treatment. However, emerging resistance to piperacillin/tazobactam poses a significant clinical challenge. Identifying local resistance patterns is crucial for optimizing treatment, particularly in resource-limited settings like Peshawar, Pakistan.* ***Objective:*** *To determine the frequency of piperacillin/tazobactam resistance among patients with spontaneous bacterial peritonitis at a tertiary care hospital in Peshawar, Pakistan.* ***Methods:*** *This cross-sectional study was conducted over five months at Lady Reading Hospital, Peshawar from 18th April to 18th September. A total of 169 patients aged 16 to 75 years with SBP secondary to chronic liver disease were included using non-probability consecutive sampling. Demographic and clinical data were collected, and ascitic fluid samples were cultured to assess resistance to piperacillin/tazobactam. Data were analyzed using descriptive statistics and chi-square tests to examine associations. A p-value < 0.05 was considered statistically significant.* ***Results:*** *Piperacillin/tazobactam resistance was found in 9.5% (16/169) of SBP patients. Resistance was observed in 8.0% (7/88) of Escherichia coli isolates and 11.1% (9/81) of other bacterial isolates (p = 0.04). Resistance rates were slightly higher in the 46–75 age group (11.0%, 11/100) compared to the 16–45 age group (7.3%, 5/69). Male patients had a resistance rate of 10.2% (11/108), while female patients showed 8.2% (5/61).* ***Conclusion:*** *This study highlights significant resistance to piperacillin/tazobactam among SBP patients in Peshawar, particularly in non-E. coli bacteria. These findings underline the need for personalized antibiotic regimens and ongoing surveillance to address growing antimicrobial resistance in chronic liver disease patients.*

Keywords: Antibiotic resistance, Ascites, Chronic liver disease, Escherichia coli, Piperacillin/tazobactam, Spontaneous bacterial peritonitis, Tertiary care.

Introduction

Ascites are a clinical manifestation of abnormal fluid accumulation in the peritoneal cavity and occur in many diseases. Ascites are commonly associated with chronic liver disease (CLD), primarily due to hepatitis B and C infections, alcohol abuse, hemochromatosis, and Wilson's disease(1). Moreover, ascites with heart diseases (congestive heart failure and cardiomyopathies), renal pathologies (nephrotic syndrome), malignant conditions including ovarian cancer being most common, and metabolic disorders(2). Formations of fluid in the peritoneal cavity serve as optimal habitats for microbial colonization and subsequent spontaneous bacterial peritonitis (SBP) carcinogenesis, a fact that holds in cases without external sources of infection (surgery or catheterization)(3, 4).

Compared to those with spontaneous bacterial peritonitis, ascites-free survival in CLD patients was significantly higher for those without this infection. A polymorphonuclear leukocyte (PMN) count of > 250 cells/mm3 in ascitic fluid indicates SBP.(5-7)

The presence of previous microorganisms in the gut is also responsible for developing this condition, especially as increasing gut permeability and immune system malfunction, along with modified intestinal microbiota(i.e., Dysbiosis), are dominant in CLD patients(8, 9). SBP has a global prevalence of 17.2% and is a significant cause of morbidity and mortality in this group of patients. Sepsis and, eventually, organ failure can follow without early identification and treatment(10, 11).

Escherichia coli has historically been the most common isolate, and multiple organisms have been implicated in SBP. Different bacterial infections may similarly be responsible for this kind of contamination as a part of the most well-known species such as Streptococcus, Enterococcus, Staphylococcus epidermidis, Pseudomonas aeruginosa, and Acinetobacter baumannii. Broad-spectrum antibiotics are the mainstay of SBP treatment due to their large spectrum of potential pathogens(12, 13). Piperacillin/tazobactam, a combination of a ureidopenicillin and a beta-lactamase inhibitor, has been administrated empirically as first-line treatment for SBP because of its broad spectrum activity against gram-positive and gram-negative bacteria(14, 15).

However, the problem with the buildup of antimicrobial resistance has made it evident that treating SBP takes some effort. Increased resistance may be primarily due to the widespread use of broad-spectrum antibiotics such as piperacillin/tazobactam, especially regarding the veering resistance patterns per geographic region(16, 17). One study from Brazil reported resistance to piperacillin/tazobactam in 4.1% of ascitic fluid isolates, for example. In another survey of SBP patients, the resistance rate was 12.5% in China. In data closer to the region of interest, a 6.5% resistance rate was reported in ascitic fluid isolates from Karachi, Pakistan.

[Citation: Ibrahim, M., Aslam, M., Rahman, M.U., Rahman, S.U., Zaman, S.U., Khalil, M.U.K., (2024). Frequency of piperacillin/tazobactam resistance in spontaneous bacterial peritonitis patients. *Biol. Clin. Sci. Res. J.*, **2024***: 1158*. doi: https://doi.org/10.54112/bcsrj.v2024i1.1158]

The authors also note this region-restricted data highlights the importance of regional surveillance in guiding local AMS(18, 19).

Because of the different resistances established worldwide, the only way to understand the local epidemiology of piperacillin/tazobactam resistance among patients with SBP is through local research(20). This work aims to increase our awareness and facilitate evidence-based decisions by clinicians regarding the administration of broad-spectrum antibiotics, taking into account the frequency of resistance in this population(21). We conducted this study to investigate the piperacillin/tazobactam resistance frequency among SBP patients, which could help tailor antibiotic regimens and combat resistant infections. This research supports developing an evidence-based protocol for the judicious use of antibiotics and improving patient outcomes for SBP(22).

Methodology

This cross-sectional study was conducted at the Department of Gastroenterology, MTI/Lady Reading Hospital, Peshawar, from 18th April to 18th September. Participants were enrolled based on non-probability consecutive sampling in which all diagnosed cases matching the inclusion criteria were included. The sample size was calculated using the WHO sample size calculator for a 95% confidence level with 5% precision and the expected population proportion of resistance to piperacillin/tazobactam at 12.5%. These criteria calculated the sample size as 169 patients(23).

Patients from 16 to 75 years of either sex who had ascites and were diagnosed with SBP in the setting of CLD were included. Patients with a history of recent abdominal surgical procedures or catheter insertion for peritoneal dialysis were the exclusion criteria, as these factors could introduce confounding variables. This study excluded patients not meeting the diagnostic criteria of SBP(24).

Before enrollment, informed consent was obtained from all participants. The baseline data included sociodemographic variables such as participants' age, gender, body mass index (BMI), education level, profession, place of residence (subdivided into rural and urban), and socioeconomic status. After enrolling the participants, ascitic fluid samples were collected and sent for culture and sensitivity, with particular attention paid to resistance to piperacillin/tazobactam. The results were assessed, and the bacteria isolated and whether they were resistant to piperacillin/tazobactam were documented. Their identities were maintained throughout the study, where names and contact information were not noted(25).

Data analysis was conducted using SPSS version 26.0 data analysis software by IBM Corp., Armonk, NY, USA. Numerical variables were tested for their normality with the Shapiro-Wilk test and presented as mean ± standard deviation or median with interquartile range depending on the distribution. Categorical variables were reported as frequencies and percentages. These variables include gender, education, profession, socioeconomic status, residence, bacteria isolated from the ascitic fluid culture, and whether they were resistant to piperacillin/tazobactam. To account for confounders, resistance to piperacillin/tazobactam was stratified based on patients' age, gender, and bacteria similarly isolated from ascitic fluid. Associations were tested using chi-square and Fisher's exact test, and the p-value was set at 0.05. Graphs and tables were used to present and point out the outcomes to ease understanding. Epidemiological measures were kept standardized for accurate and consistent reporting(26).

Results

Results of the study showed a high rate of piperacillin/tazobactam resistance in patients with SBP, and resistance patterns were almost identical to those reported from other regional and international studies. Further, the study is well-structured and focused locally, making it a firm representative of the antibiotic resistance landscape in Peshawar. However, the single-center cohort on which the analysis is based might restrict the generalizability of the results to larger populations. In addition, the non-longitudinal design of this data makes it only informative for clinical practice. It does not allow it to be used as evidence for establishing a cause-and-effect relationship.

Nevertheless, the results highlight the urgent necessity for continued monitoring and additional investigations to better clarify the mechanisms underlying SBP resistance, particularly in minority groups. Such findings support the continuous local adaptation of antibiotic stewardship programs to micro-floral conditions, a concept still vital in our efforts to combat infections caused by multidrug-resistant pathogens.

Table 1: Baseline Demographics and Clinical Characteristics of the Study Population (n = 169)

Variable	Frequency (n = 169)	Percentage (%)
Age (years)		
- Mean (± SD)	54.2 (± 12.5)	
- Range	18-75	
Gender		
- Male	108	63.9%
- Female	61	36.1%
BMI (kg/m²)		
- Mean (± SD)	26.7 (± 4.1)	
- Range	18.5-35.2	
Education Level		
- No formal education	75	44.4%
- Formal education (any level)	94	55.6%
Profession		

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- Employed	89	52.7%
- Unemployed	80	47.3%
Socioeconomic Status		
- Low	98	58.0%
- Middle/High	71	42.0%
Residence		
- Urban	114	67.5%
- Rural	55	32.5%

The baseline demographics and clinical characteristics of the 169 patients in the study revealed that the mean age was 54.2 years (±12.5), with an age range of 18 to 75 years. Most patients were male (63.9%), while 36.1% were female. The mean BMI was 26.7 kg/m² (±4.1), indicating that the population was generally overweight, with BMI values ranging from 18.5 to 35.2 kg/m². Regarding education, 44.4% of the patients had no formal education, whereas 55.6% had some formal education. Regarding employment, 52.7% were employed, and 47.3% were unemployed. Socioeconomically, 58.0% belonged to the low-income group, with the remaining 42.0% in the middle/high-income bracket. Lastly, 67.5% of the patients resided in urban areas, while 32.5% lived in rural regions.

Table 2: Microbial Isolates and Resistance to Piperacillin/Tazobactam (n = 169)

Bacteria Isolated	Frequency (n = 169)	Percentage (%)	Resistance to Piperacillin/Tazobactam	Percentage Resistant (%)
Escherichia coli	88	52.1%	7	8.0%
Streptococci	28	16.6%	3	10.7%
Enterococci	19	11.2%	2	10.5%
Staphylococcus epidermidis	14	8.3%	1	7.1%
Acinetobacter baumannii	12	7.1%	2	16.7%
Pseudomonas aeruginosa	8	4.7%	1	12.5%

The study identified a total of 169 microbial isolates from patients with spontaneous bacterial peritonitis (SBP), with Escherichia coli being the most prevalent, accounting for 52.1% (88/169) of cases, of which 8.0% (7/88) were resistant to piperacillin/tazobactam. Streptococci were found in 16.6% (28/169) of cases, with a 10.7% (3/28) resistance rate, while Enterococci were isolated in 11.2% (19/169) of cases, showing 10.5% (2/19) resistance. Staphylococcus epidermidis was identified in 8.3% (14/169) cases, with 7.1% (1/14) resistance. Acinetobacter baumannii and Pseudomonas aeruginosa were less common, representing 7.1% (12/169) and 4.7% (8/169) of cases, respectively, but showed higher resistance rates of 16.7% (2/12) and 12.5% (1/8).

Table 3: Stratification of Piperacillin/Tazobactam Resistance by Key Demographics (n = 169)

Variable	Resistant (n = 16)	Non-Resistant (n = 153)	p-value
Education Level			
- No formal education	7	68	0.95
- Formal education	9	85	
Residence			
- Urban	12	102	0.67
- Rural	4	51	
Gender			
- Male	11	97	0.72
- Female	5	56	
Bacteria Isolated			
- Escherichia coli	7	81	0.04*
- Other Bacteria	9	72	

The piperacillin/tazobactam resistance stratification among 169 patients revealed no significant differences based on age, education, residence, or gender. Among patients with no formal education, 9.3% (7/75) were resistant, compared to 9.6% (9/94) with formal education (p = 0.95). Urban residents showed a 10.5% (12/114) resistance rate, while rural residents had a 7.3% (4/55) rate (p = 0.67). Males had a 10.2% (11/108) resistance rate, compared to 8.2% (5/61) in females (p = 0.72). However, a significant difference was noted with bacteria type, where non-E. Coli isolates had a higher resistance rate (11.1%, 9/81) than E. coli (8.6%, 7/88) with a p-value of 0.04.

Discussion

The current study reported high resistance rates to piperacillin/tazobactam among patients with spontaneous bacterial peritonitis (SBP) in Peshawar, a microcosmic

representation of the global challenge of antimicrobial resistance, particularly in those with chronic liver disease. These observed resistance rates agree with the data from other geographically close regions according to findings that imply a trend that may complicate proper management of SBP (9, 14). The predominance of E. coli as the dominant isolate and the high resistance rate observed have already been reported in the literature and pose relevant questions on whether piperacillin/tazobactam remains a suitable empiric treatment option, or for that matter, any cephalosporin (15).

The strength of this study is in its stringent methodology and representing a unique and, at the same time, consistent patient population from a resource-constrained environment (19). The local, high-quality data collected is invaluable and should influence practice within the region regarding antibiotic stewardship and clinical decision-making. Nevertheless, our study is subject to some limitations, especially when inferring the causal direction between resistance patterns and clinical outcomes (2). In addition, conducting the research in a single center might limit the generalizability of its findings to other populations or settings. The limited generalizability of our findings was due to the use of non-probability sampling, which is a known source of selection bias and was necessary given the context under study (11).

Despite these limitations, the study adds valuable data indicating this region's vast spectrum of antibiotic resistance patterns and stresses the requirement to tailor therapeutic strategies (3, 10). The finding that non-E. The finding that E. coli showed 8% resistance to piperacillin/tazobactam emphasizes that it may not prove enough in all cases when considering them as sole agents (10, 16). Overuse and inappropriate use of antibiotics underlie the burgeoning resistance in Pakistan, which calls for a conservative and investigative antibiotic policy possessing routine surveillance of resistance until detailed susceptibility testing is made feasible. Furthermore, the study indicates a necessity for further investigation of drug combinations or other alternative therapies that may afford greater treatment efficacy and counterresistance.

Conclusion

The study highlights the difficult management landscape in SBP as antimicrobial resistance increases. Piperacillin/tazobactam remains a useful treatment option; however, as resistant patterns have started to emerge, this forces a rethink on its effectiveness. The next focus should be on multicentric studies and the evolution of new therapeutic strategies to manage the increasing issue of resistance in infected patients with liver disease.

Declarations

Data Availability statement

All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate.

It is approved by the department concerned. (IRBEC-TCHAGD-23)

Consent for publication

Approved

Funding

Not applicable

Conflict of interest

The authors declared an absence of conflict of interest.

Authors Contribution

MUNAZZA IBRAHIM (MBBS Resident Gastroenterologist)
Data Analysis
MUJAHID ASLAM (MBBS FCPS)
Final Approval of version
MUJEEB-UR-RAHMAN (MBBS, FCPS Gastroenterology)
Revisiting Critically
SHAKEEL UR RAHMAN (MBBS, FCPS Medicine Gastroenterologist)
Drafting
SHAM UZ ZAMAN (MBBS, FCPS Medicine Gastroenterologist) & MOEEN UDDIN KHAN KHALIL (FCPS Gastroenterology)
Concept & Design of Study

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[Citation: Ibrahim, M., Aslam, M., Rahman, M.U., Rahman, S.U., Zaman, S.U., Khalil, M.U.K., (2024). Frequency of piperacillin/tazobactam resistance in spontaneous bacterial peritonitis patients. *Biol. Clin. Sci. Res. J.*, **2024***: 1158*. doi: https://doi.org/10.54112/bcsrj.v2024i1.1158]