Bacterial Isolates and Characteristics of Children With Febrile Neutropenia on Treatment for Cancer at Moi Teaching and Referral Hospital, Kenya.

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Abstract

Purpose

This study aimed at identifying the patient characteristics of children with febrile neutropenia, the associated bacterial organisms, and their sensitivity patterns.

Methods

A descriptive cross-sectional study was carried out at the MTRH, paediatric oncology ward, from June 2021 to April 2022. A total of 110 children who developed fever and neutropenia while on chemotherapy were enrolled. Blood samples for culture were drawn aseptically. Patient characteristics were presented in frequency tables. Antimicrobial sensitivity patterns were plotted in tables against the bacterial isolates cultured. Chi-square/Fischer's exact test were used to determine any association between patient characteristics, bacterial growth and antimicrobial sensitivity.

Results

Majority 66 (60%) were males. The median age was 6.3 (SD 3.7) years. Majority of the patients 71 (64.5%) had haematological malignancies, the most common being Acute Myeloid Leukaemia (AML). There was a significant association between severity of neutropenia and haematological malignancies p = 0.028. In total, 31/110 (28.2%) blood cultures were positive for bacterial growth. Gram-positive bacteria were more frequent at 20 (58.1%). The most common organism was *Escherichia coli* 6 (18.2%), followed by *Staphylococcus aureus* at 5 (15.2%.) All the isolates were sensitive to linezolid and vancomycin and also showed good sensitivity towards meropenem at 10/11 (90.9%). High resistance to cephalosporins was noted with ceftriaxone at 5/6 (83.3%), cefepime at 4/7 (57.1%) and ceftazidime at 3/4 (75%).

Conclusion

The most common malignancy associated with febrile neutropenia was AML. Gram-positive bacteria were the most common isolates. There was high resistance towards cephalosporins but all were sensitive to linezolid and vancomycin.

Introduction

Each year, an estimated 400,000 children and adolescents (0–19 years) develop cancer. In high-income countries, more than 80% of children with cancer are cured, but in many Low- and Middle-Income Counties (LMICs) only 30% are cured (1).

Some of the reasons for lower survival rates in LMICs include delay in diagnosis, inaccurate diagnosis, inaccessible therapy, abandonment of treatment, relapse, death from toxicity, and complications from treatment (2). Most childhood cancers are treated with chemotherapy, including surgery and radiotherapy (3). Treatment with chemotherapy leads to bone marrow suppression which is the source of many of the adverse side effects of cancer treatment including infection and sepsis (4). Bone marrow suppression due to chemotherapy leads to disruption in the production of blood cells including WBCs which form an important part of cell mediated immunity hence predisposing patients to infections by bacteria due to a blunted immune response.

Febrile neutropenia is defined by a temperature of > 38°C, in patients with an absolute neutrophil count (ANC) < 1,000 cells/µL. Febrile neutropenia is a serious and often fatal complication of chemotherapy and continues to be a significant cause of death among children with cancer.

Children on treatment for cancer who develop chemotherapy-induced neutropenia are often at risk of developing febrile neutropenia as a complication of treatment. In patients who develop febrile neutropenia, the prevalence of bloodstream infections is about 11%-38% with overall mortality reaching about 40% (5). Patients with febrile neutropenia therefore should be investigated early for bacteraemia and started on treatment early in order to avoid and prevent complications.

The challenge in the management of febrile neutropenia is made even more difficult with the increase in antimicrobial resistant bacterial species. The extensive emergence of multi-drug (MDR) resistant bacteria has increased the burden of morbidity and mortality among cancer patients with bloodstream infections (6). The development of antimicrobial resistance is driven by a lack of proper antimicrobial surveillance and stewardship measures.

This study aimed at identifying the bacterial organisms associated with febrile neutropenia in children with cancer admitted at MTRH, their sensitivity patterns and the patients' clinical-demographic characteristics.

Materials and Methods

This was a descriptive cross-sectional study that was carried out between June 2021 to April 2022 in the paediatric oncology ward at the Moi Teaching and Referral Hospital (MTRH) in Uasin Gishu County, Kenya. Moi Teaching and Referral Hospital (MTRH) is the second-largest tertiary hospital in Kenya. It serves a population of about 24 million spread across at least 22 counties in Kenya and also includes patients from, parts of Eastern Uganda and Southern Sudan.

The paediatric oncology unit at MTRH has two paediatricians, one medical officer, three registered clinical officers and general nurses.

Consecutive sampling was adopted to recruit the participants. whose clinical and demographic characteristics were extracted from their medical records. The samples for blood culture were then

collected from a peripheral venipuncture site which was either the antecubital fossa of the patient's arm or at the dorsum of the hand, after carefully disinfecting the area by applying an alcohol or 70% spirit swab. About 2-5mls of blood was drawn from the patients for blood culture into the BACTEC Peds Plus blood culture collection bottle.

The blood culture samples were incubated in the BACT/ALERT automated blood culture machine. While in the machine, if there is bacterial metabolism from the blood culture, a gas is produced which is sensed by the machine. Once the machine senses the gas, the machine produces a red flag indicator, meaning the culture is positive for bacterial growth. The sample is then removed and inoculated on three media which are 'Blood agar', Chocolate agar' and MacConkey'. It is then incubated for 18–24 hours, after which the bacterial colonies from the plates were examined and gram staining was done to identify gram-positive and gram-negative bacteria colonies. These colonies are then directly inoculated into the VITEK 2 COMPACT MACHINE which uses specific antibiotic susceptibility testing (AST) and identification (ID) cards to identify the isolates at the species level.

The data collected was analysed descriptively, categorical variables were recorded as frequencies and percentages and plotted in tables to show the distribution. A univariate analysis was used to test for association between the outcome variable which was the blood culture results and the patients 'clinical and demographic characteristics and to also test for association between severity of neutropenia and categorical variables. A p-value of < 0.05 in all analyses done was considered to be statistically significant.

Results

A total of 112 patients with fever and neutropenia who were admitted to the paediatric oncology ward in S4A, MTRH were identified, and 110 were recruited into the study. Two were excluded because we were not able to obtain consent from them. Out of the 110 participants who were recruited into the study males were more at 60% while 40% (n = 44) were female. The age of patients ranged from 6 months to 15 years with a mean of 6.3 (SD 3.7) years, (Table 1).

Seventy-one (64.5%) of the participants had haematological malignancies.

Table 1: Patient Characteristics

Characteristics	No. n = 110 (%)
Sex	
Male	66 (60%)
Female	55(40%)
Age category (years)	
0 - 4 years	26 (23.63%)
5 – 10 years	58 (52.7%)
11 – 15 years	26 (23.63%)
Malignancy type	
Haematological malignancies	71 (64.5%)
Solid tumours	39 (35.5%)
ANC	
< 500 cells/µL	85 (77.27%)
> 500 - <1000 cells/µL	25 (22.73%)
Weight-Height Z-score	
Normal (z-score > -2)	105 (95.45%)
Moderate malnutrition (-3 > z-score < -2)	3 (2.72%)
Severe malnutrition (z-score < -3)	2 (1.81%)

The most frequent cancer among study participants was Acute Myeloid Leukaemia (24.54%), followed by, nephroblastoma at (22.7%), Acute Lymphoblastic Leukaemia at (21.81%) and Burkitt lymphoma (15.4%) Table 2.

Table 2
Distribution of malignancy type

Variable	Category	Frequency	Percentage
Diagnosis	Acute Myeloid Leukemia	27	24.5
	Nephroblastoma	25	22.7
	Acute Lymphoblastic Leukemia	24	21.8
	Burkitt lymphoma	19	17.3
	Retinoblastoma	3	2.7
	Rhabdomyosarcoma	3	2.7
	Nasopharyngeal carcinoma	2	1.8
	Germ cell tumours	2	1.8
	Osteosarcoma	2	1.8
	Ewing sarcoma	1	0.9
	Hodgkin Lymphoma	1	0.9
	Neuroblastoma	1	0.9

Factors associated with Neutropenia.

Majority of the patients had severe neutropenia (77.27%) with ANC of < 500 cells /μL, and there was a significant association between severity of neutropenia and haematological malignancies (p = 0.015) when compared to solid tumours (Table 3)

Table 3
Level of ANC in relation to Patient Characteristics

		ANC		
Variable	**Category**	**Non-severe**	**Severe**	**p-value**
Gender	Male	14 (21.1%)	52 (78.8%)	0.642[c]
	Female	11 (25%)	33 (75%)	
Diagnosis	Solid	14 (35.9%)	25 (64.1%)	0.015[c]
	Hematological	11 (15.5%)	60 (84.5%)	
Diagnosis	AML	1 (4.3%)	22 (95.7%)	0.028[c]
	ALL	6 (26.1%)	17 (73.9%)	
	Other Hematological	4 (16%)	21 (84%)	
	Solid tumours	14 (35%)	25 (64.1%)	
Age	Mean (SD)	5.2 (3.3)	6.7 (3.8)	0.091[t]
W-H z score	Normal	25(23.8%)	80 (76.2)	0.586[f]
	Malnourished	0	5 (100%)	

[c] Chi square

[f] Fischer's Exact

[t] *t* test

Severe neutropenia was noted to be more in those with AML (97.5%) in comparison to other malignancies. This was noted to be statistically significant (p = 0.028).

Bacterial Isolates

Of the 110 blood cultures taken, 31 (28.18%); were positive for bacterial growth. Two of the cultures were polymicrobial while the rest were caused by a single bacterial isolate. A total of 33 microorganisms were grown from all the positive blood cultures.

Out of the 33 isolates, 57.6% (n = 20) of the microorganisms were gram positive while the rest were gram negative. The most prevalent gram negative organisms were *Escherichia coli* 6 (18.18%) followed by *Klebsiella Pneumoniae* (9.1%). Staphylococcus aureus 5 (15.15%) was the most frequent for gram-positive organisms, followed by *Enterococcus faecium* 4 (12.1%). (Table 4).

According to the total number of positive cultures (n = 31), the highest rates of blood stream infections were noted to be more in those with ALL, AML and Burkitt lymphoma (25.8%, 19.35%; and 19.35% respectively) compared to those isolated among nephroblastoma (9.7%).

Eight (34.8%) isolates were obtained from the total specimen (n = 24) taken from patients with Acute Lymphoblastic Leukemia (Table 4)

Table 4: Bacterial isolates in relation to patient diagnosis

Bacterial isolates	AML (19.35%)	Nephroblastoma (9.6%)	ALL (25.8%)	BL (19.35%)	RMS (6.5%)	Nasopharyngeal ca. (6.5%)	HL (3.2%)	Osteosarcoma (6.5%)	RB (3.2%)	
Gram positive										
Staphylococcus aureus(5)	1(14.3)		1(12.5)	1(14.3)		1(50)			1(100)	15.15%
Enterococcus faecium(4)		1(33.3)		1(14.3)	1(50)		1(100)			12.1%
Staphylococcus hominis(3)			1(12.5)	1(14.3)	1(50)					9.1%
Staphylococcus hemolyticus(3)	1(14.3)	1(33.3)	1(12.5)							9.1%
Staphylococcus epidermidis(3)	1(14.3)	1(33.3)		1(14.3)						9.1%
Streptococcus parasanguinis(1)			1(12.5)							3.03%
Enterococcus gallinarum(1)	1(14.3)									3.03%
Gram negative										
Escherichia coli(6)	3(42.9)		1(12.5)	1(14.3)				1(50)		18.18%
Klebsiella pneumoniae(3)			1(12.5)	2(28.6)						9.1%
Pseudomonas aeruginosa(1)						1(50)				3.03%
Pseudomonas strutzei(1)			1(12.5)							3.03%
Acinetobacter lwoffii(1)								1(50)		3.03%

ALL, Acute Lymphoblastic Leukaemia; AML, Acute Myeloid Leukaemia; BL, Burkitt Lymphoma;

From the table above, there is no specific diagnosis that we could point to be associated with a specific organism

4.2 Antimicrobial Sensitivity Patterns

All the cultured bacterial isolates were found to be resistant to benzylpenicillin and ampicillin at 100%. High resistance rates were also observed towards most cephalosporins, with ceftriaxone at 83.3% and ceftazidime at ceftazidime (75%). However, all the bacterial species were sensitive to both linezolid and vancomycin (Table 5).

Table 5
Antimicrobial Sensitivity Patterns

Diagnosis	Sensitive	Resistant	Total
Ampicillin	0	12 (100%)	12
Benzylpenicillin	0	17 (100%)	17
Gentamicin	10 (35.7%)	18 (64.3%)	28
Levofloxacin	5 (26.3%)	14 (73.7%)	19
Linezolid	15 (100%)	0	15
Vancomycin	18 (100%)	0	18
Amikacin	7 (63.6%)	4 (36.4%)	11
Amoxiclav	1 (12.5%)	7 (87.5%)	8
Nitrofurantoin	16 (76.2%)	5 (23.8%)	21
Rifampicin	9 (75%)	3 (25%)	12
Clindamycin	6 (54.6%)	5 (45.4%)	11
Meropenem	10 (90.9%)	1 (9.1%)	11
Cefepime	3 (42.9%)	4 (57.1%)	7
Ceftriaxone	1 (16.7%)	5 (83.3%)	6
Ceftazidime	1(25%)	3(75%)	4
TMP/SMX	1(12.5%)	7(87.5%)	8
Piperacillin/tazobactam	2 (40%)	3 (60%)	5

Discussion

This study set out to describe the clinical and demographic characteristics of children with febrile neutropenia on treatment for cancer at MTRH and to identify the common bacterial isolates associated with it. It is the first study on bacterial isolates in children on treatment for cancer with febrile neutropenia in MTRH.

Male subjects were the majority of patients in this study. These findings were similar to studies done in Egypt which showed a male predominance of (51.3%); and also similar to a study done in Indonesia where male participants were more at (58%) (7, 8).

This study noted that the most common malignancies were leukaemias (AML and ALL), nephroblastoma and Burkitt lymphoma, from the enrolled participants. This was similar to a study done in India, where the most common malignancies were acute lymphoblastic leukaemia, non-Hodgkins lymphoma, nephroblastoma and acute myeloblastic leukaemias (9). Furthermore, it was noted that the most common malignancy type among those with febrile neutropenia in this study was acute myeloid leukaemia. Haematological malignancies especially AML require more intensive myeloablative chemotherapy regimens that are associated with severe myelosuppression, leading to a disruption in the normal hematopoiesis (10).

From this study, the positive bacterial growth from the blood cultures collected was 28.18%. This was comparable to that of studies done in Colombia (11) where the cumulative incidence of BSI was 29.23% (92/315) and a study done in India which documented a bacterial growth rate of 27.8% from 155 blood culture samples collected (12). Our findings are comparable to the estimated bacterial growth rate according to the Infectious Disease Society of America (IDSA), which stated that bacteraemia occurs in 10–25% of patients with febrile neutropenia. Another study also supported this, stating that overall bacteraemia can be detected in about 20% of patients with febrile neutropenia (13). This could be because not all episodes of febrile neutropenia result from bacterial infection and in some cases in the absence of a clinical or microbiological evidence of infection, FN is marked as a fever of unknown origin.

Gram-positive bacteria were isolated more frequently than gram-negative bacteria in this study. This was also the case seen in different studies done in Sweden and Qatar (14, 15) which reported a predominance of gram positive bacteraemia in their studies. It can be speculated that over time, the increase in the use of efficient antimicrobial prophylaxis with agents such as fluoroquinolones, targeting gram-negative bacteria has led to the emergence of gram positive bacteria as the dominant species associated with bacteraemia in febrile neutropenic patients. Furthermore, *Streptococci* and CONS reside in the mucosal barriers, therefore, chemotherapy induced mucositis is associated with early onset gram positive bacteraemia (16).

The most common gram positive organisms seen were *Staphylococcus aureus* at 15.15%, and *Enterococcus faecium* while the most common gram negative bacteria were *E. coli* (18.18%) followed by *K. pneumoniae*. This has been documented in other studies done in Italy and India (10, 17). These findings were also supported by a meta-analysis which was conducted that reported findings from 17 different studies worldwide which showed that *E. coli* was the dominant pathogen constituting a median of 21% of all BSI strains in the 17 studies followed by *Klebsiella pneumoniae* with a median of 11% while the common gram positive species were *S. aureus* varying from 1–13% and CONS ranging from 2–42% (18).

Most of the gram-negative organisms had resistance to broad spectrum cephalosporins which are usually the first-line treatment for patients with febrile neutropenia in our set up. The increasing resistance to cephalosporins seen in this study was also observed in a study in Lebanon whereby 29.3% of the total bloodstream infections were caused by third-generation cephalosporin resistant gram-

negative bacteria (19). The reason could be their overuse as broad-spectrum antibiotic coverage for infections.

Additionally, another study stated that many centers no longer considered the use of ceftazidime a third generation cephalosporin as a suitable monotherapy in patients with FN due to its low activity against many gram-positive microorganisms such as streptococci (20).

The bacteria cultured were sensitive to Meropenem, Vancomycin and Linezolid with rates of 90.9%, 100% and 100% respectively. This was also observed in studies done in Uganda and South Africa in studies (21, 22). This is probably due to the fact that they are usually reserved for second line use and are mostly indicated in cases of severe infections pending blood culture results.

Limitation

There was a lack of standardization of disks used in the antibiotic sensitivity test. Different antibiotic disks were tested for different isolates.

In some instances, there would be a delay in the incubation of the collected blood samples from the time of collection in the Oncology ward, however, they were all stored in a thermostable specimen collection box and kept at room temperature of < 30^{o}C after collection.

Conclusion

In conclusion, most of the study participants were between the ages of 5 and 10, and the most common malignancy among those with febrile neutropenia was AML. Haematological malignancies especially, AML, were noted to be associated with febrile neutropenia and BSI Gram positive isolates were slightly more common than gram negative ones. The most common organisms were *E. coli, Staph aureus* and *E. faecium.* All organisms were sensitive to linezolid and vancomycin. There was also high sensitivity towards meropenem at 90.9% but 100% resistance was noted towards benzylpenicillin and ampicillin.

We recommend that empirical antimicrobial management of febrile neutropenia at MTRH Paediatric Oncology ward should consist of meropenem as monotherapy or in combination with an aminoglycoside; linezolid or vancomycin should be reserved for second line treatment indicated in patients with meropenem resistant organisms.

Declarations

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Author contributions

Kipchumba S. wrote the main manuscript text and figures. Kipchumba S., Nyandiko M. and Njuguna F. reviewed and edited the manuscript.

Statements and Declarations

Ethical considerations

This study was performed in line with the principles of the Declaration of Helsinki. Approval to conduct the study was obtained from Institutional Research and Ethics Committee (IREC) of Moi University/MTRH (Reference IREC/2019/294; Approval number 0003587); Administrative approval was obtained from the CEO, MTRH.

Consent to participate.

Informed written consent was sought from the patients' parents or legal guardians.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

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