Prospective Monitoring of Adverse Drug Reactions in Pediatric Cancer Patients with Febrile Neutropenia

Running Title: *Antibiotic Prescribing in Paediatric Febrile Neutropenia*

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Abstract:

Context: Paediatric malignancies represent a major global health concern, with febrile neutropenia (FN) being one of the most frequent and life-threatening chemotherapy-related complications. Understanding antibiotic prescribing practices, microbial profiles, and adverse drug reactions (ADRs) is vital to improving treatment outcomes in this vulnerable group.

Aims: To analyse antibiotic prescribing patterns and ADRs among paediatric cancer patients presenting with febrile neutropenia.

Settings and Design: A prospective observational study was conducted over six months at the department of Paediatric Haemato-Oncology in a tertiary care centre in Southern India.

Methods and Material: Paediatric patients below 18 years of age with malignancies receiving chemotherapy who developed FN were enrolled. Data were collected on demographics, microbial cultures, antibiotic use, and ADRs using a validated proforma. ADRs were assessed using the Naranjo probability scale.

Statistical analysis used: Descriptive statistics including means, standard deviations, frequencies, and percentages were analysed using SPSS version 22.0.

Results: A total of 193 paediatric oncology patients with mean age 7.21 ± 4.43 years were studied. Leukaemia was the most common malignancy 76.68%. Gram-negative bacteria for 31.08% of cases predominantly *Burkholderia cepacia* and *Escherichia coli*, were the major isolates. Sixty ADRs were identified, 90% classified as probable and 65% attributed to antineoplastic agents.

Conclusion: Multidrug-resistant gram-negative infections and frequent ADRs highlight the urgent need for antimicrobial stewardship and vigilant pharmacovigilance in paediatric FN management.

Key-words: Adverse Drug Reaction; Antimicrobial Resistance; Febrile Neutropenia; Paediatric Oncology

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Introduction

Paediatric malignancies represent a critical global health issue due to their significant contribution to morbidity and mortality among children and adolescents. Annually, approximately 400,000 new cancer cases are diagnosed worldwide in individuals aged 0–18 years with leukaemia's, lymphomas, and solid tumours such as neuroblastoma and Wilms tumour comprising the majority[1,2]. Leukaemia notably acute lymphoblastic leukaemia (ALL), remains the most common childhood cancer, accounting for 27–

35% of paediatric malignancies and exhibiting improved survival rates in high-income settings[3,4]. Despite advances in treatment modalities, chemotherapy-associated complications continue to pose substantial clinical challenges[3,4].

Febrile neutropenia (FN) is among the most serious and frequent complications in paediatric oncology patients undergoing chemotherapy[5,6]. **Febrile neutropenia** is defined as a single temperature of **≥38.3°C** or a sustained temperature of **≥38.0°C for more than one hour** in patients with an **absolute neutrophil count (ANC) <500 cells/µL (0.5 × 10⁹/L).** It represents a medical emergency in immunocompromised children, who are highly susceptible to severe infections and require prompt empirical antibiotic therapy to minimize morbidity and mortality[5,6]. The incidence of FN is particularly high within the initial two weeks after chemotherapy initiation, which is a critical period for infection-related complications[7]. Globally, FN occurs in approximately 13–21% of patients receiving standard myelosuppressive chemotherapy regimens, with the highest rates observed during the first chemotherapy cycle (23–36%)[8].

The overall incidence of neutropenia varies widely, ranging from 2% to 50%, depending on patient-related risk factors, cancer type, chemotherapy regimen, and genetic susceptibility[8]. Among patients with haematological malignancies, FN incidence can reach up to 80%, compared to 10–50% in those with solid tumours[9]. In developing countries and low- and middle-income countries, the burden of FN is disproportionately higher, with reported incidence rates ranging from 50% to 70.7% in some African and South Asian cohorts, attributable to limited access to prophylactic granulocyte colony-stimulating factors (G-CSFs), delayed diagnosis, higher rates of multidrug-resistant organisms, and inadequate supportive care infrastructure[10,13]. In India specifically, studies have documented FN incidence rates of approximately 27–36% among paediatric oncology patients, with bacteraemia detected in 20–30% of culture-positive cases, underscoring the significant infection-related morbidity in this region[11,12].

Prompt empirical antibiotic therapy, ideally within one hour of fever onset, is the cornerstone of FN management. Current IDSA (2011), ESMO (2016), and 2017 Lehrnbecher consensus guidelines recommend anti-pseudomonal beta-lactams as first-line empirical therapy, with blood cultures collected before initiation[5,7]. The growing burden of multidrug-resistant organisms (MDROs) in low- and middle-income countries (LMIC) settings makes institution-level surveillance studies such as the present one critically important[12,14]. Antimicrobial resistance (AMR) further complicates treatment decisions, necessitating continuous local surveillance and stewardship[13,14].

Paediatric cancer patients are at heightened risk of ADRs, particularly from chemotherapeutic agents and antibiotics used during FN episodes[15,16]. In this study, ADR documentation is restricted to chemotherapy- and antibiotic-related reactions, as these directly bear on the primary objective of antibiotic prescribing safety[15]. Timely identification of such ADRs is essential to prevent treatment interruptions and improve outcomes[16].

Given the limited institution-level data on febrile neutropenia management in paediatric oncology in India, this study was conducted at a tertiary care centre in southern India to assess antibiotic prescribing patterns, identify bacterial isolates and their resistance profiles, document adverse drug reactions related to chemotherapy and antibiotics, and analyse clinical outcomes in paediatric febrile neutropenia patients, aiming to contribute to evidence-based optimization of antimicrobial use and patient safety in this population[11,19].

Subjects and Methods:

A prospective observational study was conducted over a period of six months in the Department of Paediatric Haemato-Oncology at a tertiary care teaching hospital in South India. The study included patients below 18 years of age receiving chemotherapy for haematological or solid malignancies who developed febrile neutropenia or were anticipated to develop neutropenia within 48 hours of chemotherapy. Written informed consent was obtained from parents or legal guardians before enrolment. Patients requiring intensive care unit admission at presentation and those whose guardians declined consent were excluded from the study.

A structured and validated data collection proforma was used to record patient demographics, cancer diagnosis, chemotherapy details, clinical presentation, laboratory investigations, microbiological findings, antibiotic therapy, adverse drug reactions, and treatment outcomes. Blood cultures were obtained before initiating empirical antibiotic therapy whenever clinically indicated, and subsequent modifications in antimicrobial therapy were based on culture and sensitivity reports as per institutional protocols.

Chemotherapy-related and antibiotic-related ADRs were identified and assessed using the Naranjo Adverse Drug Reaction Probability Scale. The severity, management, and outcomes of ADRs were also documented.

The collected data were entered into Microsoft Excel and analysed using IBM SPSS Statistics version 22.0. Descriptive statistics, including frequencies, percentages, means, and standard deviations, were

used to summarize the study findings. Associations between selected clinical variables and antibiotic prescribing patterns were analysed using appropriate statistical tests, with a p-value <0.05 considered statistically significant. Ethical approval for the study was obtained from the Institutional Ethics Committee before commencement. (No: KLECOPBGMEC/D001-2024).

Results:

This prospective observational study included a total of 193 paediatric cancer patients aged <18 years mean age 7.21 ± 4.43 years with febrile neutropenia were prospectively enrolled. The male-to-female ratio was 1.57:1 (118 males. 75 females). All patients were managed at the Department of Paediatric Haemato-Oncology, a tertiary care centre in southern India.

The underlying malignancies included leukaemia (76.68%, n=148), non-Hodgkin lymphoma (10.36%, n=20), bone and soft-tissue sarcomas (5.18%, n=10), neuroendocrine tumours (4.66%, n=9), and Hodgkin lymphoma in (3.11%, n=6). The predominance of leukaemia is consistent with its known high incidence in the paediatric age group.

Table 1: Demographic and Clinical Characteristics

Clinical Parameter	Category	Patient Count (n)	Percentage (%)
Gender Distribution	Male	118	61.13
	Female	75	38.87
Age Classification	0–12 Years	156	80.82
	13–17 Years	37	19.18
Primary Oncological Diagnosis	Leukaemia	148	76.68
	Non-Hodgkin's Lymphoma	20	10.36
	Bone & Soft-Tissue Sarcomas	10	5.18
	Neuroendocrine Tumours	9	4.66
	Hodgkin's Lymphoma	6	3.11

Out of the 193 evaluated febrile neutropenia episodes, bloodstream cultures yielded no microbial growth in 44.04% (n = 85) of cases. Conversely, active microbiological isolation was successful in the remaining 55.96% (n = 108) of the cohort episodes. Within this culture-positive subset, Gram-negative bacterial pathogens were more prevalent, accounting for 31.08% (n = 60) of the total patient population, whereas Gram-positive pathogens accounted for 24.87% (n = 48).

A granular analysis of the Gram-negative spectrum (n = 60) revealed that *Burkholderia cepacia* was the predominant pathogen, representing 35.00% (n = 21) of all Gram-negative isolates. This was followed in frequency by *Escherichia coli* at 20.00% (n = 12) and *Acinetobacter baumannii/haemolyticus* at 13.33% (n = 8). Within the Gram-positive cohort (n = 48), coagulase-negative *Staphylococcus* species (CoNS) and *Staphylococcus epidermidis* were isolated in identical frequencies, with each pathogen accounting for 35.42% (n = 17) of the Gram-positive subtype. Additionally, Methicillin-Resistant *Staphylococcus aureus* (MRSA) constituted 10.42% (n = 5) of the isolated Gram-positive microorganisms.

Gram-positive isolates	n (%)
Coagulase negative Staphylococcus species	17 (35.42)
Enterococcus faecalis	1 (2.08)
Enterococcus faecium	3 (6.25)
Methicillin-Resistant Staphylococcus aureus	5 (10.42)
Staphylococcus aureus	1 (2.08)
Staphylococcus epidermidis	17 (35.42)
Staphylococcus haemolyticus	4 (8.33)
Gram-negative isolates	n (%)
Acinetobacter baumanii/ haemolyticus	8 (13.33)
Acinetobacter lwoffi	4 (6.67)
Burkholderia cepacia	21 (35)
Citrobacter freundii	1 (1.67)
Escherchia coli	12 (20)
Empedobacter brevis	2 (3.33)
Enterobacter cloacae	2 (3.33)
Klebsiella pneumoniae	4 (6.67)
Pseudomonas aeruginosa	6 (10)

Table 2: Pathogen Distribution of Culture-Positive Bloodstream Infections total of 60 distinct adverse drug reactions directly associated with primary therapeutic regimens (chemotherapy and systemic antibiotics) were recorded. Clinical profiling by organ system involvement showed that gastrointestinal toxicities (including severe mucositis, vomiting, and diarrhoea) predominated, comprising 43.33% (n = 26) of all recorded events. Haematological toxicities, characterized by severe cytopenias exceeding baseline therapeutic expectations, constituted 31.67% (n = 19) of cases. Dermatological toxicities, which presented as pruritus, urticaria, or maculopapular rashes, made up 15.00% (n = 9) of the reactions.

Etiological stratification indicated that antineoplastic chemotherapeutic drugs were the primary agents responsible for these reactions, linked to 65% (n = 39)

of the occurrences. Systemic empirical antibiotics utilized during febrile neutropenia management accounted for 15% (n = 9) of the ADRs, while other core supportive care medications (such as systemic corticosteroids or antifungals) triggered the remaining 13.33% (n = 8).

Causality monitoring was executed using the objective Naranjo Adverse Drug Reaction Probability Scale. Based on specific criteria, including clinical timeline matching, reactions following drug introduction, improvements upon dechallenge, and absence of alternative confounding explanations-the scale classified 90.00% (n = 54) of the events as Probable (Naranjo score 5–8). The remaining 10.00% (n = 6) of toxicities were categorized as Possible (Naranjo score 1–4). No events met the criteria for Definite (≥ 9) or Doubtful (≤ 0) causality.

Table 3: Systemic Types, Drug Aetiology, and Naranjo Causality Breakdown of ADR

Analytical Dimension	Category		Number of ADRs (n)	Percentage (%)
Organ System Type	Gastrointestinal	Mucositis, Severe Vomiting, Diarrhoea	26	43.33
	Haematological	Cytopenias, Neutropenia, Anemia	19	31.67
	Dermatological	Maculopapular Rash, Pruritus, Urticaria	9	15.00
	Metabolic/Renal	Electrolyte Disturbances, Elevated Creatinine	6	10.00
Suspected Drug Class	**Antineoplastic Agents**	Vincristine, Arsenic trioxide, Methotrexate, ATRA (Tretinoin), Daunorubicin, Azacitidine, Cytarabine, Cyclophosphamide, PEG-asparaginase, 6-Mercaptopurine, Rituximab, Doxorubicin, Dacarbazine	39	65.00
	Systemic Antibiotics	Amoxicillin–Clavulanate, Aztreonam, Piperacillin–Tazobactam, Meropenem	9	15.00
	Corticosteroids	Hydrocortisone, Prednisolone, Dexamethasone	8	13.33
	Others	Cyclosporine, Sodium Valproate, Ketamine, Hemorel A, Filgrastim, Fluconazole	4	6.67
Naranjo Causality Assessment	Definite	Score ≥9	0	0.00
	Probable	Score 5–8	54	90.00
	Possible	Score 1–4	6	10.00
	Doubtful	Score ≤0	0	0.00

Discussion:

This study provides important insights into the antibiotic prescribing practices, antimicrobial resistance patterns, and adverse drug reactions encountered in paediatric cancer patients presenting with febrile neutropenia in a tertiary care hospital in India.

The predominance of leukaemia (76.68%, n = 148) in our study aligns with established global paediatric

oncology epidemiology, where haematological malignancies consistently comprise the majority of childhood cancers[1,3]. Furthermore, the observed male predominance (61.13%, n = 118; male-to-female ratio of 1.57:1) is consistent with international literature reporting a higher incidence of acute lymphoblastic leukaemia in male children[20,21].

Age stratification showed that the vast majority of patients were between 0 and 12 years old (80.82%, n = 156). This concentration highlights the biological vulnerability of younger children to severe myelosuppression during intensive cytotoxic chemotherapy induction phases[7]. Conversely, the lower presentation rate among adolescents aged 13–17 years (19.18%, n = 37) mirrors the lower background incidence of acute leukemias typically seen in older paediatric cohorts[20].

Microbiological evaluation of the 193 febrile neutropenia episodes revealed that bloodstream cultures yielded no growth in 44.04% (n = 85) of cases. This substantial proportion of culture-negative episodes is common in contemporary oncology literature[13]. The phenomenon is typically driven by the immediate administration of empirical antibiotics at the first sign of fever, low circulating bacterial volumes in paediatric patients, or difficulties in isolating fastidious, slow-growing pathogens from immunocompromised hosts[13].

Among the culture-positive cases (55.96%, n = 108), Gram-negative isolates were more prevalent (31.08%, n = 60) than Gram-positive pathogens (24.87%, n = 48). This shift toward Gram-negative dominance is increasingly reported across tertiary care centers in low- and middle-income countries[12,22]. This trend presents a major clinical challenge, as systemic Gram-negative bacteremia in neutropenic children is associated with rapid clinical decline, severe sepsis, and higher mortality rates driven by multidrug-resistant organisms (MDROs)[12,24].

A granular assessment of the Gram-negative spectrum (n = 60) identified *Burkholderia cepacia* as the primary pathogen, accounting for 35.00% (n = 21) of all Gram-negative isolates. This is a notable finding; *B. cepacia* is an opportunistic nosocomial pathogen known for complex intrinsic resistance mechanisms especially against common aminoglycosides and selective beta lactams and its presence traditionally correlates with poor clinical outcomes in neutropenic settings[24,25]. Other resistant Gram-negative pathogens isolated included *Escherichia coli* (20%, n = 12), *Acinetobacter baumannii/haemolyticus* (13.33%, n = 8), and *Pseudomonas aeruginosa* (10.00%, n = 6). The diversity and resistance profiles of these specific pathogens justify the initial selection of broad-spectrum empirical coverage[14].

Within the Gram-positive group (n = 48), coagulase-negative *Staphylococcus* species and *Staphylococcus epidermidis* were isolated in identical frequencies, each accounting for 35.42% (n = 17) of the Gram-positive subtype. While historically dismissed as benign skin contaminants, these organisms have emerged as primary nosocomial pathogens in modern paediatric oncology[23]. Their prominence is heavily tied to the widespread use of long-term indwelling central venous catheters and chemotherapy-induced mucosal barrier damage, which pave the way for catheter-related bloodstream infections (CRBSIs)[23]. Furthermore, the isolation of methicillin-resistant *Staphylococcus aureus* at 10.42% (n = 5) and *Staphylococcus haemolyticus* at 8.33% (n = 4) underscores a parallel burden of resistant Gram-positive organisms within this setting[21,23].

Antibiotic utilization profiles in our center showed a clear reliance on primary combination therapy featuring piperacillin/tazobactam and amikacin. This empirical selection reflects major international guideline recommendations, which advocate for rapid, simultaneous coverage of both pathogenic Gram-negative bacilli and virulent Gram-positive cocci[5,25].

Escalation to carbapenems (specifically meropenem) was restricted to 7.96% of clinical episodes. This controlled utilization aligns with core principles of institutional antimicrobial stewardship, which seek to reserve carbapenem therapies for cases with confirmed or highly suspected multidrug-resistant infections, thereby limiting the selection pressure for carbapenemase-producing organisms[12,24].

Antimicrobial susceptibility mapping uncovered concerningly low sensitivity rates across multiple standard drug classes, particularly among Gram-negative isolates. The resistance of *B. cepacia* to key frontline agents underscores the emergence of multidrug-resistant strains capable of breaking through standard empirical protocols[12]. Conversely, the preserved therapeutic sensitivity of isolated *S. aureus* and MRSA strains to vancomycin supports its continued use as a directed secondary agent, though it demands careful monitoring to prevent the development of vancomycin-intermediate or vancomycin-resistant phenotypes[23].

Beyond infectious complications, prospective safety monitoring identified 60 distinct adverse drug reactions associated with the active therapeutic regimens. Organ system tracking revealed that gastrointestinal toxicities predominantly manifesting as severe mucositis, intractable vomiting, and diarrhea comprised 43.33% (n = 26) of all recorded events. This was followed by hematological toxicities (31.67%, n = 19), characterized by profound cytopenias extending well beyond expected therapeutic baselines, and

dermatological toxicities (15%, n = 9), presenting as acute pruritus, urticaria, or maculopapular rashes.

The 60 ADRs documented, 90.00% were classified as probable by the Naranjo causality scale. Antineoplastic agents accounted for the largest share (65%), reflecting their well-documented toxicity profiles across haematological, gastrointestinal, and dermatological systems. Antibiotics contributed to 15% of ADRs, underscoring the importance of prospective pharmacovigilance during FN management. Antibiotics, corticosteroids, and other agents also contributed to ADRs, reinforcing the need for comprehensive medication monitoring during FN management.

Conclusion:

This study demonstrates that empirical therapy for paediatric febrile neutropenia is dominated by broad-spectrum combinations such as piperacillin/tazobactam with amikacin, in a cohort largely comprising leukaemia patients. Gram-negative organisms, particularly Burkholderia cepacia and Escherichia coli, along with resistant Staphylococcus epidermidis, showed substantial antimicrobial resistance, underscoring the need for locally tailored empirical regimens and strong antimicrobial stewardship. Adverse drug reactions, mainly related to chemotherapy, were identified and successfully managed using structured assessment and counselling, highlighting the importance of vigilant monitoring to enhance treatment safety.

DECLARATIONS:

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Data Availability Statement: No additional data are available beyond those included in the manuscript. The data underlying this study are presented as aggregated results within the article.

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