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Blood Stream Infections in Children with Malignancies: A Single Center Experience Risk Factors, Microbiological Isolates and Sensitivity Pattern

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Authors' contributions

This work was carried out in collaboration between all authors. Author WHA designed the study, performed the microbiological diagnosis and wrote the first draft of the manuscript. Author SME collected the patients' data. Author RMES performed statistical analysis and managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aim: To determine risk factors, microbiological isolates and antibiotic sensitivity pattern of blood stream infections of pediatric malignancies.
Study Design: A prospective single center cohort study included Children with malignancies that developed one or more episodes of septicemia during the period of their treatment and follow up.
Place and Duration of Study: We included 46 children who were admitted to the Pediatric oncology Unit of Tanta University Hospitals, Egypt, over the period of six months. The included children had a microbiologically confirmed blood stream infections.
Methodology: Positive blood cultures by BacT/ALERT were sub cultured on MacConkey agar,

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blood agar, chocolate agar, and sabouraud agar. VITEK 2™ Compact 15 was used for verification of bacterial identification and MIC determination.

Results: Sixty seven blood stream infections were detected in 46 patients. Hematological malignancies (67.4%) and neutropenia (69.7%) were the major risk factors. Gram positive bacteria represented (53.7%) including mainly coagulase negative *Staphylococci* (38.9%) and *Streptococci* (30.6%). Methicillin resistance was detected in all *S. aureus*, 71.4% of Coagulase negative *Staphylococci* that were sensitive to ciprofloxacin (85.7%, 100%), gentamycin (85.7%, 100%) and clindamycin (71.4%) respectively. Gram negative bacteria represent (46.3%) mainly *Klebsiella pneumoniae* (38.7%). ESBL in *Enterobacteriaceae* was (81.3%) with sensitivity to ciprofloxacin, amikacin, piperacillin/ tazobactam and sulbactam/ cefoperazone (100%, 100%, 69.2%, 53.8%) respectively. Carbapenem resistance was detected in one isolate of *K. pneumoniae*, two *P. aeruginosa* and two *A. baumanii*. Intestinal translocation of *Klebsiella pneumonia*e in (41.7%, 5/12) and *P. aeruginosa* (40%, 2/5), as well as in the four detected cases of central line blood stream infections.

Conclusion: The application of infection control guidelines and the strict antibiotic policy are mandatory for each institute. Selective digestive decontamination is considered to limit translocation. Carbapenem resistance was alarming and mandating more evaluation of β-lactam/β-lactamase inhibitors in treatment of ESBL *Enterobacteriaceae*.

Keywords: Blood stream infections; pediatric cancer; risk; microbiology.

1. INTRODUCTION

Despite early diagnosis and proper treatment of pediatric malignant diseases, cancer remains a major psycho-social and health problem with a complex protocol of treatment. During the period of treatment, pediatric patients with cancer are at increasing risk of healthcare-associated infections especially bloodstream infections (BSIs) [1].

These children who are receiving cytotoxic chemotherapy and other anti-neoplastic therapy are at increased risk of neutropenia as a common consequence of their treatment, also the indwelling central line along with loss of the mucosal integrity of the gastrointestinal tract can predispose these patients to bacteraemia and sepsis. Febrile episodes are observed in 34% of neutropenic periods in children treated for cancer, with bacteraemia identified in 10-20% of cases [2].

Bacterial BSI is considered an acute life-threatening condition especially in immunosuppressed patients. This condition should be treated immediately with intravenous antibiotics and supportive measures for at least 72 hours to prevent mortality due to potential pathogens [2].

So it is important to know the local profile of causative pathogens within a particular institution to allow appropriate management strategies, such as the choice of first line empirical antibiotics and infection control programs.

The aim of this study is to determine the incidence of BSI in children with malignancies, associated risk factors, microbiological profiles and the sensitivity pattern of isolated organisms.

2. MATERIALS AND METHODS

2.1 Setting

Pediatric Oncology Unit of Tanta University Hospitals, Egypt, that consists of 18 beds. Approximately 100 new referrals were made each year mainly patients with hematological malignancies. The Unit caters for its patients from all regions of the country.

2.2 Study Design

This a prospective single center cohort study including all oncology patients on treatment, or follow-up, who developed one or more episodes of septicemia during their entire course of treatment during six month period. Blood cultures yielding the same microorganism with the same sensitivity pattern within a seven day period were considered to be as the same septicaemic episode; however if the sensitivity pattern was different, it was considered as a different episode [2].

2.3 Data Collection

The following list of information was collected from patient data records: (1) Patients' characteristics which included demographic data

(e.g. age, sex, race), site of admission during episode, and the underlying diagnosis; (2) The presence of a central venous catheter during septicaemic episode; (3) The presence of predisposing infections (e.g: gastrointestinal, respiratory, wound); (4) The use of steroid therapy; (5) The results of the investigations (absolute neutrophil count during septicaemic episode, microbiological results including type of isolated organism and antibiotic sensitivity pattern).

2.4 Microbiological Investigations

2.4.1 Sampling

One Blood sample was taken at the onset of fever before starting antimicrobial therapy in all patients. Further, blood samples were collected for those patients every 48 hours till blood culture became negative according to the Hospital policy. Blood cultures were drawn from peripheral vein under complete aseptic technique with also existing central venous catheters, if present.

2.4.2 Culture

Bacteremia was defined as at least one positive blood culture, irrespective of the pathogen detected, using a qualitative automated culture system (BacT/ALERT 3 D 60, bioMérieux, Marcy-l'Etoile, France) [3]. Positive blood cultures by BacT/ALERT were subcultured on MacConkey, blood agar and chocolate, and incubated in 5-10% CO2, at 37℃ for 24 hours, while sabouraud agar was incubated at room's temperature.

2.4.3 Identification

Identification of the bacterial isolates was performed as per standard procedures including morphology and traditional biochemical reactions, with verification of suspected isolates by VITEK 2TM Compact 15 (bioMérieux, Geneva Marcy-l'Etoile, France).

2.4.4 Antimicrobial susceptibility testing by two methods

2.4.4.1 Disk diffusion method

Susceptibility testing was performed using the Kirby–Bauer Method as per the Clinical and Laboratory Standards Institute guidelines [4].

2.4.4.2 MIC determination by VITEK2^{TM} compact 15

Susceptibility testing was performed using AST-P592 cards for gram positive, AST-XN05 test cards for gram negative and AST-YS07 for yeast. Interpretation was done according to CLSI guidelines [4]. Quality control tests were performed according to the manufacturer's guideline by using the following control strain *Escherichia coli* ATCC ® 25922TM, *Pseudomonas aeruginosa* ATCC ® 27853TM, *Staphylococcus aureus* ® 29213TM and *Enterococcus faecalis* ® 29212 TM. The following antibiotic susceptibility pattern was recorded: sensitivity to penicillin, oxacillin/methicillin and vancomycin) for gram-positive bacteria; sensitivity to ceftazidime, meropenem, amikacin, piperacillin/tazobactem, cefoperazone/sulbactam, ciprofloxacin, tigecycline and colistin for gram-negative rods).

2.5 Defnitions

2.5.1 Bloodstream infection (BSI)

was defined as the isolation of a bacterial or fungal pathogen from at least one blood culture with the presence of at least one of the following signs of infection: fever (> 38℃), a systolic blood pressure < 60 mmHg, or signs of localized infection (inflammation) in a major organ/system [5]. For coagulase-negative staphylococci (*CoNs*), corynebacteria other than Corynebacterium jeikeium, and other common skin contaminant, at least two consecutive positive blood cultures, drawn in different occasions, are needed [6].

2.5.2 Laboratory diagnosis of catheter related bloodstream infections (CRBSI)

The presence of positive blood culture from the peripheral vein with absence of apparent cause except central line along with fever was considered catheter related blood stream infection. In addition, one of the following should also present: A positive semi-quantitative (>15 CFU/catheter segment) [7] or quantitative (>10^3 CFU/catheter segment) [8] catheter tip culture also, the same organism (species and anti-biogram) is isolated from the catheter segment and peripheral blood culture. Simultaneous quantitative paired blood cultures with a >5:1 ratio CVC versus peripheral, or positivity of the blood culture drawn from the CVC that becomes 2 hr earlier than the peripheral blood culture, is a new method for the diagnosis of CRBSI without removing the catheter [9].

2.5.3 Fever

Fever was defined as an axillary temperature > 38℃.

2.5.4 Neutropenia

Neutropenia was defined as an absolute granulocyte count < 1000/mL [5].

2.6 Antibiotic Policy

All FN patients received cefoperazone/sulbactum empirically with addition of amikacin in (acute myeloid leukaemia, Burkitt's lymphoma, induction, reinduction, reintensification, relapse and vital instability). Then antibiotics were modified according to the microbiological culture report. However, in culture negative patients same antibiotic was continued. Vancomycin was administered additionally to the patients, who had persistent fever, hypotension, redness or tenderness at central line insertion site and pneumonia. Amphotericin B was initiated empirically in patients in whom fever persisted despite antibiotics on day 4 or 5, in sinusitis with suspected fungal infection, pleuritic chest pain or chest X-ray suggested presence of fungal ball. In culture negative and stable patients intravenous antibiotics were continued for 5–7 days or until ANC recovered to >500/µl.

2.7 Statistical Analysis

Data were analyzed using statistical package of social science (SPSS) version 21. Qualitative data were described using number and percent and was compared using Chi square, statistical significance is $p \leq 0.05$. Spearman test was used to calculate the correlation coefficient between different variables. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median.

3. RESULTS

During six months observation, 67 BSIs were detected in 46 pediatric cancer patients, 52% were males. The two major risk factors for BSIs were hematological malignancies (67.4%) mainly leukaemias and neutropenia (70%) with statistical significance (p=0.018, 0.008) respectively. There was strong correlation between hematological malignancies neutropenia and presence of indwelling CVC (correlation coefficient=0.95, table not shown). As regard central line insertion, there were 10 cases (21.7%) and four of them (40%) had CLABSIs by the following isolates: Two *Pseudomonas aeruginosa*, one *Acinetobacter baumanii* and one *Enterococcus faecium* that were found as a stool colonizer (Table 1).

Table 1. Characteristics of patients with BSIs events

Characteristic (46)	No. (SD)	%	P
Sex:			
Male	24	52.2	0.768
Female	22	47.8	
Age (**months):**			
Mean	44.5		
Median± SD	36 ± 35.12		
Range	4 month-12 years		
Underlying disease:			
Hematological malignancy	31	67.4	
Solid tumor	15	32.6	0.018*
Neutropenia:			
Yes	32	69.6%	0.008*
No	14	30.4%	
Indwelling CVC:			
Yes	10	21.7	0.008*
No	36	78.3	
In hospital before fever:			
Yes	21	45.7	
No	25	54.3	0.000*
Steroid therapy:			
Yes	9	19.6	
No	37	80.4	0.000*

SD: Standard deviation, CVC: central venous catheter, P≤0.05 significant

There was predominance of gram positive bacteria (GPB) (54.5%). The most commonly isolated GPB was CoNS represent (38.9%, 14/36), followed by *Streptococcus* spp (30.6%, 11/36) that include (5) *VGS*, (2) *S. pneumoniae*, (2) *Granulicatella adiacens*, (1) *Granulicatella elegans* and one *S. pyogenes* isolate. There were two isolates of *Enterococci* (one isolate *E. faecium* and the other was *E. faecalis*). Gram negative bacteria (GNB) represent (45.5%) with predominance of *Klebsiella pneumonia*e (11/30, 36.7%) (Table 2).

Table 2. Bacterial isolates distribution in BSIs

Organism	No. of isolates (%) (67)
Gram positive isolates	**36(53.7%)**
CoNS	14(38.9%)
Staphylococcus aureus	7(19.4%)
Streptococcus spp	11(30.6%)
Enterococcus spp	2(5.6%)
Rothia dentocariosa	2(5.6%)
Gram negative isolates	**31(46.3%)**
Klebsiella pneumoniae	12(38.7%)
Eschericia coli	4(12.9%)
Pseudomonas aeruginosa	5(16.1%)
Salmonella spp	3(9.7%)
Acinetobacter baumanii	2(6.5%)
Enterobacter cloaca	1(3.2%)
Stenotrophomonas maltophilia	1(3.2%)
Brucella melitensis	1(3.2%)
Chrysobacterium meningeosepticum	1(3.2%)
Aeromonas salmonicida	1(3.2%)

CoNS: Coagulase negative Staphylococci

As regard susceptibility pattern of *K. pneumonia* (83.3%, 10/12), *E. coli* (75%, 3/4) was Extended-spectrum β-lactamase (ESBL) producers. Sensitivity of ESBL producers to ciprofloxacin was (100%), amikacin (100%), piperacillin/ tazobactam (TZP) (69.2%, 9/13) and cefoperazone/ sulbactam (CFS) (53.8%, 7/13). Carbapenem resistance was detected in one isolate of *K. pneumoniae* (that was sensitive only to amikacin, gentamycin, colistin and tigecycline), also was detected in one isolate of *P. aeruginosa* that was isolated from a CLABSI case and was sensitive to amikacin, gentamycin, ciprofloxacin and colistin. The two isolates of *A. baumanii* were resistant to all antibiotics except colistin and tigecycline (Table 3).

In GPB all *S. aureus* isolates and (71.4%, 10/14) of CoNS were methicillin resistant without detection of vancomycin resistance. Sensitivity of *S. aureus* and CoNS to ciprofloxacin (100%, 85.7%) and gentamycin (100%, 85.7%) and clindamycin (71.4%) respectively. All isolated *VGS* isolates were penicillin sensitive and one of two isolates of *S. pneumniae* was penicillin resistant, however was vancomycin sensitive. High level gentamycin resistance was detected in one isolate of *E. faecium* without appearance of vancomycin resistant *Enterococci* (Table 4).

4. DISCUSSION

BSIs are considered as major challenge in pediatric oncology. The source of infection is generally endogenous or exogenous. Low granulocyte count, mucosal damage and the presence of central venous catheters (CVC) expose patients to the risk of bacterial infections, especially shortly after chemotherapy, while prolonged neutropenia is a classic risk factor for bacterial infections [1].

Neutropenic episodes represent (32/46, 70%) in the current study, so febrile neutropenia is an important complication of cancer therapy associated with higher morbidity and mortality. Therefore, It should be considered a medical emergency, and a prompt administration of empirical antibiotic therapy is mandatory [1]. Thus administration of growth factors has been reported to reduce the degree and duration of post chemotherapy neutropenia, also the patients can be safely discharged to receive either outpatient or home antibiotic therapy thereby decreasing costs of treatment [10].

Table 3. Antibiotic susceptibility of the five most common gram negative isolates

Organism	Antibiotic sensitivity					
	CAZ	**TZP**	**CFS**	**AK**	**CIP**	**MER**
Klebsiella pneumonia (12)	1(8.3%)	8(66.7%)	6 (50%)	12(100%)	11(91.7%)	11(91.7%)
E. coli (4)	1(25%)	3(75%)	3(75%)	4(100%)	4(100%)	4(100%)
Pseudomonas aeruginosa (5)	2(40%)	3(60%)	3(60%)	3(60%)	3(60%)	4(80%)
Acinetobacter spp (2)	0	0	0	0	0	1(33.3%)
Salmonella spp (3)	3(100%)	2(66.7%)	2(66.7%)	0	3(100%)	3(100%)

CAZ: ceftazidime, TZP: piperacillin/tazobactam, CFS: cefoperazone/ sulbactam, AK: amikacin, CIP: ciprofloxacin, MER: meropenem

Table 4. Antibiotic susceptibility of the most common gram positive isolates

Organism	Antibiotic sensitivity N(%)							
	OXA	E	DA	CIP	GEN	VAN	TEI	LNZ
CoNS (14)	4(28.6)	8(57.1)	10(71.4)	12(85.7)	12(85.7)	14(100)	12(85.7)	14(100)
Staphylococcus aureus (7)	0	2(28.6)	5(71.4)	7(100)	7(100)	7(100)	5(71.4)	7(100)
Streptococcus spp (11)	10(90.9)	8(72.7)	8(72.7)	11(100)	11(100)	11(100)	11(100)	11(100)
Enterococcus spp (2)	0	0	0	0	1	2	0	2
Rothia dentocariosa (2)	2	2	2	2	2	2	2	2

OXA: oxacillin, E: erythromycin, DA: clindamycin, CIP: ciprofloxacin, GEN: gentamycin, VAN: vancomycin, TEI: teicoplanin, LNZ: linezolide, CoNS: Coagulase negative Staphylococci

Central line associated blood stream infections (CLABSI) were detected in four cases (4/10, 40%) in the current study. The presence of an indwelling catheter has been shown in other studies to be an important prognostic factor in febrile neutropenic patients [11]. The incidence of CVC-associated BSIs in neutropenic patients could be significantly reduced (e.g. from 24.3 to 16.2 per 1000 neutropenic days) by good training and education [12]. However not all CLABSI can be prevented by strict adherence to current CLABSI prevention bundles [13].

The present study showed that the traditional concept of catheter-related infections being mainly due to gram-positive cocci may not be completely true. Indeed, in recent years, an increasing role played by gram-negative bacteria in causing catheter-related infections has been reported by several investigators, including ours [5,14,15]. In the present study, gram-negative bacteria were reported in (3/4) of catheter-related infections and a large proportion of the isolated strains belonged to the group of bacteria that are usually associated with gut translocation. Many studies have hypothesized the translocation of bacteria across the mucosal barrier, rather than their introduction through percutaneous central venous catheter, as a common mechanism of CLABSI in neutropenic patients [16,17]. Therefore, in a recent manual on CLABSI, the definition of Mucosal Barrier Injury-Laboratory Confirmed Bloodstream Infection (MBI-LCBI) has been introduced as "Blood culture positive for one of the following intestinal organisms such as *Enterobacteriaceae, viridans Streptococci, Bacteroides* spp*., Enterococcus* spp*., Fusobacterium, Peptostreptococcus, Prevotella or Clostriudium* in a neutropenic patient or in a HSCT recipient with severe gastrointestinal graft-versus-host disease or diarrhea [6].

In accordance with our study, several risk factors in neutropenic patients influence the occurrence of BSIs such as mucositis, the presence of CVC, gastrointestinal bacterial colonization, prolonged hospital stay, acute myeloid leukemia and previous antibiotic treatments [18,19]. Latiff et al. [10] found none of the risk factors which were analyzed significant. These include the chemotherapy status, underlying disease, use of steroids and inpatient status at the onset of fever, although the presence of a central venous catheter conferred a higher risk but without statistical significance (p=0.11).

As regard type of isolated organisms, there was predominance of GPB (53.7%, 36/67), however GNB represent (46.3%, 31/67). CoNS (38.9%) was the most common GPB. The predominance of CoNS may be attributed to long-term invasive devices in oncology children that can be the exogenous sources of bacteria into the blood stream that may reflect defects in hygienic precautions [2].

The second common GPB was *Streptococci* (30.6%, 11/36) especially *Viridans group Streptococci* (VGS) (5/11), which are prominent members of the oral flora. They are the most common cause of streptococcal infections in patients with cancer, particularly in episode of neutropenia [20]. We reported two case of *Granulicatella adiacens* and one case of *Granulicatella elegans*, was originally known as 'nutritionally variant streptococci', it is a normal component of the oral flora, but reported as a cause of bacterial endocarditis and advised to be treated in the same way as *Enterococcal* endocarditis [21]. So they can be considered as a cause of BSIs in immune compromised patients.

The predominance of GPB reported in our study was in agreement with an Italian study that reported 191 BSIs in 156 patients from 18 pediatric hematology and oncology centers, Gram-positive cocci caused 48.7% (93/191) of BSIs with predominance of VGS (20) and CoNS (43). Gram-negative rods 47.1% (90/191) with predominance of *Pseudomonas* spp (28) and *Klebsiella* spp (22) and fungi 10.9% (21/191) [5].

Also, 250 patients with 328 BSI in a retrospective study at the National Cancer Institute (this center is a 90 bed tertiary care, Cairo University, Egypt), found predominance of gram-positive bacteria (168, 51.2%) including mainly CoNS (53, 16.2%), *Staphylococcus aureus* (44, 13.4%) and VGS (27, 8.2%). Gram-negative bacteria accounted for (97, 29.6%) of the total number of BSIs. Within gram negative isolates, *Acinetobacter* spp (22, 6.7%) *were* the most prevalent, followed by *Pseudomonas* spp (18, 5.5%). Fungal isolates were 30 of the total number of isolates [22]. In evaluation of 14-bedded pediatric oncology unit over a period of 3 years, 313 septicemia episodes were recorded in 131 children and Low-level pathogens such as CoNS account for 70% of these infections [2]. Another study in National Cancer Institute and Pediatrics, Egypt, found 348 BSIs in acute leukemia patients with predominance of GPC 239(68.7%) of the total isolates (mainly *Staphylococci* either *staph aureus* (111), CoNS(56) while Gram-negative organisms accounted for 68(19.5%), (18 *Pseudomonas* spp, 18 *Acinetobacter* spp, 18 *E. coli* spp) and fungemia was detected in 11 patients only (3.1%) [23]. Another study was done in Switzerland and Germany included 67 patients with febrile neutropenia episodes with bacteremia, a total of 83 pathogens were identified; 54 (65%) were GPB (27 CoNS, 20 VGS) and 29 (35%) were GNB (15 *E. coli*) [24].

In the current study *Klebsiella pneumoniae* (38.7%, 12/31) was the predominant GNB followed by *pseudomonas aeruginosa* (16.1%, 5/31). We found a case of *Aeromonas salmonicida*, that is mainly a fish pathogen and considered to be non-pathogenic for humans as it cannot grow at 37℃, although this the second case report from human blood [25].

Our study was in accordance with a surveillance study at the pediatric oncology unit of the University Hospital in Kuala Lumpur, Malaysia, that found *Klebsiella pneumoniae*, the most commonly isolated gram-negative bacteria, accounting for up to 20% of blood-culture isolates yearly. We found stool colonization with *Klebsiella pneumonia*e in (41.7%, 5/12) and *Pseudomonas aeruginosa* (40%, 2/5) in cases of septicemia with the same organism that is explained by gut translocation. Other studies proved the same finding that bacteraemia was preceded by the stool colonization with resistant organisms. In 43 bacteraemia episodes in patients with acute leukemia, 39 of them were preceded by surveillance cultures from various locations yielding the same organism [26]. Tancre`de and Andremont [27] had similar results showing stool colonization preceded bacteraemia with the same *Enterobacteriaceae* in 31/38 case. Wingard et al. [28] also found that 25% of patients with bone marrow transplant colonized with a resistant organism went on to have an infection by the same organism while only 6% of patients developed an infection from a resistant organism that was not previously identified by surveillance stool cultures. Three criteria need to be fulfilled in order for microorganisms to cause septicemia due to translocation: Gut overgrowth, defined as $\geq 10^5$ micro-organisms per g of feces, increased permeability of the intestinal wall and immunosuppression [27,29].

Decolonization will remain a controversial procedure to be considered before the onset of neutropenia but there is few data about its benefit [1]. By use of, oral gentamycin or a combination of oral gentamycin and colistin, the eradication rate of carbapenem resistant enterobacteraicae was 40-50% [30,31]. Infectious Disease Society of American guidelines [19] and the National Comprehensive Cancer Network Guidelines [32] suggested the use of fluoroquinolone as a prophylaxis in neutropenic patients at intermediate or high risk of infection with expected durations of prolonged and profound neutropenia. Possibility of selecting resistance to the last antibiotics that used for treatment of MDR(multidrug resistant) bacteria, is the main disadvantage of decolonization [1]. The rate of post-decolonization resistance was 25% and 45% to gentamycin and 40% to colistin in two studies [31,33]. However, the results of meta analyses indicated a strong protective effect of the full protocol of parenteral and enteral non-absorbable antimicrobials of SDD (selective decontamination of digestive tract) on pneumonia and BSIs with resistance being controlled and reduction in mortality [2,34]. These guidelines were based on studies conducted in adults and but there is limited data about prophylaxis in pediatric patients with careful measurement of risks and benefits [35]. Due to increased resistance from use of prophylactic antibiotics, the use of synbiotics (prebiotic and probiotic) as a prophylaxis for bacterial translocation can be suggested.

Cancer is one of the leading causes of increased antibiotic resistance. Regarding resistance pattern of GPB in this study, methicillin resistance was detected in (10/14, 71.4%) CoNS and in all isolates of *Staphylococcus aureus*. Resistance to ciprofloxacin and gentamycin was in two isolates of CoNS (2) and not found in *Staphylococcus aureus*. No appearance of vancomycin resistance. All isolates of *Streptococci* were penicillin sensitive except one isolate of *S. pneumonia*e. High level gentamycin resistance was detected in one isolate of *Enterococcus faecium* without appearance of vancomycin resistance. In agreement with our results, resistance to oxacillin was (33/43) in CoNS and (16/19) in *S. aureus*. Penicillin resistance was (8/20) in VGS [5]. A study in National Cancer Institute, Egypt, Methicillin resistant *Staphylococcus aureus* (MRSA) was (12/44, 27.3%). In addition, Vancomycin resistant Gram-positive strains were found in (33, 28.2%) [22]. A systemic review found that MRSA in cancer patients appears to be on the rise [36]. In the United States, penicillin resistance was reported in approximately 20% of invasive Cases of *S. pneumoniae* in 2010–2011 [37].

Regarding resistance of GNB in the present study, ESBL producing *Enterobacteriaceae* was (13/16, 81.3%) (10/12 *K. pneumonia*e, 3/4 *E. coli*), all these isolates were sensitive to ciprofloxacin and amikacin. The high percentage of ESBL make the empirical therapy with cephalosporins or piperacillin/tazobactam ineffective, this was in agreement with other studies [38,39]. ESBL producing *Enterobacteriaceae* is mainly detected in *K. pneumoniae* more than *E. coli* as found by Prabhash et al. [40] who detect ESBL in (15.15%) of *Enterobacteriaceae* and more frequently in *K. pneumoniae* (62.86%) than *E. coli* (50.94%) and *Enterobacter cloacae* (9.09%). Also in one year study bacteremia due to ESBL was more common in *K. pneumoniae* (11/14) than *E. coli* (15/87) and all the isolates were susceptible to carbapenems (meropenem and imipenem–cilastatin) [41].

Viscoli et al. [5] found different resistance pattern for GNB, (5/58, 9%) strains tested were resistant to both amikacin and ceftriaxone, (10/78, 13%) to both amikacin and ceftazidime, to fluroquinolones were (12/80, 15%) and (11/59, 19%) to the carbapenems. Also Ali El-Din et al. [22] found resistance of GNB to Ceftazidime (60%), to Amikacin and Imipenem (50%) and (40%) for Piperacillin-tazobactum, Cefoperazone, Cefepime and Ciprofloxacine.

In the present study, carbapenem resistance was detected in one isolate of *Klebsiella pneumoniae*, one isolate of *Pseudomonas aeruginosa* and the two isolates of *Acinetobacter baumanii* that were sensitive to colistin. Although a study done in pediatric unit of National Cancer Institute during one year duration extending from first January to end of December 2014 ,reported carbapenem resistance in *Enterobactreacae* isolates (95 /207, 45.9%) with increased incidence in *Klebsiella pneumonia*e (31/80, 39%). Also carbapenem resistance was (12/19, 63%) of *Acinetobacer baumanii*, (3/7, 42%) of *Stenotrophomonas maltophilia*, and (9/47, 19%) of *Pseudomonas aeruginosa*. colistin resistance was detected also in *Enterobactreacae* isolates (10/223, 44%) and Non-Fermenters (6/76, 8%) with increased mortality rate [42].

Although most studies detect high resistance whether in GPB or GNB that differs according to the antibiotic policy at each institute, a study in the oncology unit at Alder Hey hospital, England, found rare antibiotic resistance. No detection of methicillin resistance or vancomycin resistance in 164 CoNS and 19 *Staphylococcus aureus* isolates. In 27 pseudomonas, two only were MDR, in 11 *E. coli*, no MDR, in 11 *Klebsiella* spp, only one isolate was ESBL [2].

In this study, the sensitivity of ESBL producing *Enterobacteriaceae* to TZP and CFS was (69.2%, 53.8% respectively). These observations had greatly helped selecting empirical antibiotic treatment in febrile neutropenia. In our institute, first-line empiric antibiotic therapy was CFS or combination of CFS and amikacin according to the patient criteria, that showing appropriate sensitivity pattern that has been given edge in the literature also [43]. This was supported by Prabhash et al. [40] that found the sensitivity of the β-lactam/β-lactamase inhibitors (BLBLIs) combinations was better in the overall activity against GNB [48.8% susceptibility for TZP and 58.5% for CFS] with reported resistance to carbapenem (28.8%). Also in a study that include (141/269) *Enterobacteracae* ESBL and conclude carbapenems were the most sensitive followed by cefepime-tazobactam (CPT), cefepime, CFS and TZP [44]. Twenty-four (92%) of the ESBL-producing organisms were susceptible to either piperacillin-tazobactam or amikacin and recommend use of piperacillin-tazobactam plus amikacin or isepamicin instead of carbapenem, as an empirical therapeutic options for patients with neutropenic fever who are at high risk of developing bacteremia with ESBL-producing pathogens [45]. Also in a study that isolated

(210, 52.5%) isolates that were ESBL producers, (89, 22.25%) were AmpC producers, and (101, 25.25%) produced both types of enzymes in 400 total isolates, found that 88% sensitive to Cefepime/Tazobactum, 76% to amikacin and 66% to CFS, so these antibiotics can empirically serve as carbapenem sparing agents in the treatment of infections other than BSIs, in hemodynamically stable patients [46]. Also Harris et al. [47] found BLBLIs appear to have a similar efficacy to carbapenems in the treatment of cefotaxime-resistant *E. coli* and *Klebsiella pneumoniae*, (92) BSIs by making *in vivo* trial without significant difference in death rate, resolution of systemic inflammatory response syndrome, length of hospital stay, difference in isolation of carbapenem resistance, *Cl. difficile* isolation and relapsed BSI. So therapy with a BLBLI, when susceptibility is proven, may represent an appropriate carbapenem-sparing option. These findings direct the use of BLBLIs combinations especially, the TZP as alternative for carbapenems in treating of bacteremia caused by ESBL-producing organisms to decrease carbapenem resistance that increased globally [48]. There is also report of a case of MRSA-associated CRBSI successfully treated with the combination of fosfomycin, CFS and rifampin followed by fusidic acid and rifampin as has been supported by evidence from *in vitro* studies [49].

5. CONCLUSION

We believe our study is one of the few studies in Egypt which spotted the light on the various types of organisms causing BSIs, along with their susceptibilities, risk factors and management. Infection with resistant bacteria is the challenge in pediatric oncology. So comprehensive hospital infection control practices, and judicious antibiotic usage will improve the problem in developing countries. More studies also needed to evaluate the benefits of selective decontamination of digestive tract in decreasing blood stream infections in neutropenic pediatrics. Further studies are needed for evaluation of β-lactam/β-lactamase inhibitors in treatment of ESBL *Enterobacteriaceae* to decrease incidence of carbapenem resistance that is increased worldwide.

CONSENT

All authors declare that written informed consent was obtained from the patient's parents.

ETHICAL CONSIDERATION

It was approved by the Ethical Committee of the Faculty of Medicine, Tanta University, Egypt.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Gustinetti G, Mikulska M. Bloodstream infections in neutropenic cancer patients: A practical update. Virulence. 2016;7(3): 280–297.
2. Paulus S, Van Saene HK, Hemsworth S, Hughes J, Ng A, Pizer BL. A prospective study of septicaemia on a paediatric oncology unit: A three-year experience at The Royal Liverpool Children's Hospital, Alder Hey, UK. Eur. J. Cancer. 2005;41: 2132–2140.
3. Agyeman P, Aebi C, Hirt A, Niggli FK, Nadal D, Simon A, Ozsahin H, Kontny U, Kühne T, Beck Popovic M, Leibundgut K, Bodmer N, Ammann RA. Predicting bacteremia in children with cancer and fever in chemotherapy-induced neutropenia: Results of the prospective multicenter SPOG 2003 FN study. Pediatr Infect Dis J. 2011;30:e114–e119.
4. CLSI. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fifth Informational Supplement. CLSI document M100-S25. Wayne, PA: Clinical and Laboratory Standards Institute; 2015.
5. Viscoli C, Castagnola E, Giacchino M, Cesaro S, Properzi E, Tucci F, Mura RM, Alvisi P, Zanazzo G, Surico G, Bonetti F, De Sio L, Izzi G, Di Cataldo A, Ziino O, Massolo F, Nardi M, Santoro N, Binda S. Bloodstream infections in children with cancer: A multicentre surveillance study of the Italian Association of Paediatric Haematology and Oncology. Supportive Therapy Group-Infectious Diseases Section. Eur J Cancer. 1999;35(5):770-774.

6. CDC. Device associated module BSI. Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central line-associated Bloodstream Infection); 2016. Available:http://www.cdc.gov/nhsn/PDFs/pscManual/4PSC_CLABScurrent.pdf
7. Maki DG, Weise CE, Sarafin HW. A semiquantitative culture method for identifying intravenous-caheter-related infection. N Engl J Med. 1977;296:1305–9.
8. Brun-Buisson C, Abrouk F, Legrand P, Huet Y, Larabi S, Rapin M. Diagnosis of central venous catheter-related sepsis - critical level of quantitative tip cultures. Arch Intern Med. 1987;147:873–7.
9. Seifert H, Cornely O, Seggewiss K, Decker M, Stefanik D, Wisplinghoff H. Bloodstream infection in neutropenic cancer patients related to short-termnontunnelled catheters determined by quantitative blood cultures, differential time to positivity and molecular epidemiological typing with pulsed-field gel electrophoresis. J Clin Microbiol. 2003;41:118–23.
10. Latiff Z, Zulkifli SZ, Jamal R. Risk assessment and microbiological profile of infections in paediatric cancer patients with febrile neutropenia. Malaysian J Pathol. 2002;24(2):83–89.
11. Boersma RS, Jie KS, Verbon A, Van Pampus EC, Schouten HC. Thrombotic and infectious complications of central venous catheters in patients with hematological malignancies. Ann Oncol. 2008;19:433–42.
12. Chaberny IF, Ruseva E, Sohr D, Buchholz S, Ganser A, Mattner F, Gastmeier P. Surveillance with successful reduction of central line-associated bloodstream infections among neutropenic patients with hematologic or oncologic malignancies. Ann Hematol. 2009;88:907-12.
13. Sexton DJ, Chen LF, Anderson DJ. Current definitions of central line–associated bloodstream infection: Is the emperor wearing clothes? Infect Control Hosp Epidemiol. 2010;31(12):1286–1289.
14. Groeger JS, Lucas AB, Thaler HT, Friedlander-Klar H , Brown AE, Kiehn TE, Armstrong D. Infectious morbidity associated with long-term use of venous access devices in patients with cancer. Ann Intern Med. 1993;119:1168-1174.
15. Castagnola E, Garaventa A, Viscoli C, Carrega G, Nantron M, Molinari C, Moroni C, Giacchino R. Changing pattern of pathogens causing broviac catheter-related bacteraemias in children with cancer. J Hosp Infect. 1995;29:129-133.
16. DiGiorgio MJ, Fatica C, Oden M, Bolwell B, Sekeres M, Kalaycio M, Akins P, Shane C, Bako J, Gordon SM, Fraser TG. Development of a modified surveillance definition of central line–associated bloodstream infections for patients with hematologic malignancies. Infect Control Hosp Epidemiol. 2012;33(9):865–868.
17. Lukenbill J, Rybicki L, Sekeres MA, Zaman MOR, Copelan A, Haddad H, Fraser T, DiGiorgio MJ, Hanna R, Duong H, Hill B, Kalaycio M, Sobecks R, Bolwell B, Copelan E. Defining incidence, risk factors, and impact on survival of central line-associated blood stream infections following hematopoietic cell transplantation in acute myeloid leukemia and myelodysplastic syndrome. Biol Blood Marrow Transplant. 2013;19(5):720–724.
18. Meyer E, Beyersmann J, Bertz H, Wenzler-Rottele S, Babikir R, Schumacher M, Daschner FD, Ruden H, Dettenkofer M, ONKO-KISS Study Group. Risk factor analysis of blood stream infection and pneumonia in neutropenic patients after peripheral blood stem-cell transplantation. Bone Marrow Transplant. 2007;39:173-8.
19. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh KA, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2011;52:427-31.
20. Dix D, Cellot S, Price V, Gillmeister B, Ethier MC, Johnston DL, Lewis V, Michon B, Mitchell D, Stobart K, Yanofsky R, Portwine C, Silva M, Bowes L, Zelcer S, Brossard J, Traubici J, Allen U, Beyene J, Sung L. Association between corticosteroids and infection, sepsis and infectious death in pediatric acute myeloid leukemia (AML): Results from the Canadian infections in AML research group. Clin Infect Dis. 2012;55:1608–14.
21. Shailaja TS, Sathiavathy KA, Unni G. Infective endocarditis caused by *Granulicatella adiacens*. Indian Heart J. 2013;65(4):447–449.
22. Ali El-Din NH, Sidhom I, Zamzam MA, El-Mahalawy HA. Blood stream infections in pediatric cancer patients, epidemiology and outcome analysis. Journal of the

Egyptian Nat. Cancer Inst. 2003;15(4): 363-372.

23. Sayed HA, El-Mahallawy HA, Kaddah AM, Ismael HT, Talaat SM. Profile of infections in newly diagnosed patients with acute leukemia during the induction phase of treatment. Journal of the Egyptian Nat. Cancer Inst. 2009;21(4):315-322.
24. Agyeman P, Kontny U, Nadal D, Leibundgut K, Niggli F, Simon A, Kronenberg A, Frei R, Escobar H, Kühne T, Beck-Popovic M, Bodmer N, Ammann RA. A prospective multicenter study of microbiologically defined infections in pediatric cancer patients with fever and neutropenia. Pediatr Infect Dis J. 2014; 33(9):219-225.
25. Tewari R, Dudeja M, Nandy S, Das AK. Isolation of *Aeromonas salmonicida* from human blood sample: A case report. J Clin Diagn Res. 2014;8(2):139-140.
26. Schimpff SC, Young VM, Greene WH, Vermeulen GD, Moody MR, Wiernik PH. Origin of infection in acute nonlymphocytic leukemia. Significance of hospital acquisition of potential pathogens. Ann Intern Med. 1972;77:707–714.
27. Tancre`de CH, Andremont AO. Bacterial translocation and gram negative bacteremia in patients with hematological malignancies. J Infect Dis. 1985;152:99–103.
28. Wingard JR, Dick J, Charache P, Saral R. Antibiotic-resistant bacteria in surveillance stool cultures of patients with prolonged neutropenia. Antimicrob Agents Chemother. 1986;30:435–439.
29. Van Saene HKF, Taylor N, Donnell SC, Glynn J, Magnall VL, Okada Y, Klein NJ, Pierro A, Lloyd DA. Gut overgrowth with abnormal flora; the missing link in parenteral nutrition related sepsis in surgical neonates. Eur J Clin Nutr. 2003; 57:548–553.
30. Zuckerman T, Benyamini N, Sprecher H, Fineman R, Finkelstein R, Rowe JM, Oren I. SCT in patients with carbapenem resistant *Klebsiella pneumoniae*: A single center experience with oral gentamicin for the eradication of carrier state. Bone Marrow Transplant. 2011;46:1226-30.
31. Tascini C, Sbrana F, Flammini S, Tagliaferri E, Arena F, Leonildi A, Ciullo I, Amadori F, Di Paolo A, Ripoli A. Oral gentamicin gut decontamination for prevention of KPC-producing *Klebsiella pneumoniae* infections: relevance of concomitant systemic antibiotic therapy. Antimicrob Agents Chemother. 2014; 58:1972-6.
32. National Comprehensive Cancer Network. Practice Guidelines in Oncology. Prevention and Treatment of Cancer Related Infections; 2008.
Available:www.nccn.org
33. Lubbert C, Faucheux S, Becker-Rux D, Laudi S, Durrbeck A, Busch T, Gastmeier P, Eckmanns T, Rodloff AC, Kaisers. Rapid emergence of secondary resistance to gentamicin and colistin following selective digestive decontamination in patients with KPC-2-producing *Klebsiella pneumoniae*: A single-centre experience. Int J Antimicrob Agents. 2013;42:565-70.
34. Silvestri L, van Saene HKF. Selective decontamination of the digestive tract: an update of the evidence. HSR Proc Intensive Care Cardiovasc Anesth. 2012; 4(1):21-29.
35. Alexander S, Nieder M, Zerr DM, Fisher BT, Dvorak CC, Sung L. Prevention of bacterial infection in pediatric oncology: What do we know, what can we learn? Pediatr Blood Cancer. 2012;15:59(1):16–20.
36. Montassier E, Batard E, Gastinne T, Potel G, de La Cochetiere MF. Recent changes in bacteremia in patients with cancer: A systematic review of epidemiology and antibiotic resistance. Eur J Clin Microbiol Infect Dis. 2013;32:841–50.
37. Richter SS, Heilmann KP, Dohrn CL, Riahi F, Diekema DJ, Doern G. Pneumococcal serotypes before and after introduction of conjugate vaccines, United States, 1999–2011(1.). Emerg Infect Dis. 2013;19:1074–83.
38. Mikulska M, Del Bono V, Raiola AM, Bruno B, Gualandi F, Occhini D, di Grazia C, Frassoni F, Bacigalupo A, Viscoli C. Blood stream infections in allogeneic hematopoietic stem cell transplant recipients: reemergence of Gram-negative rods and increasing antibiotic resistance. Biol Blood Marrow Transplant. 2009; 15:47-53.
39. Mikulska M, Viscoli C, Orasch C, Livermore DM, Averbuch D, Cordonnier C, Akova M. Fourth European Conference on Infections in Leukemia Group (ECIL-4), a joint venture of EBMT, EORTC, ICHS, ELN and ESGICH/ESCMID. Aetiology and resistance in bacteraemias among adult

and paediatric haematology and cancer patients. J Infect. 2014;68:321-31.

40. Prabhash K, Medhekar A, Ghadyalpatil N, Noronha V, Biswas S, Kurkure P, Nair R, Kelkar R. Blood stream infections in cancer patients: A single center experience of isolates and sensitivity pattern. Indian J Cancer. 2010;47(2):184-8.
41. Kim SH, Kwon JC, Choi SM, Lee DG, Park SH, Choi JH, Yoo JH, Cho BS, Eom KS, Kim YJ, Kim HJ, Lee S, Min CK, Cho SG, Kim DW, Lee JW, Min WS. *Escherichia coli* and *Klebsiella pneumoniae* bacteremia in patients with neutropenic fever: Factors associated with extended-spectrum β-lactamase production and its impact on outcome. Ann Hematol. 2013;92:533–541.
42. Khedr RA, Hussein M, Elswify M, El-Mahallawy HA, Rafeh N. Current prevalence of Colistin resistance and its impact on mortality among pediatric cancer patients in Egypt. ECCMID, Amsterdam – Netherlands; 2016.
43. Lakshmaiah KC, Malabagi AS, Govindbabu, Shetty R, Sinha M, Jayashree RS. Febrile neutropenia in hematological malignancies: Clinical and microbiological profile and outcome in high risk patients. J Lab Physicians. 2015;7(2): 116–120.
44. Biswas S, Kelkar R. Cefepime-tazobactam: a new antibiotic against ESBL producing *Enterobacteriaceae* in cancer patients. Antimicrob Resist Infect Control. 2013; 2(1):81.
45. Kim SH, Kwon JC, Choi SM, Lee DG, Park SH, Choi JH, Yoo JH, Cho BS, Eom KS, Kim YJ, Kim HJ, Lee S, Min CK, Cho SG, Kim DW, Lee JW, Min WS. *Escherichia coli* and *Klebsiella pneumoniae* bacteremia in patients with neutropenic fever: Factors associated with extended-spectrum β-lactamase production and its impact on outcome. Ann Hematol. 2013;92:533–541.
46. Amreliwala S, Durgad S, Poojary A. Carbapenem sparing options for the treatment of ESBL and AmpC producing *Enterobacteriaceae* in hemodynamically stable patients an *in vitro* study Int. J. Curr. Microbiol. App. Sci. 2015;4(2): 513-521.
47. Harris PNA, Yin M, Jureen R, Chew J, Ali J, Paynter S, Paterson D, Tambyah PA. Comparable outcomes for β-lactam/β-lactamase inhibitor combinations and carbapenems in definitive treatment of bloodstream infections caused by cefotaxime-resistant Escherichia coli or *Klebsiella pneumonia*e. Antimicrob Resist Infect Control. 2015;4:14.
48. Kang CI, Park SY, Chung DR, Peck KR, Song JH. Piperacillin–tazobactam as an initial empirical therapy of bacteremia caused by extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumonia*e. Journal of Infection. 2012;64(5):533–534.
49. Apisarnthanarak A, Mundy LM. Successful treatment of disseminated methicillin-resistant *Staphylococcus aureus* with fosfomycin, cefoperazone/ sulbactam and rifampin followed by fusidic acid and rifampin. Int J Infect Dis. 2007;11(3):283–284.

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