

## Blood Stream Infections in Pediatric Cancer Patients, Epidemiology and Outcome Analysis

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### ABSTRACT

**Background:** Knowledge of the pattern of blood stream infections (BSI) in pediatric oncology patients can help determine factors governing these infections, hence antibiotic prescription policy and infection control procedures. Ultimately, quality preventive and quality management programs are targeted in our institution.

**Patients and methods:** Survey of BSI in pediatric oncology units at the National Cancer Institute (NCI), Cairo University, over 12 months mounted to 328 episodes of bacteremia and fungemia in 250 children with cancer.

**Results:** A total of 328 BSI occurred in 1135 febrile episodes in pediatric cancer patients at NCI during 1999. Hospital acquired infections (HAI) contributed to 37.5% of these episodes. Gram-positive pathogens were isolated in 168 episodes (51.2%) and 59% of the total isolates (either single or mixed), Gram-negative in 97 (29.6%) and mixed infections in 45 (13.7%). The common causative agents of blood stream infections in the present study were coagulase negative Staphylococci (Co NS) (16.2%), Staphylococcus aureus (*S. aureus*) (13.4%), Streptococcus spp. (12.1%), followed by Acinetobacter spp. (6.7%) and Pseudomonas spp (5.5%). The present study revealed that determinants of a more serious blood stream infection in pediatric oncology patients included hospitalization at time of diagnosis of febrile episode with prolonged hospital stay, intensified chemotherapeutic protocols, prolonged neutropenia, lower respiratory tract infections and multiple coexisting organisms. The same criteria can be used as prognostic features of blood stream infectious episodes with the addition of fungemia and state of disease, as uncontrolled cancer and induction phase of acute leukemia.

**Conclusions:** More understanding of the importance of a quality infection control policy with a close surveillance system aiming at early detection of outbreaks, early detection of newly emerged resistant pathogens, presence of isolation systems, strict antibiotic policy and continuous evaluation of the antimicrobial therapy practice are all needed to control the high rates of antibiotic resistance encountered at our institution.

**Key Words:** Blood stream infections - Hospital acquired infections - Antibiotic resistance - Immuno-compromised - Pediatric - Oncology patients.

### INTRODUCTION

Blood stream infections (BSI) remain a major cause of morbidity and death in patients undergoing treatment for cancer [1]. Cancer patients are predisposed to BSI for several reasons. Alteration in anatomic barriers both internal and external, enhance access of bacteria and fungi to the blood stream. Changes in both cell-mediated and humoral immunity occur related to primary tumor and subsequent treatment [2]. Infectious complications in the pediatric hematology-oncology patients have been significantly associated with the presence of indwelling catheters [3]. Although many infections in this immunocompromised population of patients may not be preventable through infection control measures, the careful evaluation of specific infection rates permits the identification of risk factors that may be targeted by infection control policies [4].

There is no doubt that immediate empirical broad-spectrum anti-microbial therapy is a standard rule in BSI. Clinical and conventional radiology signs of infection may be either absent or inadequate. However, the urgent anti-microbial strategy applied results in over-treatment of a considerable percentage of neutropenic patients [5]. Nowadays, there is a growing interest in risk stratification of febrile neutropenia in cancer patients based on predictive models from large studies in order to apply

risk directed therapy in this population of patients and to apply suitable preventive and management strategies accordingly. In fact, successful attempts have been made to stratify patients into high risk and low risk groups and differentiate treatment options respectively [6,7,8]. Hence, the aim of the present study is to evaluate the impact of different risk factors contributing to more serious blood stream infectious episodes encountered in the pediatric oncology service in order to collect the needed information to set the suitable guidelines for the prevention and management of BSI in our institution accordingly.

### PATIENTS AND METHODS

#### *Study design:*

During in the period from January 1<sup>st</sup> to the end of December 1999 at the National Cancer Institute, Cairo University, the medical records of pediatric cancer patients who gave a positive blood culture were retrospectively reviewed. This center is a 90 bed tertiary care institution receiving an average of 1000 new cases per year. Blood cultures were performed on the occurrence of fever in any cancer patient either newly diagnosed or under chemotherapy, whether neutropenic or not.

#### *Definitions:*

Fever was defined as a single temperature of 38.5°C or at least 2 readings of 38°C taken 2 hours apart; rectal measurement to be avoided. Patients were considered neutropenic if their absolute neutrophil count (ANC) at the onset of therapy was < 1000/ $\mu$ l or fell below that level (< 500/ $\mu$ l) in the 2 days following initiation of therapy. Blood stream infections included both bacteremia and fungemia. Hospital acquired infection was considered if no fever or any other clinical evidence of infection was present at admission and that fever occurred at least after 4 days of symptom free hospital stay [9]. When the blood culture revealed a potential contaminant, other clinical evidence of ongoing BSI as rigors, hypotension, or documented infection at a second site with the same organism was required for verification.

#### *Microbiology:*

Two blood culture sets were usually drawn from each patient within the first day of fever

from two separate veins. If the cannula site, portacath, or central venous catheter (CVC) was suspected as the source of infection, a blood sample was obtained from each in addition to the peripheral vein samples. Collected blood was directly injected into Bactec® (Becton Dickinson, USA) culture vials. Vials were incubated in the Bactec® 9050 incubator after collection. Identification of isolates was carried out utilizing Sensitizer AP80 and AP90 auto-identification plates (Accumed International Ltd. Interhorne Lane East Grinstead, West Sussex, UK) for Gram negative and Gram positive organisms, respectively. Plates for minimum inhibitory concentration (MIC), were also supplied by the same company.

*Clinical data:* retrieved included patient hospital number (ID number), age, sex, episode date and episode number (if multiple in the same patient), type of malignancy, state of disease during episode, and protocol of chemotherapy received. Data at the time of blood stream infection were collected including clinical aspects as temperature, ANC, empirical antimicrobial therapy, the presence of possible sites of infections as oral cavity and upper respiratory tract, mucositis, intravenous catheter site, skin abrasions, perianal area, urinary tract infections and lower respiratory tract. Lower respiratory tract infection (LRTI) was confirmed by CT and/or broncho-alveolar lavage.

*Anti-microbial therapy:* All febrile neutropenic patients were treated promptly with empiric I.V. broad spectrum antibiotics, a third generation cephalosporin combined with an aminoglycoside. They were given either Cefatazidime 150 mg/kg daily in three divided doses combined with Amikacin 15 mg/kg once daily or Ceftriaxone 100 mg/kg once daily combined with Amikacin [10]. If fever persisted for more than 72 hours, addition of Vancomycin 10 mg/kg/dose given in four divided doses a day, was followed in those who had severe mucositis, documented catheter related infection with site inflammation, or colonization with resistant Gram-positive organisms, hypotension or severe sepsis and have been on quinolone prophylaxis [11]. Otherwise, shift to another line of antibiotics Imipenem 60 mg/kg daily in four divided doses, with continuation of Amikacin was followed. Empirical I.V. antifungal therapy (amphotericin B 0.7 mg/kg given once daily)

was added if fever was present on day 7 [3]. Antibiotic therapy was continued until the patient became afebrile and the neutrophil count exceeded 500/ $\mu$ l.

The episode was considered as successfully controlled when fever and clinical signs improved after 72 hours. Persistence of fever for more than 7 days defined the morbid status of the episode. Endpoint of the study was considered if the episode ended with death within a month of positive culture. Cause of death was judged.

#### *Statistical methods:*

SPSS was used for data management. Multiple episodes of infection in the same patient were considered as independent events. As a retrospective study, data set for different variables may not add up each time to total number of the outcome variable encountered in the heads of different tables. So, percentages are calculated for valid data (excluding missing). The first part of the analysis was descriptive. Outcome variables were defined as continuous fever by the 7<sup>th</sup> day of admission as a morbid condition and death as an end status of disease. Chi-square test was used for comparing categorical independent variables and *t*-test for continuous data. In the second part of the analysis, a multivariate model was fitted to the data by application of a stepwise backward procedure. For the final model, odds ratio with 95% confidence intervals were calculated. All of the provided significance probabilities are two tailed.

## RESULTS

#### *Patient characteristics:*

Out of 3687 admissions in the pediatric inpatient service, a total of 1135 febrile episodes (a median of 308/1,000) were encountered from January to December 1999. From the latter figure, 328 were blood stream infections (median of 87 BSI/1,000 admissions) identified in 250 patients and constituted 28% (24%-45%) of total febrile episodes. Forty-two percent were treated on payable basis and 58% free of charge. Fig. (1) shows the distribution of rates of febrile episodes and BSI over the 12-month study period. Febrile episodes ranged from 218 to 713 episode/1,000 admission and BSI ranged from 62 to 186 episodes/1,000 admissions.

Median age was 6 years and ranged from 2-21 years. Fifty nine percent were males and 41% females. The original diagnoses of patients were acute lymphoblastic leukemia (ALL), acute myloid leukemia (AML), lymphomas and solid tumors in 36.6%, 22.3%, 14.9% and 26.2% of cases, respectively. Disease status during febrile episodes was as followed: 41.3% in maintenance or complete remission, 37.6% in relapse, 14.7% during induction phase and 6.4% as newly diagnosed cases. In 83 (25.3%) of the episodes, patients were receiving intensified courses of chemotherapy; whereas standard protocols were given in 219 (66.8%) of the episodes. In 26 (7.9%) of the episodes, patients were not under chemotherapy.

#### *Hospital acquired infections (HAI):*

Hospital acquired infections (HAI) contributed to 37.5% (n = 123) of the episodes. Table (1) shows that HAI was significantly correlated to the type of service of the pediatric wards. Incidence was more frequent in the of-charge unit than insured and private units, 65% versus 35%, respectively,  $p = 0.035$ . Risk factors of BSI from skin infections, LRTI and cannula site infection were all accompanied by highly significant proportions of HAI,  $p = 0.07$ , 0.02 and 0.001, respectively. Prolonged hospitalization characterized episodes of HAI compared to community acquired episodes (median 10 days versus 7 days, respectively,  $p < 0.001$ ). Gram-negative bacilli characterized HAI than Gram positive cocci,  $p = 0.04$ ; together with multiplicity of organisms,  $p < 0.001$ . Compared to solid tumors, hematologic malignancies constituted 90.2% of HAI,  $p < 0.001$ . Persistent fever after 7th day and persistent neutopenia (ANC below 500/ $\mu$ l) highly accompanied HAI,  $p < 0.001$ . Corresponding numbers and percentage are shown in table (1). In the same table, HAI showed a poorer outcome than community acquired episodes.

#### *Foci of infection:*

Of the 328 febrile episodes, 277 (84.5%) had an evident focus of infection. Mucositis grade 3 or 4 was the most frequent (151) site of upper GIT infection (46%). Lower respiratory tract infections were recorded in 127 (38.7%) of the occurrences. Gastro-enteritis manifested by diarrhea +/- vomiting and abdominal pain was present at the time of BSI in 67 (20.4%)

of episodes. Other sites of infection included the skin (perianal cellulites or ulcers, facial cellulites, skin abscesses, infected bed sores and others) and cannula site infections were met in 49 (14.9%) and 45 (13.7%) of episodes, respectively. Urinary tract infections were the least recorded in our population of patients, as it was found in 6 (1.8%) patients.

#### *Neutrophils and fever:*

At the onset of febrile episodes, ANC were  $< 500/\mu\text{l}$  in 77.2% of episodes. At day 4 and day 7 of evaluation, 68.3% and 54.8% of episodes were associated with ANC below  $500/\mu\text{l}$ . Persistent fever at day 4 was encountered in 53% and for a week in 30.25%.

#### *Microbiologic pattern:*

As a single isolate, Gram-positive organisms were the most frequently observed cause of BSI, accounting for 168 (51.2%) of the episodes. *Staphylococcus aureus*, coagulase negative staphylococci and viridans streptococci were the most frequent Gram-positive isolates. Gram-negative organisms accounted for 29.6% ( $n = 97$ ) of the total number of BSI. Within gram-negative isolates, *Acinetobacter* species were the most prevalent, followed by *Pseudomonas* spp. Mixed infections (polymicrobial) were detected in 45 of the episodes (13.7%), of which 35 were Gram-positive cocci, 25 were Gram-negative, 21 fungal isolates and 2 Gram positive bacilli. Fungal isolates were 30 of the total number of isolates, being pure in 9 of them and mixed in 21. Fungi were isolated from catheter site in 12; whereas, fungemia i.e. isolated from a peripheral blood sample, was found in 18 patients. Results of the etiologic agents of the 328 episodes of BSI are summarized in table (2).

*Antibiotic pattern:* Results of the minimal inhibitory concentration (MIC) for the bacterial agents are summarized in table (3), with the detailed results of Gram positive versus Gram negative organisms for each antibiotic.

#### *Antimicrobial resistance:*

Out of 44 episodes caused by *Staphylococcus aureus*, 12 (27.3%) were Methicillin resistant strains of *Staphylococcus aureus* (MRSA). In addition, Vancomycin resistant Gram-positive strains were found in 33 episodes out of 117 tested for Vancomycin (28.2%).

#### *Morbidity and mortality:*

Age and gender were not found to influence morbidity or mortality. Persistence of fever for a week after diagnosis was correlated to source of infection as HAI, hematologic malignancies, intensified courses of chemotherapy, LRTI, multiple co-existing microbes, presence of fungemia and persistent neutropenia. Mortality after BSI found to be correlated to the same attributes correlated to morbidity except for disease type as hematologic malignant disorders had borderline significance ( $p = 0.06$ ). The overall mortality rate was 20.4% (51/250) and blood stream attributable mortality was 72.5% (37/51). BSI was judged to have either contributed to or caused the terminal event through septicemia. Though Gram negative bacteremia was more frequently observed among patients with continuous fever and deceased patients than Gram positive cocci, yet observed differences did not reach statistical significance. Factors related to morbidity and mortality are summarized in tables (4 & 5), correspondingly.

#### *Multivariate analysis:*

Multivariate analysis came in support of the univariate analysis previously described. HAI was found to be intimately related to the hospital premises being more expected (Odds ratio, OR = 1.8, 95% CI 1.0-3.2) among patients treated for free and with prolonged hospital stay. Also, risk of acquiring HAI was significantly higher among patients having a cannula site infection (OR = 2.3, 95% CI 1.1-5.1). For those patients with solid malignancies and ANC higher than  $500/\mu\text{l}$  at day 7, the likelihood of HAI was much lower than patients having hematologic tumors or persistent neutropenia. Odds ratios were 0.2 (0.08-0.46) and 0.46 (0.26-0.80), respectively (table 6). The co-morbid conditions found on multivariate analysis correlated to persistence of fever after the first week are shown in table (7). The odds of having unfavourable outcome after episode of BSI were significantly dependent on source of infection, being higher with HAI, disease being during a relapse or induction phase of leukemia compared to complete remission, presence of LRTI or fungemia and polymicrobial infections. Odds ratio or risk of death along with its confidence intervals with the presence of these risk factors are shown in Table (8).

Table (1): Hospital acquired and community acquired blood stream infections in 328 episodes recorded in pediatric wards in the year 1999.

	BSI episode				<i>p</i> value*
	Hospital acquired N = 123		Community acquired N = 205		
	No.	%	No.	%	
Median age (Range)	8.0	(2-21)	6.0	(2-19)	0.52
<i>Sex:</i>					
Males	68	55.3	126	61.5	0.27
Females	55	44.7	79	38.5	
<i>Unit:</i>					
Free	80	65	109	53.2	0.04
Insured	43	35	96	46.8	
<i>LOS:</i>					
Median (range)	10	(3-35)	7	(3-30)	< 0.001
<i>Disease type:</i>					
Hematologic	111	90.2	131	63.9	< 0.001
Solid tumor	12	9.8	74	36.1	
<i>Foci of infections (#):</i>					
Mucositis	56	45.5	95	46.3	0.89
Skin infections	24	19.5	25	12.2	0.07
Cannula site	27	22	18	8.8	0.001
Lower respiratory tract	58	47.2	69	33.7	0.02
<i>Episode:</i>					
Single isolate	98	79.7	185	90.2	0.007
Polymicrobial	25	20.3	20	9.8	
<i>Bacteremia:</i>					
Gram +ve	51	54.8	117	68	0.03
Gram -ve	42	45.2	55	32	
<i>Fungemia</i>	10	8.1	8	3.9	0.1
<i>Persistent neutropenia at day 7:</i>					
Count < 500 mm <sup>3</sup>	75	72.8	85	45.5	< 0.001
Count ≥ 500 mm <sup>3</sup>	28	27.2	102	54.5	
<i>Persistent fever at day 7</i>	56	45.5	43	21	< 0.001
<i>Fate of episode:</i>					
Patient dead	35	28.5	16	7.8	
Patient alive	88	71.5	189	92.2	< 0.001

\* *p* is significant at 0.05 level.

LOS = Length of hospital stay.

# More than a focus of infection may be present in the same patient.

Table (2): The causative organisms in 328 BSI in pediatric oncology inpatient units, NCI, Cairo, during 1999.

General	Species	Number	Percent
Gram +ve cocci		(168)	(51.2)
	Staphylococcus aureus	44	13.4
	CoNS	53	16.2
	Streptococci	27	8.2
	Strept. pneumoniae	7	2.1
	Strept. pyogenes	6	1.8
	Enterococci	13	4.0
	Micrococci	5	1.5
	Other gram +ve cocci	13	4.0
Gram -ve bacilli		(97)	(29.6)
	Klebsiella	5	1.5
	Pseudomonas	18	5.5
	Acinobacter	22	6.7
	Enterobacter	9	2.7
	E coli	7	2.1
	Citrobacter	2	.6
	Pasteurella	6	1.8
	Gram -ve opportunistic	24	7.3
	Salmonella	2	.6
	Serratia	2	.6
Fungi		(9)	(2.7)
Gram +ve bacilli		(3)	(0.9)
Mixed isolate		(45)	(13.7)
	Fungi & gram +ve cocci	12	3.7
	Fungi & gram -ve bacilli	9	2.7
	Mix of gram +ve cocci	7	2.1
	Gram +ve cocci & -ve bacilli	15	4.6
	Gram +ve cocci & +ve bacilli	1	.3
	Gram -ve & +ve bacilli	1	.3
Unidentified		(6)	(1.8)
Total		328	100.0

CoNS = Coagulase negative staphylococci.

+ve = Positive.

-ve = Negative.

Table (3): Results of antibiotic pattern for the bacterial agents.

Antibiotic	Total % sensitivity	Gram positive sensitivity	Gram negative sensitivity	Mixed sensitivity
Amikacin	63.5	65.6	52.7	72.7
Ampicillin/Sulbactam	55.6	62.1	44.0	54.8
Augmentin	53.9	68.4	22.0	57.9
Piperacillin/Tazobactam	64.5	65.8	59.7	69.0
Ceftazidime	49.4	55.7	37.8	48.4
Imipenem	56.7	59.2	52.1	57.6
Cefepime	70.6	75.8	59.4	73.3
Cefoperazone	71.8	80.6	57.4	65.2
Cephalothine	55.2	62.9	42.3	52.0
Gentamicin	71.3	75.8	58.0	75.8
Cefuroxime	56.6	67.7	35.0	53.8
Ciprofloxacin	62.3	64.9	61.7	50.0
Vancomycin	67.0	71.8	-	57.1

Table (4): Attributes to the patient febrile condition at 7<sup>th</sup> day.

	Febrile N = 99		Afebrile N = 229		<i>p</i> value*
	No.	%	No.	%	
Age (mean ± SD)	8	(2-21)	7	(2-19)	0.14
Sex:					
Male	56	56.6	138	60.6	0.53
Female	43	43.4	91	39.7	
Infection:					
Hospital AI	56	56.6	67	29.3	< 0.001
Community AI	43	43.4	162	70.7	
Disease type:					
Hematologic	84	84.8	158	69.0	0.003
Solid tumor	15	15.2	71	31.0	
State during episode:					
CR	32	34.3	93	44.3	0.17
Relapse	42	45.2	72	34.3	
New/induction	19	20.4	45	21.4	
Chemotherapy:					
No chemotherapy	7	7.1	19	8.3	< 0.001
Standard	52	52.5	157	72.9	
Intensive	40	40.4	43	18.8	
Episode:					
Single isolate	69	96.7	214	93.4	< 0.001
Ploymicrobial	30	30.3	15	6.6	
Foci of infection:					
Mucositis	51	51.5	100	43.7	0.19
Skin infection	17	17.2	32	14.0	0.46
Cannula site	16	16.2	29	12.7	0.39
Lower respiratory tract	59	59.6	68	29.7	< 0.001
Bacteremia:					
Gram +ve	36	54.5	132	66.3	0.09
Gram -ve	30	45.5	67	33.7	
Fungemia:	13	13.1	5	2.2	< 0.001
Persistent neutropenia at day 7:					
Count < 500/μl	71	77.2	99	45.4	< 0.001
Count ≥ 500/μl	21	22.8	119	54.6	
Fate of episode:					
Dead	31	31.3	20	8.7	< 0.001
Alive	68	68.7	209	91.3	

\* *p* value is significant at 0.05 level.

Table (5): Outcome of BSI as alive "favorable" or dead "unfavorable".

	Favorable N = 277		Unfavorable N = 51		<i>p</i> value*
	No.	%	No.	%	
Age (mean ± SD)	7.0	(2-20)	8.0	(2-21)	0.18
Sex:					
Male	154	59.2	30	58.8	0.62
Female	113	40.8	21	41.2	
Infection:					
Hospital AI	88	31.8	35	68.6	< 0.001
Community AI	189	68.2	16	31.4	
Disease type:					
Hematologic	199	71.8	83	84.3	0.063
Solid tumor	78	28.2	8	15.7	
State during episode:					
CR	120	46.9	5	10.4	< 0.001
Relapse	87	34.0	27	56.3	
New/induction	49	19.1	16	33.3	
Chemotherapy:					
No chemotherapy	19	6.9	7	13.7	0.03
Standard	193	69.7	26	51.0	
Intensive	65	23.5	18	35.3	
Episode:					
Single isolate	257	92.8	26	51.0	< 0.001
Ploymicrobial	20	7.2	25	49.0	
Foci of infection:					
Mucositis	129	46.6	22	43.1	0.65
Skin infection	39	14.1	10	19.6	0.31
Cannula site	37	13.4	8	15.7	0.66
Lower respiratory tract	94	33.9	33	64.7	< 0.001
Bacteremia:					
Gram +ve	157	65.1	11	45.8	0.06
Gram -ve	84	34.9	13	54.2	
Fungemia:	5	1.8	13	25.5	< 0.001
Persistent neutropenia at day 7:					
Count < 500/μl	138	52.5	32	68.1	0.05
Count ≥ 500/μl	125	47.5	15	31.9	

\* *p* value is significant at 0.05 level.

Table (6): Stepwise logistic regression results for prognostic variables that significantly correlated to HAI.

Variables	B	S.E.	<i>p</i> value	Odds ratio (OR)	95.0% C.I. for (OR)	
					Lower	Upper
Free-of-charge unit	0.60	0.30	0.04	1.82	1.03	3.2
Solid malignancy	-1.63	.44	< 0.001	0.19	0.08	0.46
Presence of cannula	0.85	.40	.03	2.33	1.07	5.10
ANC at 7 <sup>th</sup> day > 500	-.79	.29	.007	.45	.26	0.80
LOS > 7 days	0.58	0.27	0.05	1.75	1.0	3.11
Constant	-.84	.33	.01			

B stands for regression coefficient, SE = Standard error, CI = Confidence interval, *p* is significant at 0.05 level, OR = The odds of HAI acquisition, LOS = Length of hospital stay.

Table (7): Stepwise logistic regression results for prognostic variables that significantly correlated to continuity of fever at 7<sup>th</sup> day.

Variables	B	S.E.	p value	Odds ratio (OR)	95.0% C.I. for (OR)	
					Lower	Upper
Nosocomial (HAI)	.762	.309	.014	2.142	1.170	3.921
Intensive chemotherapy	1.148	.304	< 0.001	3.153	1.737	5.725
Polymicrobial episode	2.030	.426	< 0.001	7.614	3.307	17.532
LRTI	1.449	.313	< 0.001	4.261	2.307	7.869
ANC at 7 <sup>th</sup> day > 500/ $\mu$ l	-1.002	.330	.002	.367	.192	.701
Constant	-3.211	.540	< 0.001	.040		

OR = The odds of continuity of fever at 7<sup>th</sup> day.

Table (8): Stepwise logistic regression results for variables that significantly correlated to unfavorable outcome of BSI.

Variables	B	S.E.	p value	Odds ratio (OR)	95.0% C.I. for (OR)	
					Lower	Upper
Nosocomial (HAI)	1.208	.450	.007	3.346	1.386	8.075
Disease in remission (Relapsed)	1.505	.618	.015	4.502	1.340	15.126
(Induction)	1.953	.650	.003	7.048	1.972	25.193
Polymicrobial episode	2.447	.542	.000	11.556	3.996	33.420
LRTI	1.094	.445	.014	2.987	1.249	7.144
Fungemia	1.537	.801	.055	4.649	.967	22.353
Constant	-4.930	.649	.000	.007		

OR = The odds of death.

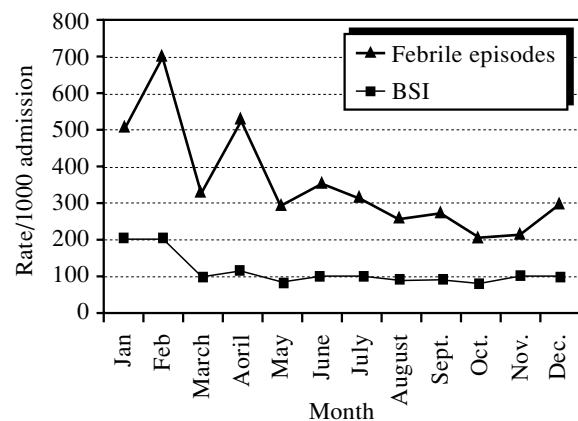


Fig. (1): Monthly incidence of febrile episodes & associated BSI rates per 1000 admissions in the pediatric inpatient units from January to December 1999.

### DISCUSSION

Infection is an expected sequel after the newer chemotherapeutic regimens for childhood cancer [2]. With the ongoing use of dose-intensive regimens and the widespread use of indwelling catheters, investigation of the infectious complications of cancer continues to be an important area of clinical research. The

identification of epidemiologic, clinical or laboratory predictors of causes of morbidity and mortality in febrile cancer patients are crucial to early treatment [12]. It was previously reported that an organism was isolated in 10 to 20% of pediatric cancer patients with febrile neutropenia [2]. Elting and his colleagues reported an overall rate of bacteremia of 22% from the results of several European studies in febrile neutropenic pediatric oncology patients [13]. In a single pediatric oncology unit and over a 5-year period, bacteremia was reported in 35.4% of febrile neutropenic episodes [14]. In the present study and over one year, BSI accounted for 328 of 1135 febrile episodes occurring in 250 patients and constituted 28% of total febrile episodes. This rate is more or less equivalent to other series.

Trends in the bacterial isolates found in cancer patients have varied over the past few decades. The results of the present study are going on with the changing epidemiology of infections in patients with neutropenia and cancer towards Gram-positive organism predominance [3]. In the studies of the International Anti-microbial Therapy Cooperative Group of

the European Organization for Research and Treatment of Cancer (EORTC), there has been a clear shift in infecting organisms causing BSI, so that now 60-70% of a BSI with a single organism are due to Gram-positive cocci [15]. Previously and at our institution, it was found that Gram-positive cocci were the predominant cause of BSI in pediatric cancer patients constituting 68.9% of isolated organisms [16]. In the present study, done over a longer period, Gram-positives were found to account for 59% of the total isolates (either single or mixed with other isolates) and 51% of the causes of BSI. This observed difference could be explained by the increase in mixed and fungal infections due to increased use of more intensified protocols of chemotherapy and probably due to better detection after using the Bactec® system.

The common causative agents of blood stream infections in the present study were Co NS 16.2%, *Staphylococcus aureus* 13.4%, *Streptococcus* spp. 12.1% followed by *Acinetobacter* spp. 6.7% and *Pseudomonas* spp. 5.5%; whereas 13.7% of the episodes were polymicrobial. Similar patterns were found in other studies. Out of 399 episodes of BSI in 273 patients with neutropenia, Gram-positive organisms were isolated in 55% of the episodes, Gram-negatives in 40% and *Candida* spp. in 5%. In the same study, the commonest pathogens isolated were *S. aureus* 18%, Co NS 16%, *Klebsiella* spp. 10%, *E. coli* 10%, Enterococci 8% and *Pseudomonas* spp. 6% [17]. In a multi-center study, the most frequently isolated pathogens causing bacteremia in children with cancer were Co NS 43%, *S. aureus* 16%, *E. coli* 9%, *Klebsiella* spp. 8%, *Pseudomonas* spp. 5% and *Candida* spp. 4% [18].

Resistance patterns of pathogens isolated from febrile neutropenic patients have emerged as a significant challenge. It is clear from data presented in table (3) that pathogens causing bacteremia in pediatric cancer patients at our institution show high resistance rates to many antimicrobial agents. Methicillin resistant *S. aureus* (MRSA) accounted for 27.3%. In a similar study, a significant increase in Gram positive antibiotic resistance has been noted as Co NS was found to be 55% resistant to Methicillin, *S. aureus* was 44% resistant and the resistance of *Streptococcus* spp. to penicillin reached 50% [18]. Although Gram positives demonstrated

better sensitivity than Gram negatives in this study, still 28.2% of Gram positives were resistant to vancomycin which warrant additional surveillance of the antimicrobial therapy practice. As regards Gram negative pathogens, very high resistance rates were reported in the present study reaching 60% for Ceftazidime, 50% for Amikacin and Imipenem and 40% for Piperacillin-tazobactam, Cefoperazone, Cefepime and Ciprofloxacin. The most probable explanation of these findings is the increased use of antibiotics in our hospital as evidenced by a more profound resistance to both Amikacin and Ceftazidime that have been used as first line of empirical therapy for prolonged duration. Fortunately, this high resistance pattern was not significantly associated with persistence of fever at day 7, or with the outcome. In addition, the line of antibiotic therapy used in this study did not significantly affect persistence of fever, nor the outcome. The discrepancy between in vitro susceptibility and clinical response suggests that, in the neutropenic patient, outcome is a function of multiplicity of host and microbial factors. In support of this hypothesis, it was previously concluded that among the host factors, persistence of neutropenia and the occurrence of complicated infection such as pneumonia, were found by multivariate analysis to significantly influence the outcome [13]. However, the high antibiotic resistance rates encountered in the present study emphasize the need to investigate the link between antimicrobial prescribing behavior and antimicrobial resistance.

Immunocompromised febrile cancer patients usually lack an evident focus of infection accompanying BSI, perhaps because of the inability to mount an adequate inflammatory response [2]. In our study, an evident focus of infection was present at a high frequency accompanying BSI (84.5%). Elting and his colleagues concluded that major organ infection and extensive tissue involvement do occur and that their presence significantly influences the prognosis of neutropenic patients. The same authors recommended that the frequency and response rates associated with deep tissue infection complicating bacteremia should be routinely included in reports of trials of antibiotic therapy for cancer patients to obtain a good estimate of outcome of these most serious infections [13]. The commonest evident focus of infection in our popu-

lation was mucositis (46%), followed by lower respiratory tract (RT) infections (38.7%), diarrhea (20.4%) and then catheter-related infections (13.7%). A considerable association of RT infections with BSI was previously observed. This problem was reported indicating that RT served as a classical predisposing factor for bacteremia in neutropenic pediatric cancer patients. Paganini and his coworkers found clinical evidence of infection in 47% of pediatric febrile neutropenia during anticancer therapy and the most common site was the upper RT in 81% [8]. In another study, a correlation between BSI and the presence of an indwelling catheter was found in 20% (23/114) of episodes among neutropenic cancer patients [19].

Concerning the outcome of BSI in our population the co-morbid conditions contributing to a more serious blood stream infection were prolonged neutropenia (i.e. ANC < 500/ $\mu$ l at day 4 and day 7) rather than ANC at the onset of fever, hematological malignancies, hospital acquired infections, intensified protocols of chemotherapy and lower respiratory tract infection. In agreement with these findings, it was stated that being an inpatient (HAI) at time of diagnosis of fever and neutropenia in oncology patients assign the patient to the high risk group, in addition to either concurrent co-morbidity or uncontrolled cancer [6]. Nosocomial infections usually occurred in patients who were hospitalized longer than the average length of stay [20]. In this study, prolonged hospitalization characterized episodes of HAI more than community acquired episodes (median of 10 days versus 7 days respectively,  $p < 0.001$ ). It is to be mentioned that HAI in this study significantly correlated to the system of financing being higher among those treated for free. This result might actually reflect the socioeconomic level with its implications on hygiene and health of these patients rather than a different quality of treatment. This belief could agree with the result of a study conducted in 4 Norwegian hospitals where they switched from 100% global budgeting to a combination of two different financing systems. In order to monitor quality of care, HAI was observed for a period and no change in the occurrence of HAI was found during the observation period [21].

In our study, patients with HAI proved to have prolonged periods of neutropenia which

predisposes to infectious complications. Evident foci of infections as cannula site and lower RT were significant in HAI. Multiple coexisting microbes were significantly higher among patients with HAI suggesting multiple sources and routes of infection. In spite of the shift in the cause of bacteremia in cancer patients towards Gram positive organisms, still Gram negatives are the most threatening causes of bacteremia in this population of patients. Morbidity rates are significant among patients with Gram negative bacteremia with a high risk of complications, such as septic shock and early death [3]. In this study, despite the increased frequency of Gram positive infections, Gram negative pathogens were significantly more encountered among patients with HAI. Although they did not reach significance level, morbidity and mortality of the infectious episodes were correlated to Gram negative pathogens. It is to be mentioned that fungemia and multiple coexisting microbes were significantly associated with a more morbid episode of infection and unfavourable outcome. Persistent fever at day 7 was reported in 30% of episodes; whereas an unfavorable outcome occurred in 20.4% (51/250). In a multi-center surveillance study, the overall mortality rate within 30 days from the first positive blood culture was 11% and was significantly higher among fungemia and polymicrobial infections than in single Gram positive or Gram negative bacteremia [19].

The results of the present study revealed that determinants of a more serious blood stream infection in pediatric oncology patients included hospital acquired infections, prolonged hospital stay, intensified chemotherapeutic protocols, prolonged neutropenia, lower respiratory tract infections and multiple coexisting organisms. The same criteria can be used as prognostic features of blood stream infectious episodes with the addition of fungemia and state of disease, as uncontrolled cancer and induction phase of acute leukemia.

Recommendations: More understanding of the importance of a quality infection control policy with a close surveillance system aiming at early detection of outbreaks, early detection of newly emerged resistant pathogens, presence of isolation system, strict antibiotic policy and continuous evaluation of the antimicrobial therapy practice are all needed to control the high

rates of antibiotic resistance encountered at our institution.

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