Original Article

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Types of bacteria among pediatric oncology patients in Basra

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ABSTRACT

Background: Infectious agents are the main factor that causes children suffering from cancer to be more susceptible to treatment failure. They complicate their course of therapy, thus shortening their lives. **Aim**: To find out the most notorious pathogen affecting pediatric malignancy in Basra Children Specialty Hospital to provide the best antimicrobial therapy choice and map out the future empirical therapy. **Methods**: One hundred and ten pediatric oncology patients in the pediatric hemato-oncology unit aged 16 years and less were involved in this retrospective study from March 1, 2021 to the end of February 2022. Different types of culture tests were taken in various stages of malignancy besides other investigations, including CBC, RFT, LFT and imaging. According to studies, these were important, since they help to spot the infection even if the culture was negative. **Results**: Acute Lymphoblastic Leukemia was the main malignancy involved in this study (42.7%). 73.6% of patients were aged 1–10 years, 58% were male, 62% were from Basra, and almost 2/3rd of them were from the periphery. Gram-positive bacteria represented 55.5% of the cases; *Staphylococcus hemolytic* and *Staphylococcus hominine* were mainly found, followed by *E. coli*, which was the major gram-negative bacteria, which seemed to manifest during induction and relapse stages. These were more likely to have a different type of antibiotic resistance to ESBL, CRE, and MRSA. **Conclusions**: Pediatric oncology patients with fever, neutropenia, and/or mucositis were more infected by gram-positive bacteria. The presence of bacteremia tends to be more critical during induction and relapse stages, as this may increase fatality. These deaths can be prevented using strict infection control measures, with the consequence of intimidating effect of the development of antibiotic resistance for existing patients as well as future patients.

Keywords: pediatric oncology, neutropenia, fever, antibiotic resistance, culture, bacteria

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INTRODUCTION

Bloodstream infections cause a considerable rise in the morbidity and mortality of patients with weak immune systems, especially in pediatric oncology. The increasing severity in the hematological type more than solid tumor due to the illness itself, aggressive cytotoxic management. These may have side effects that cause neutropenia, damage to the colonic lining or oral mucosa, which increases the hospital stay, causing more exposure to antibiotics besides the common use of CVC

(central venous catheter). All these factors increase the susceptibility of sepsis.[1–3]

Neutropenia is determined by absolute neutrophil count below 1500/mm^3 in children older than 1 year, and it is classified according to its level into mild (1500–1000 cells/m^3), moderate (1000–500 cells/m^3, severe (less than 500 cells/m^3).[4]

The prevalence of oral mucositis is 53.6% in patients with malignancy[5]. Oral mucositis is defined by the irritation of the mucosal lining in the oral cavity that causes aches, soreness, and sometimes bleeding.[6,7] Since this is a medical emergency, most of these patients need immediate intervention to save their lives, with empiric antibiotics to anticipate possible microorganisms even before the confirmation of infection. Some of these patients take antibiotics unnecessarily, which may lead to resistance.[8]

Presence of infection, especially with the recognition of ESKAPE (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumonia, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp.*), which are the most dangerous microorganisms for oncology patients, lead to the emergence of multidrug-resistant bacteria, which increases the difficulty in managing their illness.[9]

Over the past 10 years, the type of bacteria has changed from gram-negative (GN) to gram-positive (GP), with more multidrug-resistance and little to no response to antimicrobials.[8–10] The incidence of bloodstream infections in hemato/oncology patients is 11–38%, with a death rate of 40%.[8]

This study gives a vision of the most common bacteria and their resistance to guide future treatment options for our patients.

MATERIALS AND METHODS

A total of 256 samples were collected from 110 pediatric oncology patients who were of 16 years of age and less, including those with hematological diseases and solid malignancy. They were collected from the Basra children's specialty hospital from Mar 1, 2021 to the end of February 2022 from the pediatric hemato/oncology unit. The age of 81 patients (73.6%) were between 1 to 10 years, while only 2 (1.8%) cases were below 1 year and 27 (24.5%) cases were above 10 years of age.

The patients were assessed. For this, their records, including the type of malignancy and stages, their clinical and laboratory investigations, which involves fever, mucositis, Complete Blood Count (CBC), renal, liver, and chemistry, further evaluation with imaging techniques (X-ray, ultrasound, Computed Tomography (CT), Magnetic Resonance Imaging (MRI)) were used. All samples were analyzed and processed in the hematological and microbiological laboratory in the hospital.

Blood samples, along with all other types of samples (such as Cerebral spinal fluid (CSF), urine, ear, eye, throat, abscesses, pus, stool, wound, and surgical wound swab) were collected under standard conditions for culture. A blood sample was collected with strict aseptic precautions. About 1–2 mL of blood was inoculated in BacT/ALERT PF plus a pediatric blood culture bottle. All these blood culture bottles were incubated as soon as possible in a fully automated blood culture system BacT/ALERT3D to detect growth in blood culture samples. After, all the specimens were cultured in routine culture media and other selective media for each specimen. They were incubated under normal conditions aerobically at 37OC and CO2 (5–10%) for 18–24 hrs. The bacteria and antimicrobial susceptibility tests were conducted using the fully automated Vitek 2 compact (manufactured by bioMerieoux) ID/AST panel, which enables the microbiologist to determine GP bacteria by Vitek 2 GP ID /AST P580 and GN bacteria by GN ID/AST N222 panel. Moreover, these were analyzed with SPSS version 18.0.

RESULTS

The results were obtained from all departments in the hospital, including the general pediatric ward, hemato/oncology ward, solid tumor ward, pediatric surgery ward, and the NICU (Neonatal intensive care unit) and PICU (Pediatric intensive care unit) wards in Basra children's specialty hospital. The data was collected using the WHONET microbiology laboratory database software (CLSI 2021–2022) and standard reports according to hospital code ((IRQ-ID12. SQLite)) from March 1, 2021 to the end of February 2022.

In 1 year, a total of 829 samples were collected from all departments. Among this, 256 (31%) samples were obtained from 110 patients who were admitted to hematological and solid tumor wards. Among this, 117 samples were obtained once, 30 samples were gained

twice, 13 samples thrice, 4 samples 4 times, 3 samples were obtained 5 times, and 1 sample was repeated 9 times. Samples could be repeated and sometimes different samples were obtained from the same patient. For the study, 221 samples were used; 35 samples were not included due to the lack of follow up.

Among the patients, 68 of them (62%) reside in Basra city (44 patients (64%) were from the periphery), and the other 42 patients were referred from near governorates (38%), but a few cases were from other far cities. The male to female ratio was 1.4:1, with their ages from 5 months to 16 years, with a median of 6 years, as observed in Table 1.

According to the results in Table 2, the utmost prevalent case was Acute Lymphoblastic Leukemia (ALL) (47 cases (42.7%)). 14 (29.8%) cases had mucositis; 9 of them with a positive culture. 19 patients (40.4%) had neutropenia; 9 of these patients were associated with positive culture results, and 18 cases had a fever (38.3%); 7 cases had a positive culture result.

These samples were taken from 9 patients (19%) during the induction stage. Among these, 7 had a positive culture – 3 cases were positive during consolidation from 21 patients (44.7%). Further, 14 cases (29.8%) were in the relapse stage, and 7 cases had a positive result while in the maintenance stage. 3 cases only (6.4%). All 3 cases tested positive for Acute Myeloid Leukemia (AML), 16 cases (14.5%); 5 of them (31.25%) had a positive culture, 8 patients with AML (50%) had mucositis, 7 had neutropenia (43.7%), and only one patient (6.25%) had a fever.

There was one case with CML (0.9%), while solid tumors were represented in 30 cases (26.8 %). Brain tumor was seen in 6 cases (5.45%), Wilms tumor was seen in 4 cases (3.6%), Neuroblastoma (NB) was seen in 6 cases (5.45%), Germ cell tumor was seen in 5 cases (4.5%), Rhabdomyosarcoma (RMS) was seen in 3 cases (2.7%), Hemophagocytic Lymphohistiocytosis (HL) was seen in 4 cases (3.6%), and bone tumor was seen in 2 cases (1.8%). There was no significant difference between most parameters used in this study; the p value (0.487) was larger than 0.05.

The results of the positive cultures were 82/256 (32%), and from these results, bacterial growth (GP and GN) was found in 53/82 cases (64.63%), and nonpathogenic bacteria isolated was found in 23/82 cases (28.1%). Further, Normal flora was found in 5/82 cases (6.1%) and Candida albicans was found in 1/82 cases (1.22%). At the same time, the negative culture results were 174/256 (68%) (Fig. 1).

There was no significant difference between most bacterial types; the p value (0.501) was higher than 0.05.

Regarding antibiotics resistance in ALL patients, Carbapenem-resistant Enterobacteriaceae (CRE) had Extend spectrum Beta Lactamase (ESB) in 3 samples (6%), ESBL in 1 sample (2%) and Methicillin-resistant *Staphylococcus aureus* (MRSA) in 1 sample (2%). On the other hand, AML had resistant antibiotics in 2 samples with ESBL (12.5%) (Table 2), which show no significant difference between different phenotype (ESBL, CRE, MRSA) that was used in this study; p value was 0.655, which is more than 0.05.

Unfortunately, 14 patients (12.7%) died. A Chronic Myeloid Leukemia (CML) patient died following a Bone Marrow transplant (BM), which was complicated by Graft Versus Host Disease (GVHD). This patient superimposed by positive blood culture for *staph. hominis,* eventually leading to their death (Table 2).

The infantile ALL boy died due to liver failure and a GP blood infection with Staph. Aureus with MRSA. Another 5 cases of ALL died in the relapse stage, one of them with *Acinetobacter Bummanii* in the blood culture. Another patient with ALL during induction phase had E. coli present in a wound swab with ESBL positive. There were 2 cases with AML in the relapse stage; 1 of them had Staph. Hominis blood culture during consolidation. The last patient had Non-Hodgkin Lymphoma (NHL) (also during consolidation) with Nonpathogenic Bacteria Isolate (NPBI) in stool culture (non-compliance). Another patient with Neuroblastoma (NB) had a recurrence. Lastly, a patient died from brain tumor, who had a positive blood culture for E. coli carrying both ESBL+CRE (Table 2).

According to the type of samples in this study, blood culture was the most common test in 168 samples, followed by urine culture (42), stool culture (23), ear culture (13), wound culture (3), CSF (2), and abscesses (2), while eye, sputum, and throat cultures had one sample each (Fig. 2).

GP bacteria consist of 30 specimens (55.5%) from 54 positive growth samples, while GN bacteria consist of 23 specimens (42.6%), and 1 sample show (1.9%) Candida Albicans. So, GP bacteria were more predominant in our study, which include: *Staphylococcus hemolytic, Staphylococcus hominis, Staphylococcus epidermidis, Staphylococcus aureus, Staphylococcus simulans, and Enterococcus faecalis* consecutively (Table 3).

GP bacteria include *E. coli*, the most common causative bacteria, followed by *Citrobacter freundii, Pseudomonas aeruginosa, Acinetobacter Bumannii, Proteus mirabilis, and Acinetobacter lwoffii* (Table 3).

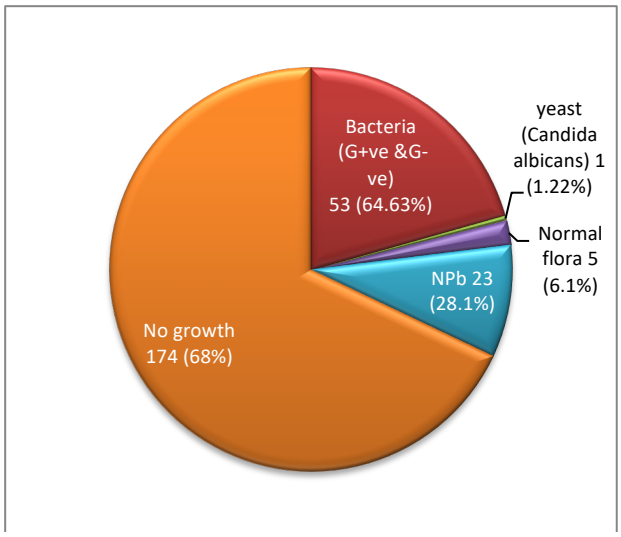

Figure 1: Type and number of microorganisms for oncology patients. N

PB = Nonpathogenic bacteria

Table 1: Demography of patients and residence with culture-positive and mortal (N= 110)

Characteristic	No.	%
Age group:		
≤ 1y	2	1.8
>1-≤10 y	81	73.6
>10-15 y	25	26.4
>15 y	2	1.8
Residence:		
Basrah	68	62
• *Center of Basrah*	*24*	*35.3*
• *Periphery of Basrah*	*44*	*64.7*
Others Governorates	42	38
Sex:		
Male	64	58
Female	46	42
Total culture positive	39	35.4
Mortality	14	12.7

Table 2: Characteristics of types of malignancy with clinical and laboratory findings with staging and type of resistance and mortality

Underlying disease	No. (%)	Positive culture No. (%)*	Mucositis	Neutropenia	Fever	Stage	Type of resistance	Death
Hematological Disease	80 (72.7%)							
ALL	47 (42.7%)	20 (42.5%)	14 (29.8%) +ve9 (45%)	19 (40.4%) +ve9(47%)	18 (38.3%) +ve7 (39%)	Induction 9(19%) 7 Consolidation 21(44.7%) 3 Maintenance 3(6.4%) 3 Relapse 14(29.8%) 7	ESBL3 (6%) ESBL+CRE 1(2%) MRSA 1 (2%)	6 (12.7%)
AML	16 (14.5%)	5 (31.25%)	8 (50%) +ve2 (25%)	7 (43.7%) +ve2 (28.5%)	1 (6.25%)	Induction – (T3) Consolidation 2(40%) T6 Relapse 3(60%) T7	ESBL2 (12.5%)	4 (25%)
CML	1 (0.9%)		-	1	1	-----		1
Solid tumor	30 (27.3%)							
Brain	6 (5.45%)	2 (33.33%)	-	-	-		ESBL1 (16.66) ESBL+CRE 1 (16.66%)	1 (16.66%)
NB	6 (5.45%)	2 (33.33%)	2 (33.33%)	1	2 (33.33%)			1 (16.66%)
Wilms	4 (3.6%)	2 (50%)	-	2 (50%)	-		ESBL+CREin 1 (25%)	
HLH	4 (3.6%)	-	1 (25%)	-	-			
Germ cell tumor	5 (4.5%)	2 (40%)	-	-	-			
RMS	3 (2.7%)	-	1 (33.33%)	2 (66.66%)	-			

* No significant difference was found between the positive blood cultures in hematological and solid tumours (P-value 0.487)

(ALL: Acute Lymphoblastic Leukemia, AML: Acute Myelogenous Leukemia, CML: chronic Myloid Leukemia, NB: Neuroblastoma, HLH: Hemophagocytic Lymphohistiocytosis, RMS: Rabdomyosarcoma)

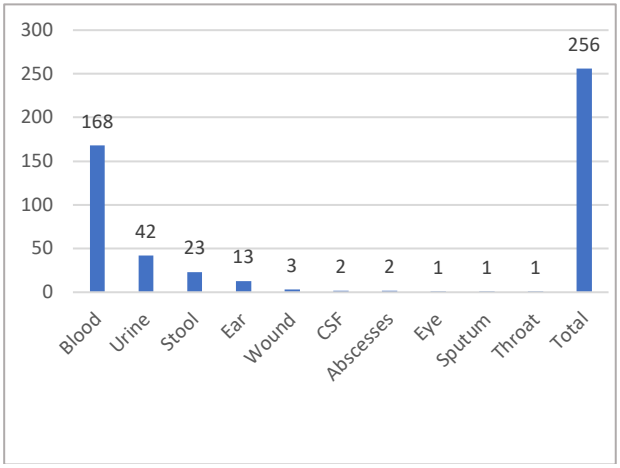

Figure 2: Distribution of examined samples according to source

Table 3: Types of microorganisms for all samples

Microorganism	No.	%
Gram positive bacteria	**30**	**55.5**
Staphylococcus haemolyticus	10	18.5
Staphylococcus hominis	7	13.0
Staphylococcus epidermidis	6	11.1
Staphylococcus aureus	5	9.3
Staphylococcus simulans	1	1.9
Enterococcus faecalis	1	1.9
Gram negative bacteria	**23**	**42.6**
E. Coli	12	22.2
Citrobacter freundii	3	5.6
Pseudomonas aeruginosa	3	5.6
Acinetobacter bumannii	2	3.7
Proteus mirabilis	2	3.7
Acinetobacter lwoffii	1	1.9
Yeast: *Candida albicans*	**1**	**1.9**

DISCUSSION

Hemato/oncology samples represent 72.7% of this study, and the utmost prevalent type of cases were 47 ALL cases (42.7%). Among these patients, 20 cases (42.5%) had positive culture, as mentioned in Al-Mulla et al.[11] Both Lymphoma and AML patients had a comparable score – 5 patients (33.3%) and 5 patients (31.25%) respectively. All solid tumor cases come together after that – 30 cases (26.66%).

These samples were taken from 9 patients who had ALL (19%) during the induction stage. Among them, 7 had positive culture results (77%); 3 cases (14%) had positive results during consolidation from 21 patients (44.7%). In contrast, among the 14 cases (29.8%) in the relapse stage, 7 patients 50% had a positive result, and in maintenance stage, 3 cases (6.4%) had a positive result.

This means patients in the induction and relapse stages are more likely to have an infection and positive culture due to severe suppression of immunity, besides the intensifying effect of cytotoxic treatment, as mentioned by Freifeld et al.[10] The maintenance patient had 2 positive results in stool samples and 1 in an ear swab, which means there may be local defiance in their immunity.

There were 20 cases (41%) that were positively tested for ALL. Among these, 9 cases (45%) had mucositis. This result means that mucositis suggest a positive result, especially in hematological malignancy patients. This result is similar to that by Gustinette et al.[7]

Neutropenia was recognized in 19 cases (40.4%). Among ALL patients associated with a positive culture, 9 cases had neutropenia (47%). AML patients had both neutropenia and mucositis associated with positive culture but this was lower for them than ALL patients – 28.5% and 25%, respectively. This could be due to the small sample size or the stage of the disease and its therapy.

Among the cases with a hematological type of malignancy, 12 cases (15%) had fever with a positive culture, and 7 cases (39%) among ALL patients had recorded fever. In contrast, only one case with AML had associated fever with a positive culture (6.25%), indicating neutropenia. Besides, mucositis associated with fever had a more predictive factor for positive culture result, as noted by Al Mulla et al. as well.[11]

Sometimes, lack of distinctness of the presence of more than one pathogen in a culture, which has an incidence possibility of 8–32%, are more liable to cause death, and

some studies explain a few cases similar to the results in this study that has 2 pathogens or more.[3,7,12]

The epidemiology of bacterial infection among cancer patients has seen a significant difference in the last ten years, with the switch from GN bacteria to GP bacteria.[13]

The current study demonstrates that GP bacteria were more abundant than GN bacteria – 30 patients (55.5%) and 23 patients (42.6%), respectively. Hence, this result agrees with several studies that show a higher abundance of GP positive bacteria, such as Worku et al.[2] (61%), Al-Mulla et al.[11] (55%), Mattei et al.[3] (50%), Garrido et al.[8] (44.3%), Kuo et al.[13] (42.3%), Uso et al.[14] (24.9%), and Boeriu et al.[15] (40%).

On the other side, many other studies demonstrate an abundance of GN bacteria over GP bacteria. Al-Rawazq [12] shows 77.5% of GN bacteria. Likewise, Kara et al. [16] (60%), Al-Zubaidy et al.[17] (53.6%), Von Knorring et al. [18] (49%), Arman et al. (45.8%) (8), Levene et al.[19], and Rabirad et al.[20] present similar results.

The presence of GP microbe in Hematological malignant disease may be partly due to low WBC count and the inflammation of mucus membrane. This is similar to the results by Garrido et al.[6] Besides the damage to the mucosal lining of the stomach and intestine, which render it susceptible to the microbes, who then travel to different parts of the body through blood, our result may be due to protocols with a good cover of GN bacteria and less strict on GP one.

Regarding the death of 14 patients (12.7%), 9 of these patients had positive culture (64.3%), 4 cases died due to GP *staph spp*. Further, 1 case had MRSA, 2 cases had GN *E. coli*, and 2 had ESBL one with added CRE. *Acinetobacter Bummani*, in another case, a patient with a brain tumor developed Covid 19 with a blood culture that showed to be positive for *E. coli*, wth ESBL CRE in suppression. Additionally, 5 ALL patients who died had a positive culture, while 2 of them had negative cultures.

Among the 3 AML patient deaths, 1 had GP and GN (*Staph. Hemolyticus and E. coli*) poly microbial ESBL, and 1 had a negative culture. All these deaths were in the relapse stage. So, the presence of different types of antibiotic resistance may hasten the death of such unfortunate patients and carry an augmented venture for future patients who need stringent guidelines to prevent infection.

NHL and NB patients who died had negative cultures, while the death of the CML case with the complicated bone marrow transplantation had a positive culture. The case with the brain tumor was positive for Covid 19 and *E. coli* with ESBL and CRE.

Infections appear to cause death in 4 cases mainly, which represents 3.6% of the total cases, similar to the study by Mattie et al.[3] (3.9%). At the same time, other patients died due to complications of progressive illness with relapse and recurrence.

These results mean that a new era with the identification and propagation of multidrug-resistant microorganisms has been recognized, further jeopardizing oncology patients and making it more difficult to handle and heightening their fatality.[8]

Our study is comparable to the results of death in the study by Mvalo et al.[21], which had 14% due to different causes, and Al-Mulla et al.[11] by 10.8%.

This study had several limitations since it is a retrospective type. It had a small sample size. The duration was only 1 year and furthermore, our patients had few to nearly neglectable CVC, which was not included in this study to compare with other searches done in many hospitals worldwide.

CONCLUSIONS

Our pediatric oncology patients with fever or neutropenia and mucositis were more infected by GP than GN bacteria, had increased liability to infection, and the presence of bacteremia was more critical during induction and relapse stages. It must be ensured that cultures are taken during such stages, with the intimidating effect of the development of antibiotic resistance with the presence of a different strain of superbug, which further jeopardizes the quality of survival.

We recommend continuous evaluation of antibiotic protocols for children with malignancy, depending on the culture results over the years to check the disposition of microorganisms in our hospital. Additionally, strict infection control schedule must be executed for surveillance.

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