

## CLINICAL AUDIT

**Healthcare-associated infections and drug resistance in immunocompromised children with cancer in a low-middle-income country**RAHAT UL AIN<sup>1</sup>, MAHWISH FAIZAN<sup>2</sup>, HUMA ZAFAR<sup>3</sup>, RABIA AQEEL<sup>4</sup><sup>1,3</sup>Assistant Professor Paediatric Hematology/Oncology, University of Child Health Sciences, The Children's Hospital Lahore<sup>2</sup>Associate Professor Paediatric Hematology/Oncology, University of Child Health Sciences, The Children's Hospital Lahore<sup>4</sup>Senior Registrar Paediatric Radiology, University of Child Health Sciences, The Children's Hospital LahoreCorrespondence to Dr. Rahat ul Ain, Email: [dr.rkashif@yahoo.com](mailto:dr.rkashif@yahoo.com), Cell: 0092-300-8434267**ABSTRACT****Aim:** It was a clinical audit conducted over 6 months period in order to determine the clinical characteristics of healthcare-associated infections (HAIs) in immunocompromised children with cancer in a developing country.**Methods:** It was a descriptive, cohort study conducted in the department of Pediatric Hematology/Oncology, University of Child Health Sciences, The Children's Hospital Lahore. All patients age less than 16 years, admitted in the pediatric oncology unit, having neutropenia and any culture-proven HAI were included. Data was analyzed in SPSS 16.0.**Results:** The total number of HAIs was 101 while the total number of infected patients was 83. The number of infections per 1000 patient days was 6.66. The most common HAI was bloodstream infection (BSI). Sixty-nine percent of HAIs were gram-negative while 31% were gram-positive. *Klebsiella* species was the most common gram-negative and *Staphylococcus Aureus* was the most common gram-positive organism. Pan-resistance was encountered in 25.74%, Carbapenem-resistant Enterobacteriaceae in 16%, Vancomycin-resistant Enterococci in 3%, and Methicillin-resistant *Staphylococcus Aureus* in 2%. Mean hospital stay was 20.22 days, 60.25% of patients were discharged, and 39.75% expired.**Conclusion:** Drug resistance is seen in about half of the HAIs. Gram-negative infections are the most common cause of HAIs in our setup. HAI and drug resistance are associated with significant morbidity and mortality in immunocompromised children with cancer and a pose major challenge in their management especially in a resource-limited setting.**Keywords:** Childhood cancer, Drug resistance, Healthcare-associated infections, Low-middle-income country**INTRODUCTION**

Pediatric cancer patients have an increased risk of potentially life-threatening infectious complications due to their underlying illnesses and intensive anticancer treatment<sup>1,2</sup>. Despite advances in the treatment and supportive care of patients with malignancies that have led to improvements in long-term survival especially in pediatric acute lymphoblastic leukemia (ALL), infection remains the most significant complication of anticancer therapy<sup>3</sup> and infection-related mortality is a major cause of death among ALL patients in LMIC<sup>4</sup>. For over a century, Health-care associated infections (HAI) and antimicrobial resistance has been recognized as an emerging healthcare problem and a major cause of adverse healthcare outcomes<sup>5</sup>.

Large amounts of antibiotics used for human therapy resulted in the selection of pathogenic bacteria resistant to multiple drugs with notable emergence of "pan-resistant" gram-negative strains and methicillin-resistant *Staphylococcus aureus* (MRSA)<sup>6,7</sup>. Infection with antibiotic-resistant gram-negative bacteria is associated with augmented morbidity and mortality<sup>6,7</sup>.

HAIs are a world-wide challenge and its prevalence is generally higher in low-middle income countries (LMIC) than high-income countries (HIC)<sup>8</sup>. Poor compliance of hand hygiene, understaffing, overcrowding, misuse of personal protective equipment, and suboptimal infection control program are major problems in LMICs. This leads to high infection rates and spread of multi-drug resistant pathogens<sup>8</sup>. Gram-negative pathogens are commonly found as a cause of blood stream infection (BSI) in pediatric hematology-oncology patients<sup>9</sup>. Non-fermentative Gram-negative bacteria (NFGNBs) have a lower incidence than Enterobacteriaceae species but NFGNBs cause life-threatening nosocomial infections<sup>10</sup>. *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Stenotrophomonas maltophilia* are the most frequently isolated NFGNBs<sup>11</sup>. Immunosuppression, malignancy, central venous catheter, and prolonged hospitalization all have been defined as risk factors for NFGNBs infections<sup>12</sup> and Carbapenem resistance is frequently observed in children with prolonged and severe neutropenia<sup>13</sup>.

Data regarding HAIs in children with cancer in developing countries is scarce. The rationale of this study was to determine the incidence, types, resistance patterns, and outcome of HAIs among pediatric oncology patients admitted to a tertiary care hospital in a developing country.

**MATERIALS AND METHODS**

It was a prospective, single-center, observational, cohort study / clinical audit. Eighty-three patients, from age 1 month to 16 years, who were admitted to the Pediatric Oncology department at The Children's Hospital Lahore, Pakistan, with culture-proven healthcare-associated infection (HAI) were included. Patients with community-acquired infections, clinical infections not proven with cultures, viral infections, and fungal infections diagnosed radiologically. HAI was defined as per the definitions set by the United States Centers for Disease Control and Prevention (CDC)/National Health Care Safety Network (NHSN) Guidelines<sup>14</sup>.

The study was conducted over six months from April 2016 to September 2016. Ethical approval was not taken as the data was collected as a part of a clinical audit. Informed and written consent was taken from the parents. Patients fulfilling the inclusion criteria were identified and followed up prospectively. The relevant clinical information of the patient including date of admission, primary diagnosis, site of infection, type of isolated pathogens, drug susceptibilities/resistance, length of hospital stay and outcome were noted. The outcome was noted in the form of either discharge or expiry and was measured in terms of frequencies. All the data collected were analyzed with SPSS version 16.0 in terms of descriptive statistics.

**RESULTS**

The total number of culture-proven HAIs during six months period was 101 while the total number of infected patients was 83. The total number of discharges was 898 with 15159 patient days. The number of infections per 100 discharges was 11.24 while the number of infected patients per 100 discharges was 9.24. The total number of infections per 1000 patient days was 6.66. Culture-proven HAI with regards to the site of infection, underlying disorders, type of organisms, resistance patterns and outcomes are listed in Table 1.

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Bloodstream infections were the most common site of infection, gram-negative pathogens were the most common group of organisms while Klebsiella species were the most common isolates (Figures 1 & 2). Pan-resistant gram-negative organisms were encountered in 26% of infections and contributed to 37% of all gram-negative isolates. Acinetobacterbaumanni was the most common pan-resistant organism. Carbapenem-resistant Enterobacteriaceae (CRE), Vancomycin-resistant Enterococcus Faecalis (VRE), and Methicillin-resistant Staphylococcus Aureus (MRSA) were also seen.

Table 1: Health-care associated infections, resistance patterns, and outcomes (n=101)

Site of Infection	n= isolations	%age
Bloodstream infection	50	49.5
Respiratory tract infection	17	16.83
Urinary tract infection	15	14.85
Skin infection	10	9.9
Otitis media	6	5.94
Septic arthritis	2	1.98
Meningitis	1	0.99
<b>Isolated Organism</b>		
Klebsiella	19	18.81
AcinatobacterBaumannii	17	16.83
Pseudomonas Aeruginosa	15	14.85
Escherichia Coli	13	12.87
Staphylococcus Aureus	10	9.9
Coagulase -ve staphylococci	9	8.91
Enterococcus Faecalis	3	2.97
Streptococcus Pyogenes	3	2.97
Streptococcus Viridans	3	2.97
Citrobacter Species	2	1.98
Aspergillus Flavus	2	1.98
Proteus Mirabilis	1	0.99
Pentoea species	1	0.99
Salmonella species	1	0.99
StenotrophomonasMaltophilia	1	0.99
Candida Species	1	0.99
<b>Type of Organism</b>		
Gram-negative	70	69.3
Gram-positive	28	27.7
Fungi	3	1.98
<b>Underlying Disorder</b>		
Total no. of patients=83		
Acute lymphoblastic leukemia	50	60.24
Non-Hodgkin Lymphoma	22	26.5
Hodgkin Lymphoma	3	3.61
Wilms Tumor	3	3.61
Ewing Sarcoma	3	3.61
Hepatoblastoma	1	1.2
Myelodysplastic syndrome	1	1.2
<b>Antimicrobial Resistance</b>		
Total no. of isolations=101		
Pan-resistance	26	25.74
CRE*	16	15.95
VRE*	3	2.97
MRSA*	2	1.98
<b>Pan-Resistant organisms</b>		
Total no. of isolations=26		
AcinatobacterBaumannii	13	50
Klebsiella species	8	30.76
Pseudomonas species	3	11.53
Escherichia Coli	2	7.69
<b>Outcome</b>		
Total no. of patients=83		
Discharged	50	60
Expired	33	40
<b>Pathogens in expired patients</b>		
Total no. of patients=38		
Gram-negative organisms		
AcinatobacterBaumannii	9	23.68
Klebsiella species	9	23.68
Escherichia Coli	7	18.42
Pseudomonas species	5	13.15
Citrobacter species	1	2.63
Pentoea species	1	2.63
Gram-positive organisms		
CONS*	2	5.26
StaphylococcusAureus	2	5.26
Enterococcus Faecalis	1	2.63
Streptococcus pyogenes	1	2.63
<b>MDRO among expired patients</b>		
Total no. of patients=38		
Pan-resistant gram negative	21	55.26
MRSA*	2	5.26
VRE*	1	2.63

\*CRE:Carbapenam resistant Enterobacteriaceae, VRE: Vancomycin-resistant Enterococcus Faecalis, MRSA:Methicillin-resistant Staphylococcus Aureus, CONS: Coagulase-negative Staphylococcus

The mean hospital stay of patients with culture-proven HAIs was 20.22 days while 33 out of 83 infected patients (40%) expired (Figure 3). Thirty-eight infections were isolated in 33 expired patients with the majority (84%) having gram-negative infections. The most common types of pathogens that were isolated in the expired patients were Acinetobacterbaumanni and Klebsiella species. Both (100%) patients with MRSA, 55% with pan-resistant gram negative organisms, and 33% patients with VRE expired.

Figure 1: Percentage of various sites of HAI's

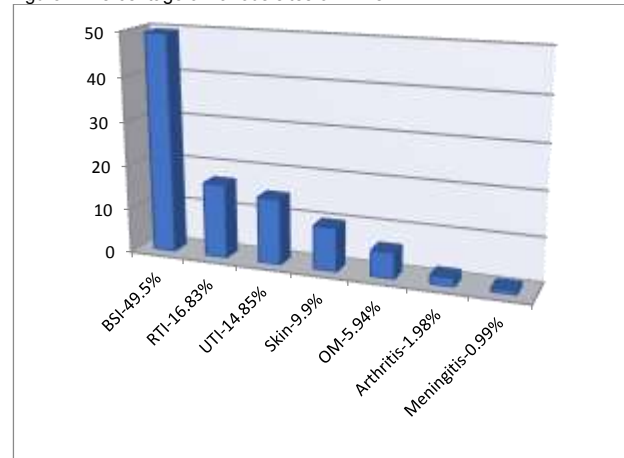


Figure 2: Percentage of groups of organisms isolated from cultures

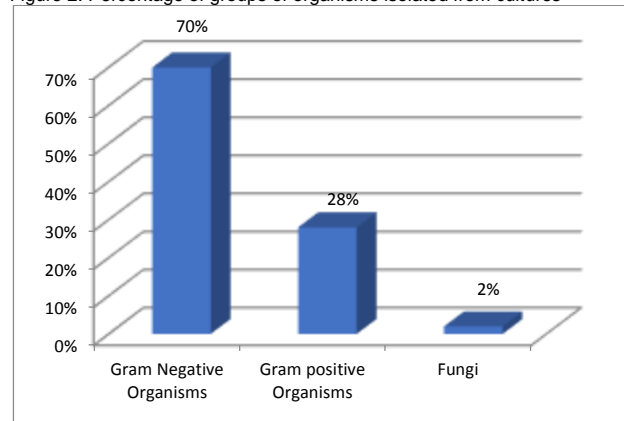
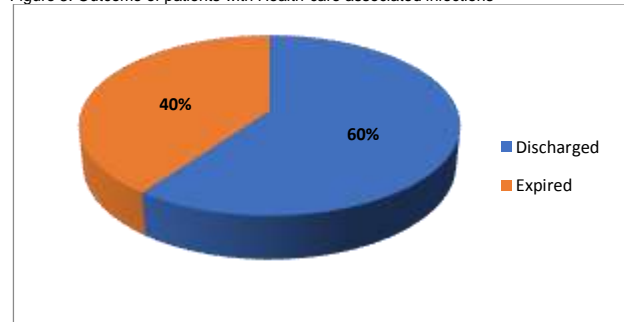


Figure 3: Outcome of patients with Health-care associated infections



## DISCUSSION

The number of infections per 1000 patient days in our study is fairly less than the number found in similar previous studies<sup>15,16</sup>. The possible reason for this could be that only culture-proven healthcare-associated infections were included in this study and not all the clinical ones. This may also be due to the fact that a

large number of patients are admitted to the inpatient facility for various other reasons than infections i.e., provision of chemotherapeutic drugs, management of chemotherapy toxicities, and complications; diagnostic and staging workup of patients. Therefore, a significant proportion of the admitted patients in this study were neither neutropenic nor had infections. Other important reasons for a large number of inpatient days are the lack of diagnostic and treatment facilities at other district and tehsil level medical centers and hospitals, poor socio-economic status of patients to afford investigations from private setups, and patients belonging to far-flung places, and lack of accommodation facilities nearby the hospital.

The most common type of infection encountered in our patients was also BSI as in a similar study from Pakistan by Siddiqui et al<sup>17</sup> but the percentage of BSI is fairly low. The reason for the low incidence of BSI could be the fact that we are not using central venous catheters (CVAD) for chemotherapy delivery rather peripheral lines are used for this purpose and we are not using the Bactec culture technique for getting blood cultures in our patients.

One multi-center study showed Gram-positive pathogens accounted for most (65%) of the cases, Gram-negative pathogens for 24%, and fungi for 11% with only a single case of candidemia<sup>14</sup>. Vancomycin resistance was seen in 11% of *E. faecium* isolates (VRE). No BSI was caused by MRSA, but 2 of 5 *E. faecium* BSI were caused by VRE.<sup>18</sup> Contrary to this, gram-negative organisms were the most common HAI seen in our study and this contrasting pattern could be due to the lack of CVAD being used in our setup. Acute Lymphoblastic Leukemia was the most common underlying disorder, followed by Non-Hodgkin Lymphoma and Hodgkin Lymphoma, similar to the previous studies<sup>17</sup>. This similarity could be because these oncological disorders have the same order of incidence in the pediatric population worldwide and the degree of myelosuppression associated with respective chemotherapy protocols. At the time of study patients with acute myeloid leukemia (AML), pediatric brain tumors and post-transplant were not being treated at our center, therefore, none of the patients from these disease groups are found in the study.

Drug resistance is a major health concern worldwide these days. We also found a significant number of drug resistance. HAI has been found to be associated with high mortality, particularly pan resistant pathogens were associated with 100% mortality. Therefore, it can be inferred that HAI in resource-limited setting is associated with very poor outcomes and pan-resistance is an extremely serious medical issue. Although limited data is available regarding the HAIs in the developing countries yet a distinct pattern of incidence, pathogens, and pan-resistance is seen in this study compared to the similar studies conducted in both low-middle-income and high-income countries<sup>14-21</sup>

The major limitations of this study were short duration, lack of inclusion of clinical infections (only culture-positive infections were included), possible poor yield of conventional blood culture techniques, and deficient clinical data of the patients like age, gender, nutritional status, and absolute neutrophil count.

## CONCLUSION

Healthcare-associated infections are an emerging challenge for clinicians in the management of immunocompromised patients. These infections are associated with significant hospital burden, morbidity, and mortality. Gram-negative organisms are the most common pathogens encountered in our setup, with a significant number being pan-resistant and associated with poor prognosis. The need for time is to take vigilant measures for infection prevention and control, and antibiotic stewardship. We have to take concrete steps to improve the surveillance for antimicrobial

resistance, regulations for the use of antibiotics and malpractice, and awareness and education of not only the public but also the medical students and doctors.

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