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Original Article

Clinical Profile of Febrile Neutropenia in Children with Malignancies in a Tertiary Care Hospital: A Prospective Observational Study

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Abstract

Introduction Febrile neutropenia is a dreadful complication associated with malignancies. Knowledge of locally prevalent pathogens and their resistance pattern is of paramount importance in guiding antimicrobial therapy.

Aims/Objectives The aim of the study was to identify the common infectious agent, antibiotic susceptibility of culture positive patients, and outcome

Methods We conducted a single-center prospective observational study. Forty-three children with febrile neutropenia episodes admitted in KKCTH, Chennai, were included in the study. The duration of the study was 1 year. Relevant patient and disease specific details were obtained, results were analyzed, and conclusions were drawn.

Results There were 90 episodes of febrile neutropenia. Overall culture positivity was identified in 37 cases (41.11%). Bacteremia (23.3%) was the most common cause of microbiologically documented infection. Gram-positive organisms (60%) were more commonly documented. Among the gram-positive organisms, coagulase-negative *Staphylococcus aureus* was the predominant isolate followed by *Streptococcus*. Central line–associated bloodstream infections were documented in 13.33%. Chemo-port removal was done in four children. Three had invasive fungal disease. The majority of the gram-negative isolates were resistant strains. Morbidity was significantly more in gram-negative infections. Overall outcome was good though three children succumbed to sepsis.

Conclusion A vigilant management of illness is essential. Chemo-port carries risk of severe infection. Protocol-based management of catheter-related bloodstream infection (CRBSI) can limit the number of chemo-port removal. Though gram-positive organisms are in the rise, gram-negative organisms are still responsible for significant morbidity. Early initiation of broad-spectrum empirical antibiotics with optimal gram-positive coverage is crucial. Children with suspected fungal infections should be aggressively evaluated and treated. An organized approach is the key in successful management.

Keywords
- acute lymphoblastic leukemia
- CRBSI
- microbiologically documented infection
- invasive fungal disease
- gram-negative organism

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Key Messages: Initiation of broad-spectrum antibiotics at the earliest during an episode of febrile neutropenia is the determinant factor of the outcome.

Introduction

The advancements in cancer care have led to better cure rates for patients suffering from various malignancies, while at the same time making them susceptible to complications of therapy. Febrile neutropenia is one such complication and one of the most common admitting *diagnoses* among *pediatric* oncology units, second only to admissions for chemotherapy.[1] A delay in appropriate management is associated with higher morbidity, mortality, a prolonged duration of hospital stay, and higher costs of treatment.[2] The strategy of using empirical antibiotics has led to a considerable decline in infection-related mortalities. Knowledge of the locally prevalent pathogens and their resistance pattern is of paramount importance in guiding antimicrobial therapy. There have been very few Indian studies looking at this changing trend of microbiome in the *pediatric population*. Our aims and objectives of this study are to identify the common infectious agent associated with febrile neutropenia, antibiotic susceptibility pattern, and outcomes.

Materials and Methods

It is a prospective observational study. The duration of study is 1 year (January 2019–January 2020).

Inclusion criteria:

- Febrile neutropenia episodes in children aged less than 18 years, with an underlying malignancy.

Exclusion criteria:

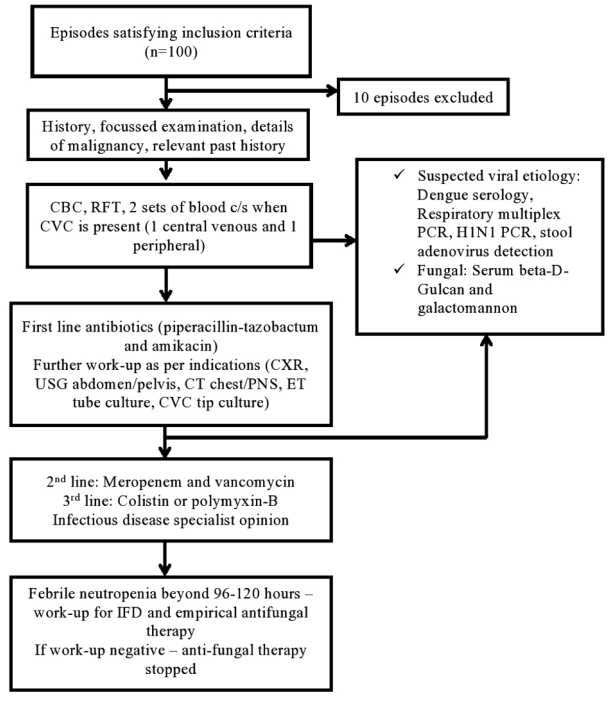
- Children who have undergone hematopoietic stem cell transplantation.
- Episodes that were pretreated elsewhere.
- Children who have a preexisting inborn error of immunity.
- Parents who refused to be a part of the final sample size of the study: 90 episodes.

Methodology

Each episode of febrile neutropenia was considered an individual event, with comprehensive bedside histories obtained to gather pertinent information regarding both the underlying malignancy and febrile illness. Detailed clinical examinations were conducted to identify potential sources of infection, and baseline investigations upon admission encompassed a complete blood count (CBC), renal function tests, and blood cultures obtained through aseptic techniques. Analysis of the culture reports focused on organism identification and antibiotic sensitivity patterns. Secondary investigations were performed based on suspected sources of infection, including urine analysis/culture, chest X-ray imaging, and abdominal ultrasonography. Patients with suspected viral etiology underwent serology tests such as respiratory biofire panel (multiplex polymerase chain reaction [PCR]), dengue NS1 antigen and immunoglobulin M (IgM)/IgG antibody *titers*, H1N1 PCR testing, or stool adenovirus detection. Those with suspected fungal etiology underwent serum galactomannan and serum beta-D-glucan level assessments, along with computed tomography (CT) scans of the chest and/or paranasal sinus to pinpoint the focus of infection (►**Fig. 1**).

Treatment initiation followed our institutional protocol. Children diagnosed with febrile neutropenia received empirical antibiotic therapy consisting of piperacillin-tazobactam and amikacin, as directed by our institutional antibiogram. Blood cultures were collected before initiating the antibiotics. After 48 hours, in the absence of microbial growth in the cultures, amikacin was discontinued. Piperacillin-tazobactam was continued until the final culture report, provided the child exhibited clinical improvement. In cases of clinical deterioration, antibiotic escalation to second-line agents was implemented. Beyond 96 to 120 hours of febrile neutropenia, empirical antifungal therapy was commenced. High-risk individuals for invasive fungal disease (IFD) received liposomal amphotericin-B, with concomitant workup for fungal infection. Conversely, preemptive antifungal treatment with azoles or liposomal amphotericin-B was implemented in low-risk patients. All children received cotrimoxazole for *Pneumocystis jiroveci* prophylaxis. Additionally, those at high risk of invasive fungal disease received either fluconazole or voriconazole prophylaxis, based on susceptibility to yeast or molds, respectively.

Monitoring included assessing antibiotic effectiveness and escalating treatment as necessary, with careful documentation of patterns and reasons for escalation. Patients unresponsive to initial antibiotic regimens or exhibiting



CBC = Complete blood count; RFT = Renal function test; c/s = culture/sensitivity; PCR = Polymerase chain reaction; CXR = Chest X-ray imaging; USG = Ultrasonography; CT = Computerised Tomography; PNS = Para-nasal sinuses; ET = Endotracheal tube; CVC = Central venous catheter; IFD = Invasive Fungal Disease

Fig. 1 Methodology flow chart.

Table 1 Definitions and descriptions

Febrile neutropenia	Single oral temperature measurement of ≥38.3°C (101°F) or a temperature of ≥38.0°C (100.4°F) sustained over a 1-h period, with <500 neutrophils/mm^3 or <1,000 neutrophils/mm^3 with a predicted decline to 500/mm^3 over the next 48 h
Clinically documented infections (CDI)	Episodes where a site of infection has been identified either clinically or radiologically and cultures and other pathogen-directed workups are negative
Acute febrile illness not otherwise specified (AFI-NOS)	Episodes of fever where an infection cannot be demonstrated neither clinically nor microbiologically
Microbiologically documented infection (MDI)	Episodes where a pathogen has been identified in microbiological samples
Paired cultures	Cultures drawn from a central venous access and from a peripheral venous access or two different peripheral venous accesses
Catheter-related bloodstream infections (CRBSI)	A definitive diagnosis of CRBSI requires that the same organism grow from at least 1 percutaneous blood sample culture and from the catheter tip or that 2 blood samples for culture be obtained (1 from a catheter hub and 1 from a peripheral vein) that meet CRBSI criteria for quantitative blood cultures or differential time to positivity (DTP)
Possible CRBSI	2 quantitative blood cultures of samples obtained through 2 catheter lumens in which the colony count for the blood sample drawn through one lumen is at least threefold greater than the colony count for the blood sample obtained from the second lumen
DTP for CRBSI	CRBSI is defined as the growth of microbes from blood drawn from a catheter hub at least 2 h prior to microbial growth being detected in blood samples obtained from a peripheral vein
High-risk conditions for invasive fungal disease	Acute myeloid leukemia, high-risk acute lymphoblastic leukemia, or relapsed acute leukemia; those with prolonged neutropenia; those receiving high-dose steroids; and those undergoing allogeneic HCT in the first year after HCT without evidence of T-cell reconstitution, those or receiving steroids or multiple immune suppressive agents to prevent or treat graft-versus-host disease
Low-risk conditions for invasive fungal disease	Febrile neutropenia, not meeting the criteria of high risk

Abbreviation: HCT, Hematopoietic cell transplantation.

clinical deterioration underwent repeat CBC and blood cultures (aerobic bacterial and fungal). Additional investigations were undertaken for pediatric intensive care unit (PICU) patients, encompassing endotracheal tube cultures for ventilated individuals, central line catheter tip cultures for those with central lines, and urinary catheter tip cultures for patients with Foley catheters (see ►**Table 1** for definitions). Furthermore, all patients needing PICU care underwent rectal swab culture screening for carbapenem-resistant Enterobacterales (CRE). Mortality and morbidity among study participants associated with febrile neutropenia were documented.

Statistical Methods

Statistical analysis was done using SPSS 16.0. Frequency tables and descriptive statistics were calculated for background variables. For data that did not follow normal distribution, nonparametric tests were used. To compare the difference in quantitative variables between two groups, the Mann–Whitney *U* test was used, whereas the Kruskal–Wallis test was used for quantitative variables in more than two groups. Chi-squared tests were employed for comparing the difference in proportions. For data that followed normal distribution, Student's *t*-test and chi-squared test were applied. For the statistical analysis, 95% confidence interval (CI) was used, and a *p*-value of less than 0.05 was considered significant.

Definitions, descriptions, and categories are presented in ►**Tables 1** and **2**.[3–6]

Ethics

The study was approved by the CHILDS Trust Medical Research Foundation (IBR approval number: ECR/676/Inst/TN/2014/RR – 17; date: February 20, 2018).

Table 2 Categories of invasive fungal disease

Category	Definition
Proven	Proof of invasive fungal disease by demonstration of fungal elements in diseased tissue of most conditions
Probable	Host factor, clinical features, and mycological evidence are present
Possible	Host factor and clinical features without mycological evidence

Helsinki Declaration

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Results

A total of 43 children with 90 febrile neutropenia episodes were enrolled in the study. Majority of the episodes were in preschool children (71%) and had *hematological* malignancy (78%). Among all the hematological malignancies, acute lymphoblastic leukemia (ALL) constituted about 66% of the cases. The risk stratification and management of ALL were implemented in accordance with the Indian Collaborative Childhood Leukemia Group (ICiCLe) study protocol. Among the children with ALL, 34 (57%) episodes made up the intermediate- and high-risk groups, whereas 26 (43%) were standard risk. Intensive chemotherapy preceded 51 (85%) episodes. More than 53% ($n = 48$) episodes did not have a clear focus of infection. The baseline characteristics are outlined in the ►**Table 3**.

All the febrile neutropenia episodes were divided into three categories: microbiologically documented infections (MDIs; 41.1%, $n = 37$), clinically documented infections (17.7%, $n = 16$), and acute febrile illness not otherwise specified (AFI-NOS; 41.1%, $n = 37$; ►**Table 1**).

Severe neutropenia (absolute neutrophil count [ANC] < 500 cells/μL) was encountered in 52.2% of episodes. Sixty-one (67.8%) episodes had neutropenia lasting for less than a week, while 39 (32.2%) episodes had neutropenia lasting for more than a week. Episodes with severe neutropenia also had a significantly prolonged duration of neutropenia, further augmenting the risk of infection, and this was statistically significant ($p = 0.029$). Children with AFI-NOS had a shorter duration of neutropenia. The majority (75.9%, $n = 22$) of episodes, which had neutropenia lasting for more than a week, had MDI. On the other hand, only 25.5% ($n = 15$) had an MDI with neutropenia lasting less than a week. The difference was statistically significant ($p < 0.0001$).

The MDIs were further classified as those with *bacteremia* and those with fungemia. Twenty-one (57%) episodes had *bacteremia* and 1 (2.7%) had candidemia. Paired cultures were found to be positive in 14 (25.9%) cases (►**Fig. 2**). Bronchoalveolar lavage revealed growth of *Candida* spp. (6.6%, $n = 1$) and *Aspergillus* spp. (6.6%, $n = 1$), while endotracheal tube cultures showed the presence of *Escherichia coli* (6.6%, $n = 1$). Pus cultures indicated the presence of methicillin-resistant *Staphylococcus aureus* (MRSA; 26.6%, $n = 4$), and stool cultures yielded CRE *E. coli* (20%, $n = 3$) and *Clostridium difficile* (6.6%, $n = 1$). Additionally, urine cultures exhibited growth of *Klebsiella* spp., CRE *E. coli*, and *Enterococcus* spp. Polymicrobial infections were documented in 6 (28.5%) episodes. All cultures indicated growth within 48 hours of incubation; earliest growth was documented to be within 6 hours. There were in total 14 episodes of suspected IFDs, comprising 3 proven cases, 3 probable cases, and 8 possible cases (►**Table 2**). All the children were receiving cotrimoxazole prophylaxis for *P. jiroveci*, while six children were additionally on fluconazole prophylaxis for yeast, and four were on voriconazole prophylaxis for further protection against molds. None of them had any breakthrough fungal infection.

Table 3 Baseline characteristics

Total episodes: 90	Frequency of episodes	Percentage
Age distribution (mean 4.6 ± SD)		
< 5 y	64	71.1
5–10 y	18	20.0
> 10 y	8	8.88
Gender distribution		
Boys	50	55.6
Girls	40	44.4
Nutritional status		
Undernourished	16	17.78
Well nourished	74	82.22
Underlying malignancy		
B-cell ALL	56	62.2
T-cell ALL	4	4.4
AML	11	18.3
NHL	5	5.5
Hodgkin's lymphoma	1	1.11
Peripheral T-cell lymphoma	1	1.11
LCH	1	1.11
Nonhematological malignancy	11	12.2
Site of infection		
No focus	46	53.3
Respiratory tract infection	18	20
Vascular access related	8	8.9
Gastrointestinal tract	5	5.6
Skin and soft-tissue infection	8	8.9
Genitourinary tract	3	3.3

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; LCH, Langerhans cell histiocytosis; NHL, non-Hodgkin's lymphoma; SD, standard deviation.

Workup for viral infection was positive in 6 (16.2%) cases. Of note, 11 (31%) did not have a clear focus. Overall, the pattern of organisms attained by various laboratory methods in variant body tissues is entailed in the ►**Figs. 3** and **4**.

Catheter-Related Bloodstream Infections

Out of the 21 (23.33%) MDI with bacteremia, 12 (13.33%) were central line–associated bloodstream infections. Nearly

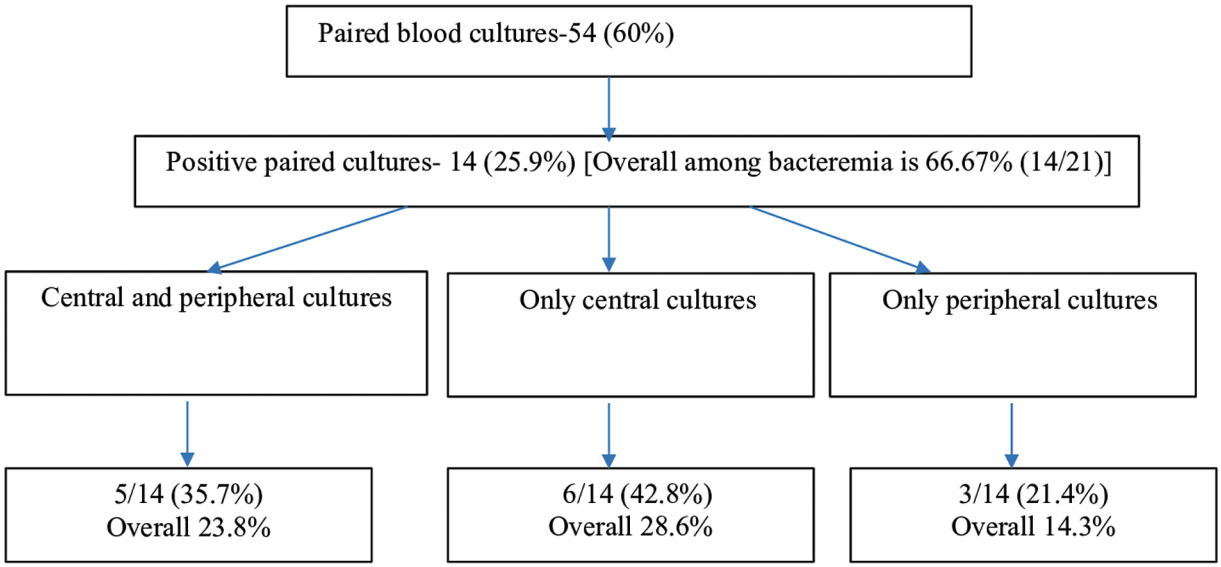


Fig. 2 Paired blood culture positivity.

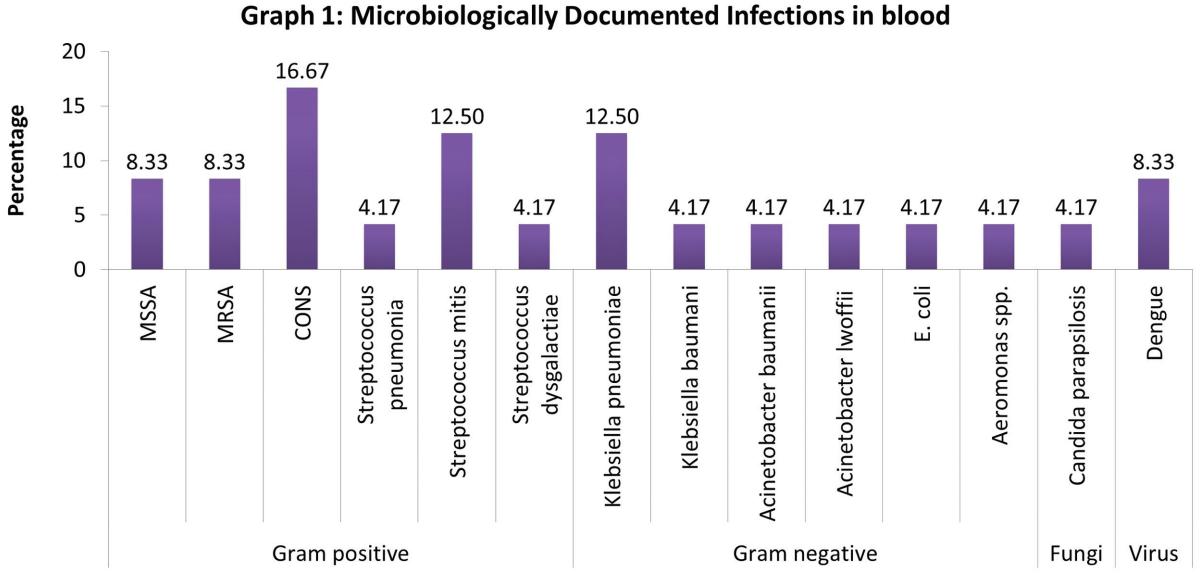


Fig. 3 Clustered column graph depicting spectrum of microbiologically documented infections in blood.

8.9% ($n = 8$) were long-term line (chemo-port) related infections and 4.4% ($n = 4$) were short-term-line-related infections. Multidrug-resistant (MDR) *Klebsiella* spp., MDR *Acinetobacter* spp., *E. coli*, MRSA coagulase-negative *Staphylococcus* (CONS), *Streptococcus mitis*, and *Candida parapsilosis* were the organisms responsible for catheter-related bloodstream infection (CRBSI) in our cohort. Management of CRBSIs was done in accordance with the Infectious Diseases Society of America (IDSA) 2009 guidelines. Four children had to undergo chemo-port removal as a part of source reduction. The antibiotic susceptibility of the pattern of the isolates in our study is shown in the ►**Figs. 5** and **6**.

Treatment

Piperacillin-tazobactam with amikacin was the first-line antibiotic in all episodes with febrile neutropenia. Escalation to second-line antibiotics was done in 31.1% of cases. Both meropenem and vancomycin were used in 21 (71.4%) episodes, 5 (17.8%) cases received only meropenem, and 3 (10.7%) cases received only vancomycin. Further escalation to colistin or polymyxin-B was done in 5 (5.55%) cases.

Seventeen (45.9%) episodes of MDIs required escalation to second-line antibiotics, whereas only 11 (20.8%) without any microbiological proof required further escalation ($p = 0.011$). Mean rank of treatment duration (58.8) and

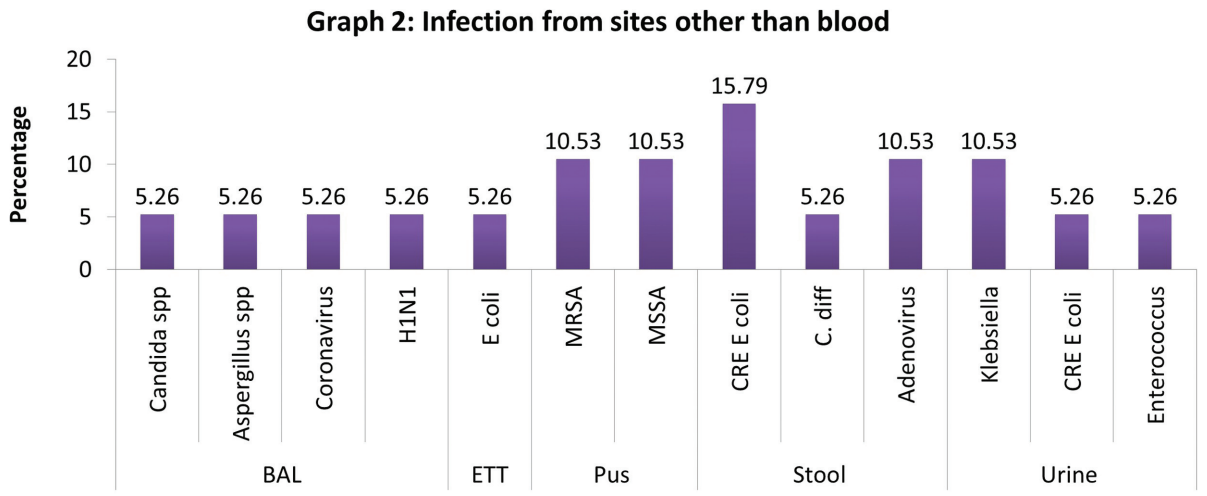


Fig. 4 Clustered column graph depicting spectrum of microbiologically documented infections in sites other than blood.

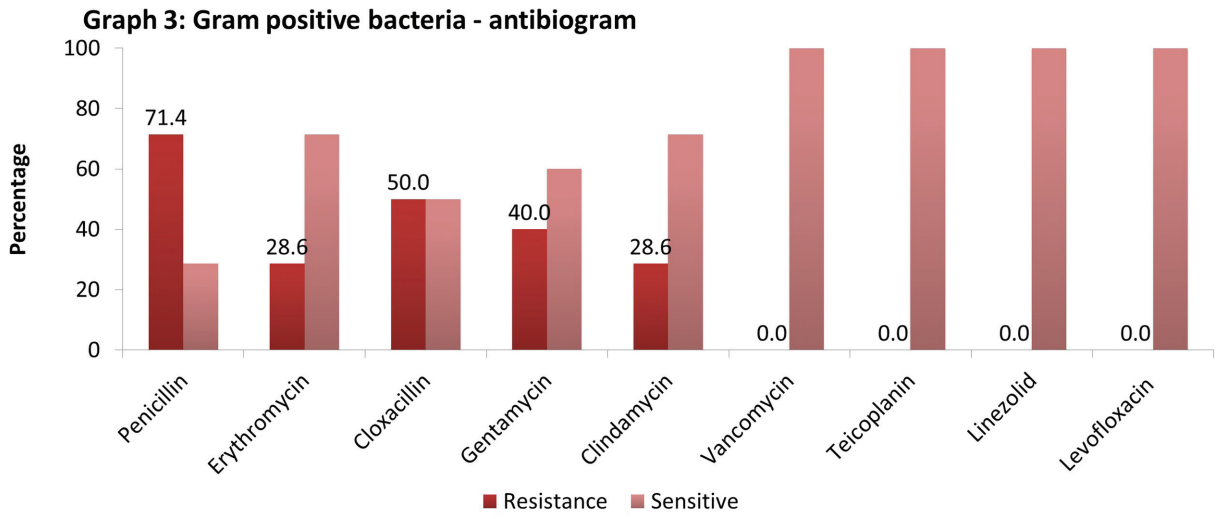


Fig. 5 Clustered column graph depicting the sensitivity pattern of gram positive bacteria.

hospital stay (62.73) were also significantly higher whenever escalation of antimicrobial drugs was required ($p = 0.001$). PICU care was often required (35.7%, $n = 10$) during the episodes requiring escalation ($p < 0.0001$). IFD was suspected in 14 (16.6%) episodes and proven in 3 episodes. Empirical antifungals were started in 6 (42.8%) episodes with liposomal amphotericin-B and 8 (57.1%) episodes with azoles.

Granulocyte colony stimulating factor (G-CSF) prophylaxis was provided in 8 (27.5%) cases (with underlying solid *tumors*) and 21 (72.4%) received it as treatment in view of profound prolonged neutropenia.

Intensive care treatment was required in 14 (15.55%) episodes. Inotrope or vasopressor requirement was observed in 4 (28.5%) cases. The need for invasive ventilation was observed in 4 (28.5%) cases. Notably, episodes with MDI (35.1%, $n = 13$) were found to require PICU care more frequently than those without (1.9%, $n = 1$) microbiological diagnosis ($p < 0.0001$). In particular, *gram-negative* sepsis (61.5%, $n = 8$) had a significantly higher requirement of PICU care than gram-positive (16.7%, $n = 3$) sepsis ($p = 0.01$).

Outcome

The median duration of hospital stay was 5.5 days (range: 3–45 days). Episodes with gram-negative sepsis had a substantially prolonged (mean-rank of 20.73 days) hospital course than gram-positive (mean-rank of 12.58 days) sepsis ($p = 0.013$). Episodes with AFI-NOS had shorter duration of hospital stay than MDIs ($p = 0.001$). Three children (3.33%) succumbed to the illness during their hospital stay. All three children had MDIs: two had gram-negative sepsis and one had dengue.

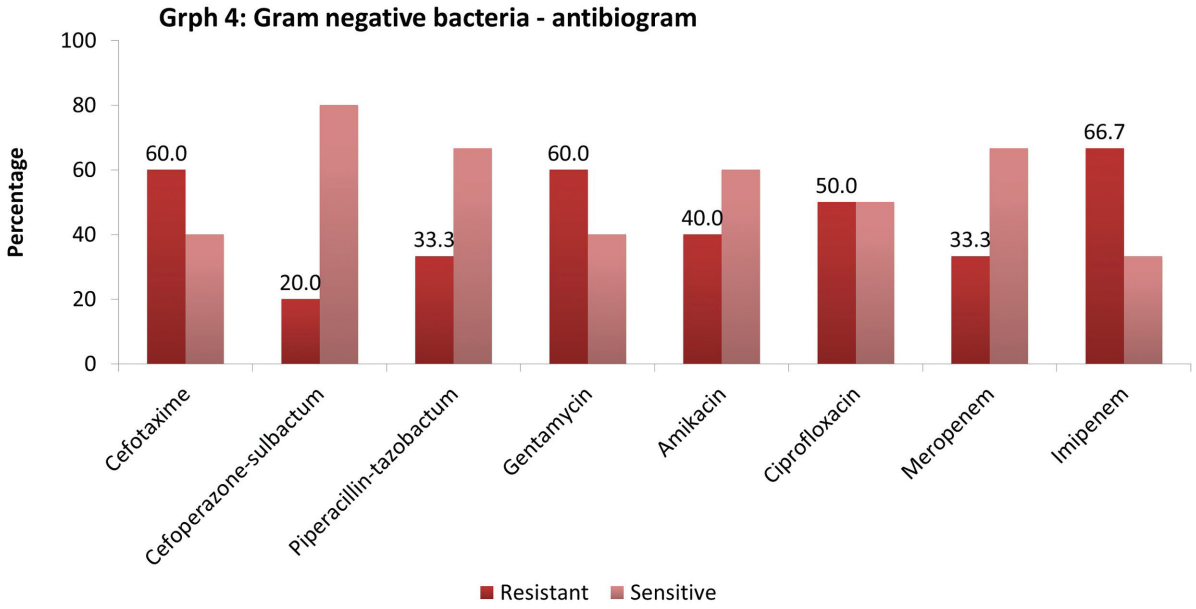


Fig. 6 Clustered column graph depicting the sensitivity pattern of gram negative bacteria.

Discussion

The significance of infectious complications in febrile neutropenia cannot be overstated, as they contribute substantially to morbidity and mortality. A comprehensive understanding of the local patterns of febrile illness is crucial for effective management.

In our study, the majority (71.1%) of febrile neutropenia episodes occurred in children younger than 5 years. Both males and females were affected in nearly equal proportions. Eighty-eight percent of cases were associated with an underlying hematological malignancy, a proportion consistent with findings reported by Babu et al[7] and Soumya and Ajit Kumar.[8] This alignment may be attributed to the elevated prevalence of hematological malignancies in the pediatric population, necessitating more intensive therapeutic interventions and consequently heightening susceptibility to serious infections. Notably, a significant number of febrile neutropenia episodes occurred during the induction phase of chemotherapy, underscoring the vulnerability of patients during this particular treatment stage.[2,9]

The primary imperative is to meticulously gather a focused patient history and promptly initiate appropriate antibiotics following blood culture collection. Our findings revealed that 17.7% of cases were clinically documented episodes, aligning with reported ranges of 20 to 40% in other studies.[10] This variance may be attributed to the extent of evaluation and stringent antimicrobial prophylaxis protocols. Remarkably, 41% of our cases fell under the category of AFI-NOS. This proportion is similar to that observed by Hakim et al, who reported almost half of febrile neutropenia episodes as AFI-NOS, even with the use of comprehensive diagnostic tools.[10] Intriguingly, all AFI-NOS episodes in our study exhibited an indolent clinical course, a trend consistent with findings in the broader literature.[2,10] Furthermore, AFI-NOS cases were associated with a significantly shorter duration of neutropenia compared to both microbiologically and clinically documented infections.

Bacteremia (56.7%) was the most common cause of MDI. Blood culture positivity rate in our study was 23.3%, while other studies showed a rate of *bacteremia* ranging from 10 to 30%.[8,10–12]

The practice of obtaining dual cultures confers several advantages, including the identification of true bacteremia, the exclusion of potential contaminants, and the prevention of unwarranted central line removal. Notably, a study revealed that 97% of health care professionals would opt for peripheral blood cultures if there was a risk of missing true bacteremia exceeding 10%.[13] In the study conducted by Handrup et al, 17% confirmed bloodstream infections were diagnosed through cultures from peripheral veins, despite simultaneously obtaining blood cultures from central venous lines yielding negative results.[6] Our study aligns with these findings, demonstrating that 14.3% of confirmed bacteremia episodes were identified based on peripheral blood culture positivity. These consistent outcomes underscore the critical importance of acquiring paired cultures in clinical practice, reinforcing the value of this approach in accurately diagnosing bloodstream infections while avoiding unnecessary interventions such as central line removal.

The presence of an indwelling central venous access poses an increased risk of infections. The CRBSI rate was 13.33%, with CONS being the predominant bacterial pathogen isolated, followed by gram-negative organisms, *S. aureus* and *Candida* spp. Our finding was consistent with the studies done by Demirel et al.[14]

IFD is an important contributor to morbidity and mortality in pediatric febrile neutropenia episodes. IFD was considered in individuals experiencing prolonged fever beyond 4 to 5 days, exhibiting poor response to antibiotics, and concurrent severe

neutropenia. In our study, fungal infection was suspected in 14 (16.6%) episodes; however, only 3 (3.3%)) were proven.

Viral infections were identified in 16% of microbiologically documented cases, with a consideration of viral etiology grounded in the local epidemiological patterns of viral epidemics. Notably, the range of 5 to 25% in viral serology positivity documented in other studies underscores the potential influence of diagnostic test availability in different settings.[10,15] The variability observed across studies may be attributed to the diverse capacities for diagnostic testing in distinct health care setups.

During the influenza epidemic, of the five suspected cases tested by PCR, one was found to be positive. Children were started on empirical oseltamivir with barrier precautions and contact prophylaxis.

As our state is an endemic area for dengue virus, high suspicion for dengue fever was maintained. Dengue fever was suspected in children who presented with fever and nonspecific complaints of vomiting, abdomen pain, and myalgia. We had two confirmed cases of dengue.

The respiratory tract continues to be the most common site of infection. Chest X-ray imaging was selectively performed in children exhibiting symptoms of respiratory tract involvement. A study demonstrated low yield of routine chest X-rays, conducted at the time of admission for febrile children with chemotherapy-induced neutropenia who lacked respiratory symptoms.[16] Our investigation identified significant findings in 14.4% of cases. Predominantly, these findings included peribronchial infiltrates, followed by acute respiratory distress syndrome (ARDS), lobar consolidation, bronchiectasis, and hyperinflation. Remarkably, 9 (75%) of cases with notable chest X-ray findings were associated with MDIs, whereas 3 (25%) cases were clinically documented infections. This underscores the utility of targeted chest X-ray imaging in identifying specific respiratory complications during episodes of febrile neutropenia.

The bacterial spectrum is undergoing a reported shift from gram-negative organisms to gram-positive organisms, attributed to factors such as aggressive empirical gram-negative antibacterial therapy and the use of implantable devices.[10,11] In our study, gram-positive organisms were more prevalent (61.9%) than gram-negative organisms (38.1%). Notably, CONS emerged as the predominant isolate among gram-positive organisms (30.7%), followed by *Streptococcus* spp. Although CONS is often considered a skin contaminant, dismissing its growth in children with neutropenia would be precarious. Consequently, we opted for treatment wherever deemed prudent. Consistent with our findings, studies by Hakim et al,[10] Kamana et al,[11] and Soumya and Ajit Kumar[8] also highlighted a shifting trend toward gram-positive sepsis.

Examining our gram-positive profile, we found that 71% were resistant to penicillin, 50% were resistant to cloxacillin, and 28% were resistant to clindamycin. However, all isolates demonstrated sensitivity to vancomycin, teicoplanin, linezolid, and levofloxacin. Turning attention to gram-negative organisms, 60% exhibited resistance to third-generation cephalosporins, 50% to fluoroquinolones, and 33% to piperacillin-tazobactam and meropenem. The resistance pattern was notably more extensive and concerning among gram-negative pathogens, as depicted in graphs 3 and 4. These findings underscore the urgent need for robust antibiotic stewardship to mitigate the emergence of MDR pathogens.

The goal of initial empirical antibiotic therapy is to prevent serious morbidity and mortality, till the culture sensitivity is available. Although gram-positive organisms were common, gram-negative bacteremia were associated with greater morbidity (16.7 vs. 61.5%) and had a higher probability of being resistant. In our study, piperacillin-tazobactam and amikacin were used as empirical antibiotics, based on the local epidemiological trend. A systematic review by Lehrnbecher et al of randomized trials on comparison between monotherapy and aminoglycoside-containing combination regimens for febrile neutropenia found that the effects were similar.[17] We initiated empirical antifungal therapy beyond day 4 of febrile neutropenia and did not notice any higher incidence of IFD than other contemporary studies.[18]

In children with acute AFI-NOS, antibiotics were given until the preliminary cultures were negative and had been afebrile for 24 hours. In children with clinically documented bacterial infection, antibiotics were continued until the bacteria were completely eradicated. Bone marrow recovery is of paramount importance in eradication of infection. Several studies have shown that the risk of recurrent fever is low in patients with definitive marrow recovery.[17,19]

Prophylactic use of G-CSF has been shown to reduce the incidence of neutropenic fever in a variety of studies and meta-analysis reports.[20] In our practice, we do not consider prophylactic G-CSF in *hematological* malignancies.

In our study, we found poorer outcomes (morbidity and mortality) among gram-negative septicemia, likely because of increasing rates of antibiotic resistance. Mortality was 3.33% in our study, whereas other pediatric febrile neutropenia studies report mortality rates ranging from 0.5 to 6.6%.[10,21]

Conclusion

Febrile neutropenia, predominantly encountered in hematological malignancies and during intensive chemotherapy phases, poses diagnostic challenges often due to a lack of inflammatory response despite harboring potentially serious pathogens. Employing paired cultures aids in identifying true bacteremia. The chemo-port carries prime importance in the management of high-risk malignancies, and protocol-based management of CRBSI is necessary as it can limit the number of chemo-port removals.

The respiratory tract remains the predominant focus, and chest X-ray imaging proves highly beneficial when clinical features suggest respiratory tract infection. Despite the rise in gram-positive organisms, gram-negative organisms still account for significant morbidity. Therefore, early initiation of empirical antibiotics with antipseudomonal and extended-spectrum beta-lactamases (ESBL) coverage, along with

optimal gram-positive coverage, is crucial. Aggressive evaluation and treatment of suspected fungal infections in children are essential. Prolonged neutropenia lasting beyond 96 hours, with persistent fever, necessitates empirical antifungal therapy in high-risk individuals. Moreover, if access to IFD workup is readily available, preemptive antifungal therapy can be considered in low-risk individuals. Additionally, viral infection workup in relevant clinical settings significantly reduces unnecessary antibiotic use. Notably, infection-related mortality was as low as 3.3% in our study, underscoring the efficacy of an organized and protocol-based approach in managing this fatal complication.

Learning Points

- Children undergoing cancer chemotherapy face heightened susceptibility to severe infections, which necessitate prompt treatment to prevent rapid deterioration.
- Crucial aspects of managing febrile neutropenia include identifying the focus of infection and determining the causative pathogens.
- Forming a multidisciplinary team comprising oncologists, infectious disease specialists, and microbiologists is crucial for crafting institutional protocols to manage febrile neutropenia, customized to local antibiogram data.
- Prompt and aggressive evaluation and treatment of febrile neutropenia are critical for optimal outcomes in pediatric cancer patients undergoing chemotherapy

Ethics Committee Approval

This study was approved by the CHILDS Trust Medical Research Foundation ethical committee (ECR/676/Inst/TN/2014/RR – 17).

Presentation at a Meeting

Oral paper presentation in Tamil Nadu State Pedicon 2019, Indian Academy of Pediatrics, in Tamil Nadu.

Authors' Contribution

A.M. contributed to the concepts, design, definition of intellectual content, literature search, clinical studies, data acquisition, data analysis, statistical analysis, and manuscript preparation. N.G.H. contributed to the definition of intellectual content, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review. A.S. contributed to the concepts, design, definition of intellectual content, manuscript editing, and manuscript review, and is also a guarantor. R.T. contributed to the concepts, design, and manuscript review, and is also a guarantor.

Patient Consent

Informed Patient consent was obtained for this study.

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None.

Conflict of Interest

None declared.

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