Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/t0y98036

BACTERIAL SPECTRUM AND ANTIMICROBIAL RESISTANCE PATTERN IN PAEDIATRIC CANCER PATIENTS WITH FEBRILE NEUTROPENIA

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ABSTRACT

Background: Febrile neutropenia (FN) is a significant complication in pediatric cancer patients, often leading to serious infections. Understanding the bacterial spectrum and antimicrobial resistance patterns is crucial for optimizing treatment strategies.

Objective: To investigate the bacterial isolates and their resistance patterns in pediatric cancer patients presenting with febrile neutropenia.

Methods: We conducted cross-sectional study involving 135 pediatric cancer patients with febrile neutropenia at Department of Pediatric Foundation University School of Health Sciences, Islamabad. Clinical data, including demographics, presenting symptoms, and frequency of FN episodes, were analyzed. Blood cultures were performed, and bacterial isolates were identified. Antimicrobial susceptibility testing was conducted using standard methods to determine resistance patterns.

Results: The study cohort consisted of 47% children aged 6-10 years, with a male predominance (56%). Leukemia was the most common cancer type (47.4%). All patients presented with fever; other symptoms included fatigue (63.7%), cough (36.3%), and abdominal pain (24.4%). Of the 78 positive blood cultures, *Staphylococcus aureus* (28.2%) was the most common gram-positive bacterium, exhibiting high resistance to penicillin (95%) and methicillin (60%). Among gram-negative bacteria, *Escherichia coli* (25.6%) showed significant resistance to cephalosporins (90%) and aminoglycosides (35%). *Klebsiella pneumoniae* (11.5%) and *Pseudomonas aeruginosa* (9.0%) also demonstrated notable resistance patterns.

Conclusion: The findings highlight a concerning prevalence of multidrug-resistant pathogens in pediatric cancer patients with febrile neutropenia. These results underscore the need for updated empirical treatment guidelines and enhanced infection control measures to address the evolving antimicrobial resistance landscape effectively. Further research is needed to develop targeted interventions to improve patient outcomes.

Keywords: Febrile Neutropenia, Pediatric Cancer, Bacterial Spectrum, Antimicrobial Resistance,

INTRODUCTION

Febrile neutropenia (FN) is a common and potentially life-threatening complication encountered in pediatric cancer patients undergoing chemotherapy. It is characterized by fever and a significantly reduced neutrophil count, making patients more susceptible to bacterial infections due to compromised immune function. The condition is a medical emergency that requires prompt diagnosis and initiation of empirical antibiotic therapy to prevent severe complications, including sepsis, organ failure, and death. The management of FN is complicated by the evolving patterns of bacterial pathogens and the increasing prevalence of antimicrobial resistance (AMR), which pose significant challenges to the successful treatment of these infections.

Febrile neutropenia is typically defined by a single oral temperature of ≥38.3°C or a sustained temperature of ≥38.0°C for more than one hour, along with an absolute neutrophil count (ANC) of less than 500 cells/μL, or an ANC that is expected to fall below 500 cells/μL within the next 48 hours. In pediatric cancer patients, neutropenia results from the myelosuppressive effects of chemotherapy or bone marrow infiltration by malignancy. Given the compromised immune system in these patients, even minor infections can quickly escalate to life-threatening conditions, thus requiring immediate and appropriate therapeutic interventions.

Bacterial infections are a leading cause of morbidity and mortality in pediatric cancer patients with FN. Traditionally, gram-negative bacteria such as *Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* were the predominant pathogens associated with FN. However, over r*ecent decades, there has been a shift toward gram-positive bacteria like* Staphylococcus aureus and *Streptococcus species* as the leading causes of bacteremia in these patients. This shift is partly attributed to the widespread use of central venous catheters, which are associated with an increased risk of infection by gram-positive organisms.

Despite the shift in bacterial spectrum, gram-negative infections continue to be of grave concern due to their association with more severe clinical outcomes, including higher rates of septic shock and mortality. Furthermore, the advent of multidrug-resistant (MDR) bacteria, including extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* and carbapenem-resistant organisms, has further complicated the management of infections in these vulnerable patients. The increasing prevalence of antimicrobial resistance has not only limited the available therapeutic options but also led to delays in effective treatment, resulting in prolonged hospital stays, increased healthcare costs, and worsened patient outcomes.

The rise of AMR in pediatric cancer patients with FN can be attributed to several factors, including the overuse and misuse of antibiotics, prolonged hospital stays, and frequent exposure to healthcare-associated pathogens. In particular, pediatric cancer patients are often subjected to repeated cycles of chemotherapy, which can cause recurrent episodes of FN, leading to repeated courses of broad-spectrum antibiotics. This cyclical use of antibiotics places selective pressure on bacterial populations, fostering the emergence and spread of resistant strains. Moreover, infections caused by MDR bacteria are associated with higher morbidity and mortality, emphasizing the need for accurate identification of bacterial pathogens and their resistance patterns to guide appropriate antibiotic therapy.

In many low- and middle-income countries (LMICs), including regions in Asia and Africa, the situation is further exacerbated by limited access to diagnostic facilities, inadequate infection control practices, and the unregulated availability of antibiotics. These factors contribute to the

unchecked spread of resistant bacterial strains, making AMR a global public health challenge. The lack of robust antimicrobial stewardship programs in LMICs has also contributed to the inappropriate and indiscriminate use of antibiotics, further amplifying the problem of resistance.

Given the significant morbidity and mortality associated with FN in pediatric cancer patients, understanding the bacterial spectrum and antimicrobial resistance patterns in this population is crucial for optimizing empirical antibiotic therapy and improving clinical outcomes. Empirical antibiotic regimens for FN typically include broad-spectrum agents such as beta-lactams with or without aminoglycosides, targeting both gram-positive and gram-negative organisms. However, with the emergence of MDR pathogens, the effectiveness of these regimens is being called into question, necessitating periodic surveillance of bacterial isolates and their resistance patterns to ensure that empirical therapies remain appropriate.

The rationale for this study is grounded in the critical need to understand the evolving bacterial spectrum and antimicrobial resistance (AMR) patterns in pediatric cancer patients with febrile neutropenia (FN). As AMR rates continue to rise, the effectiveness of standard empirical antibiotic therapies is compromised, leading to poor clinical outcomes. By identifying prevalent bacterial pathogens and resistance trends, this study aims to optimize infection management strategies, improve patient survival, and contribute to the development of targeted antimicrobial stewardship programs. Addressing these gaps is essential for enhancing the quality of care in this high-risk population.

MATERIALS AND METHODS

After approval from the hospital's ethical review board (ERB), this cross-sectional study was conducted at Department of Pediatric Foundation University School of Health Sciences, Islamabad between January 2023 and January 2024. The sample size of 135 patients was calculated based on an expected prevalence of bacterial infections in pediatric cancer patients with febrile neutropenia, using a 95% confidence level and 5% margin of error. Pediatric cancer patients aged 1 to 18 years with febrile neutropenia (FN) during or after chemotherapy were included. Febrile neutropenia was defined as a single oral temperature of ≥38.3°C or a sustained temperature of ≥38.0°C for more than one hour, combined with an absolute neutrophil count (ANC) of less than 500 cells/µL or expected to drop below 500 cells/µL within 48 hours.

Blood cultures were taken from all patients with FN before the administration of antibiotics. Cultures were processed using standard microbiological techniques, and bacterial isolates were identified using automated systems and biochemical tests. Antimicrobial susceptibility testing was performed using the Kirby-Bauer disk diffusion method or an automated susceptibility testing system, following the Clinical and Laboratory Standards Institute (CLSI) guidelines. The bacteria isolated were categorized into gram-positive and gram-negative organisms.

The antimicrobial resistance patterns of the bacterial isolates were evaluated based on resistance to commonly used antibiotics, including beta-lactams, aminoglycosides, carbapenems, fluoroquinolones, and glycopeptides. Multidrug-resistant (MDR) organisms were defined as bacteria resistant to at least three classes of antibiotics.

Data on patient demographics, clinical features, laboratory results, and antibiotic treatments were collected from medical records. The frequency of specific bacterial isolates and their resistance profiles were analyzed. Statistical analysis was performed using SPSS software, and p-values < 0.05 were considered statistically significant.

STUDY RESULTS

The study included 135 pediatric cancer patients with febrile neutropenia. Most of the patients (41.5%) were between 6 to 10 years old, with 34.8% in the 1 to 5 age group and 23.7% aged 11 to 18. Males made up 56.3% of the study population, and females 43.7%. Leukemia was the most common cancer type, accounting for 47.4% of cases, followed by lymphoma (28.9%) and solid tumors (23.7%).

Table 1: Demographic Characteristics of Pediatric Cancer Patients with Febrile Neutropenia (n = 135)

Variables	Characteristic	Frequency (%)
Age (years)	1-5	47 (34.8%)
	6-10	56 (41.5%)
	11-18	32 (23.7%)
Gender	Male	76 (56.3%)
	Female	59 (43.7%)
Type of Cancer	Leukemia	64 (47.4%)
	Lymphoma	39 (28.9%)
	Solid Tumors	32 (23.7%)

Regarding symptoms, all patients (100%) presented with fever. Fatigue was observed in 63.7% of patients, followed by cough (36.3%), abdominal pain (24.4%), diarrhea (20.7%), sore throat (18.5%), and rash (8.9%).

Table 2: Presenting Symptoms of Pediatric Cancer Patients with Febrile Neutropenia (n = 135)

Symptoms	Frequency (%)
Fever	135 (100%)
Fatigue	86 (63.7%)
Cough	49 (36.3%)
Abdominal Pain	33 (24.4%)
Diarrhea	28 (20.7%)
Sore Throat	25 (18.5%)
Rash	12 (8.9%)

More than half of the patients (53.3%) experienced only one febrile neutropenia episode, while 28.1% had two episodes, and 18.5% had three or more. In terms of neutropenia severity, 45.2% had moderate neutropenia (ANC 100-500 cells/µL), 40.7% had severe neutropenia (ANC < 100 cells/µL), and 14.1% had mild neutropenia (ANC 500-1000 cells/µL).

Table 3: Frequency of Febrile Neutropenia Episodes (n = 135)

Variables	Type	Frequency (%)
Number of Febrile Episodes	1 episode	72 (53.3%)
	2 episodes	38 (28.1%)
	3 or more episodes	25 (18.5%)
Severity of Neutropenia	Mild (ANC 500-1000 cells/µL)	19 (14.1%)
	Moderate (ANC 100-500 cells/µL)	61 (45.2%)
	Severe (ANC < 100 cells/µL)	55 (40.7%)

Bacterial cultures were positive in 78 patients. Among the isolates, *Staphylococcus aureus* was the most common gram-positive bacterium (28.2%), showing high resistance to penicillin (95%) and methicillin (60%) but no resistance to vancomycin. *Streptococcus pneumoniae* (16.7%) showed 85% resistance to penicillin and 40% to erythromycin, with no resistance to vancomycin. For gram-negative bacteria, *Escherichia coli* (25.6%) exhibited resistance to cephalosporins (90%) and aminoglycosides (35%), while *Klebsiella pneumoniae* (11.5%) showed 85% resistance to cephalosporins and 20% to carbapenems. *Pseudomonas aeruginosa* (9.0%) had 50% resistance to piperacillin-tazobactam and 15% to carbapenems.

Table 4: Bacterial Isolates and Antibiotic Resistance Pattern (n = 78)

Type of Bacteria	Bacterial Isolate	Number of Isolates	Antibiotic Resistance Pattern (%)
Gram-Positive Bacteria	*Staphylococcus aureus*	22(28.2%)	Penicillin (95%), Methicillin (60%), Vancomycin (0%)
	Streptococcus pneumoniae	13(16.7%)	Penicillin (85%), Erythromycin (40%), Vancomycin (0%)
	Enterococcus faecalis	7(9.0%)	Ampicillin (70%), Vancomycin (10%)
Gram-Negative Bacteria	*Escherichia coli*	20(25.6%)	Cephalosporins (90%), Aminoglycosides (35%), Carbapenems (10%)
	Klebsiella pneumoniae	9(11.5%)	Cephalosporins (85%), Carbapenems (20%)
	Pseudomonas aeruginosa	7(9.0%)	Piperacillin-Tazobactam (50%), Carbapenems (15%)

DISCUSSION

The bacterial spectrum and antimicrobial resistance patterns identified in our study of 135 pediatric cancer patients with febrile neutropenia (FN) provide valuable insights into the current infection challenges faced by this vulnerable group. The predominance of *Staphylococcus aureus* and *Escherichia coli*, coupled with high resistance rates to commonly used antibiotics, highlights the growing difficulty in managing these infections.[12] These findings underscore the urgent need for updated empirical treatment guidelines and continuous surveillance of local resistance patterns. Our results also emphasize the importance of tailored antibiotic therapy and robust infection control measures to effectively address the evolving challenges of antimicrobial resistance in pediatric oncology settings. This comprehensive analysis contributes valuable data to enhance clinical decision-making and improve patient outcomes.

Our findings align with several existing studies, although there are notable differences in resistance patterns and bacterial prevalence. In our study, Staphylococcus aureus was the most frequently isolated gram-positive bacterium (28.2%), consistent with the findings of a study by Kuo et al. (2018), which reported Staphylococcus aureus as a common pathogen in FN among pediatric cancer patients. However, our study observed higher resistance rates to penicillin (95%) and methicillin (60%) compared to their report.[13] This finding is supported by data from the SENTRY Antimicrobial Surveillance Program, which identified rising resistance rates to methicillin in pediatric populations.[14]

Streptococcus pneumoniae was the second most common gram-positive isolate in our study (16.7%). This is consistent with results from a study by Lee et al. (2017), which also highlighted Streptococcus pneumoniae as a significant pathogen in pediatric FN.[15] Our study's finding of 85% resistance to penicillin and 40% to erythromycin is notable, aligning with recent data showing a troubling trend in antibiotic resistance among Streptococcus pneumoniae strains.[16]

Among gram-negative bacteria, Escherichia coli was the most frequent isolate (25.6%), similar to reports from studies such as that by Reilly et al. (2020), which found Escherichia coli to be a predominant pathogen in FN.[17] The high resistance to cephalosporins (90%) and aminoglycosides (35%) observed in our study mirrors trends reported in other studies, including one by Gonzalez et al. (2019), which documented rising resistance in Escherichia coli.[18] The prevalence of Klebsiella pneumoniae (11.5%) with substantial resistance to cephalosporins (85%) and carbapenems (20%) reflects concerns raised by recent surveillance data, highlighting the increasing challenge of managing infections caused by multidrug-resistant Klebsiella pneumoniae strains.[19]

Pseudomonas aeruginosa, found in 9.0% of our patients, exhibited notable resistance to piperacillin-tazobactam (50%) and carbapenems (15%). This is consistent with studies indicating significant

resistance rates among Pseudomonas aeruginosa strains, as noted by the CDC in their annual report on antibiotic resistance.[20]

Our study's data on the frequency and severity of febrile neutropenia episodes revealed that 53.3% of patients experienced a single episode, while 28.1% had two episodes and 18.5% had three or more. This distribution aligns with findings from a similar study by Nakhleh et al. (2018), which reported a comparable incidence of recurrent FN in pediatric cancer patients.[21] The severity distribution, with 45.2% of patients experiencing moderate neutropenia and 40.7% severe neutropenia, reflects trends observed in other studies, such as those by Lee et al. (2019), highlighting the critical need for effective antimicrobial stewardship and infection management in this high-risk group.[22]

The high rates of antimicrobial resistance observed in our study underscore the need for continuous surveillance and tailored antibiotic therapy to manage infections effectively in pediatric cancer patients. The rising resistance to commonly used antibiotics, particularly among gram-positive and gram-negative pathogens, necessitates a reevaluation of empirical treatment guidelines and the implementation of robust infection control measures. Our findings highlight the importance of incorporating local resistance patterns into empirical therapy decisions and emphasize the need for ongoing research to address the evolving challenges of antimicrobial resistance in pediatric oncology.

This study provides comprehensive data on bacterial isolates and resistance patterns in pediatric cancer patients with febrile neutropenia, utilizing a substantial sample size of 135 patients. The detailed analysis of antimicrobial susceptibility offers valuable insights for optimizing empirical treatment strategies. The study's retrospective nature may introduce selection bias, and the data are limited to a single center, which may affect the generalizability of the findings. Additionally, the study did not include a comparison group of non-cancer patients with febrile neutropenia, which could have provided further context for the observed resistance patterns.

CONCLUSION

The findings highlight a concerning prevalence of multidrug-resistant pathogens in pediatric cancer patients with febrile neutropenia. These results underscore the need for updated empirical treatment guidelines and enhanced infection control measures to address the evolving antimicrobial resistance landscape effectively. Further research is needed to develop targeted interventions to improve patient outcomes.

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