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# Clinical and microbiologic determinants of serious bloodstream infections in Egyptian pediatric cancer patients: a one-year study

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**Summary**

*Objectives:* Bloodstream infections (BSI) remain a major cause of morbidity and death in patients undergoing treatment for cancer. However, all recent epidemiological and therapeutic studies underline the absolute need for knowledge of the factors governing the infections in each center. The aim of this study is to identify the factors affecting BSI in the pediatric service of the National Cancer Institute (NCI) at Cairo University. More tailored policies for the treatment of patients with febrile neutropenia following chemotherapy can then be created.
*Patients and methods:* Over a 12-month period, all children with cancer and fever, with or without neutropenia, who were admitted to the NCI for empirical therapy of febrile episodes and who had a microbiologically confirmed bloodstream infection were studied retrospectively.
*Results:* A total of 328 BSI occurred in 1135 febrile episodes in pediatric cancer patients at the NCI in one year. Gram-positive bacteria were isolated in 168 episodes (51.2%) and 61.9% 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 bloodstream infections in this study were coagulase-negative staphylococci (16.2%), *Staphylococcus aureus* (13.4%), *Streptococcus* spp. (12.1%) followed by *Acinetobacter* spp. (6.7%) and *Pseudomonas* spp. (5.5%). Fungemia was encountered in 18 episodes,

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being mixed in nine of them. A more serious BSI in terms of a prolonged episode was encountered in 30.2% of the episodes and was significantly associated with patients being hospitalized, having intensified chemotherapy, polymicrobial and fungal infection, lower respiratory tract infections and persistent neutropenia at day seven.
*Conclusions:* In a large population of children, common clinical and laboratory risk factors were identified that can help predict more serious BSI. These results encourage the possibility of a more selective management strategy for these children.


## Introduction

Bloodstream 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:

- Alterations in anatomic barriers, both internal and external, enhance access of bacteria and fungi to the bloodstream.
- Changes in both cell-mediated and humoral immunity occur related both to the primary tumor and the subsequent treatment.[2]
- Infectious complications in pediatric hematology—oncology patients have been significantly associated with the presence of indwelling catheters.[3]

Although many infections in this immunocompromized 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 standard in the management of BSI. However, conventional clinical and radiological signs of infection may be either absent or inadequate and this urgent antimicrobial strategy results in the 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. This is based on predictive models from large studies in order to apply risk-directed therapy to this population and to apply suitable preventive and management strategies. Successful attempts have been made to stratify patients into high risk and low risk groups and differentiate treatment options.[6—8]

The aim of this study is therefore to evaluate the impact of different risk factors contributing to more serious bloodstream infectious episodes encountered in the pediatric oncology service. The information collected can be used to implement guidelines for the prevention and management of BSI at the National Cancer Institute at Cairo University.

## Patients and methods

### Study design

The medical records of pediatric patients who had a positive blood culture at the pediatric oncology department at the National Cancer Institute from January to December 1999 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 occurence 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 two readings of 38 °C taken two hours apart; rectal measurements were avoided. Patients were considered neutropenic if their absolute neutrophil count (ANC) at the onset of therapy was $<1 \times 10^9$/L or if it fell below that level in the two days following the initiation of therapy. The absolute neutrophil count was further categorized according to whether the expected duration of neutropenia ($<0.5 \times 10^9$/L) extended to more than seven days. Bloodstream infections included both bacteremia and fungemia. When the blood culture revealed a potential contaminant, other clinical evidence of ongoing BSI (such as rigors, hypotension, or documented infection at a second site with the same organism) was required for confirmation of true infection.

### Microbiology

Two blood culture sets from two separate veins were usually drawn from each patient within the first day of fever. If the cannula site, portacath, or central

venous catheter were suspected to be the source of infection, a blood sample was obtained from each, in addition to the peripheral vein samples.

Collected blood was injected directly into Bactec® (Becton Dickinson, USA) culture vials. Vials were incubated in the Bactec® 9050 incubator after collection. Identification of isolates was carried out utilizing Sensititre AP80 and AP90 auto-identification plates (AccuMed International Ltd., Imberhorne Lane, East Grinstead, West Sussex, UK) for Gram-negative and Gram-positive organisms respectively. The plates for minimum inhibitory concentration (MIC) were also supplied by the same company. For mixed injections the MIC was considered as that of the predominant organism causing infection.

### Clinical data

Retrieved data included patient hospital number (ID number), age, sex, episode date and number, type of malignancy, clinical state during episode, and the protocol of chemotherapy received. Data at the time of bloodstream infection included the degree and pattern of fever, absolute neutrophil count (ANC), empirical antimicrobial therapy, the presence of possible sites of infection such as oral mucositis, intravenous catheter site infection, skin abrasions or cellulitis, urinary tract infections and lower respiratory tract (RT) infections. Diarrhea was defined as an abnormal increase in stool liquidity and more than four bowel movements per day.

### Antimicrobial therapy

All febrile neutropenic patients were treated promptly with empiric intravenous broad-spectrum antibiotics: a third generation cephalosporin combined with an aminoglycoside. They were given either ceftazidime 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.[9] If fever persisted for more than 72 hours, vancomycin (10 mg/kg/dose in four divided doses a day) was added for those who had severe mucositis, documented catheter-related infection with site inflammation, or colonization with resistant Gram-positive organisms, hypotension or severe sepsis and for those had been on quinolone prophylaxis.[10] Otherwise, the regimen was altered to imipenem 60 mg/kg daily in four divided doses with continuation of amikacin. Empirical intravenous antifungal therapy (amphotericin B 0.7 mg/kg given once daily) was added if fever was present on day seven.[3] Antibiotic therapy was continued until the patient became afebrile and neutrophil count exceeded $0.5 \times 10^9$/L.

The episode was considered to be successfully controlled when fever and clinical signs resolved after 72 hours. Persistence of fever for seven days or more defined the morbid status of the episode and the episode was then considered severe. The episode was considered to be a treatment failure if it ended with death within a month of positive culture.

### Statistical methods

SPSS software was used for data management. Multiple episodes of infection in the same patient were considered as independent events. The first part of the analysis was descriptive. Outcome variables were defined as continuous fever if on the seventh day of admission the condition was still morbid, and death indicated an end status of the disease. To make inferential comparisons between the distributions in the two populations with morbid and non-morbid conditions as well as in dead and alive population, the Chi-square test was used for categorical independent variables and the *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. Coefficients were estimated with the maximum likelihood method and tests based on likelihood ratios to exclude (or to re-enter) variables in the model. For the final model, odds ratio with 95% confidence intervals was calculated. All of the significance probabilities provided are two-tailed.

## Results

### Patient characteristics

Of 3687 admissions to the pediatric inpatient service from January to December 1999, a total of 1135 febrile episodes occurred. From the latter figure, 328 were bloodstream infections that were identified in 250 patients and constituted 29% of the total febrile episodes. The patients ranged in age from two weeks to 18 years with a median of six years. Fifty-nine percent of them were male and 41% female. The original diagnoses of patients were acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), lymphomas and solid tumors in 36.6%, 22.3%, 14.9% and 26.2% of cases respectively. Collectively, 242 of the episodes occurred in patients with hematological malignancies, whereas solid tumors were the underlying disease in 86 episodes. 41.3% of febrile episodes occurred during maintenance or complete remission, 37.6% during relapse, 14.7% during the induction phase and 6.4%

in newly diagnosed cases. Intensified courses of chemotherapy were given during 83 (25.3%) of the episodes and standard protocols were given in 219 (66.8%), while in 26 (7.9%) of episodes, patients were not under chemotherapy.

Bloodstream infections occurred once in 197 (78.8%) patients and twice or more in 53 (21.2%) of them. Patients were hospitalized in 37.5% of the episodes ($n = 123$). Gram-negative organisms were encountered more frequently in hospitalized patients than in outpatients (45.2% vs. 32.0%), whereas Gram-positive organisms were isolated less frequently in inpatients than in outpatients (54.8% vs. 68%), $p = 0.03$. Infection with more than one organism was also more common in hospitalized than outpatients (20.3% vs. 9.8%), $p = 0.007$. Persistent fever, persistent neutropenia (ANC below $0.5 \times 10^9$/L) and a poor outcome were reported more frequently in hospitalized than non-hospitalized patients, $p < 0.001$; (45.5% vs. 21%), (72.8% vs. 45.5%) and (28.5% vs. 7.8%), respectively.

## Clinical features

Either a potential focus of infection (such as mild mucositis and mild skin cellulitis) or a documented focus of infection was encountered in 277 (84.5%) of the 328 bloodstream episodes, whereas 15.5% of episodes lacked a focus. Upper respiratory tract infections were reported in 151 (46%) of the

**Table 1** Causative organisms in 328 bloodstream infections in the pediatric oncology unit at the National Cancer Institute, Cairo University, during the year 1999.

| General | Species | Number | Percent |
|---|---|---|---|
| Gram-positive cocci | | 168 | 51.2 |
| | *Staphylococcus aureus* | 44 | 13.4 |
| | Coagulase-negative staphylococci | 53 | 16.2 |
| | *Streptococcus* spp. | 40 | 12.1 |
| | *Enterococcus* spp. | 13 | 4.0 |
| | *Microococcus* spp. | 5 | 1.5 |
| | *Aerococcus viridans* | 4 | 1.2 |
| | Other | 9 | 2.7 |
| Gram-negative bacilli | | 97 | 29.6 |
| | *Pseudomonas* spp. | 18 | 5.5 |
| | *Acinetobacter* spp. | 22 | 6.7 |
| | *Enterobacter* spp. | 9 | 2.7 |
| | *E. coli* | 7 | 2.1 |
| | *Pasteurella* spp. | 6 | 1.8 |
| | *Klebsiella* spp. | 5 | 1.5 |
| | Other | 30 | 9.2 |
| Fungi | | 9 | 2.7 |
| | *Aspergillus fumigatus* | 4 | 1.2 |
| | *Candida tropicalis* | 3 | 0.9 |
| | *Candida parapsilosis* | 1 | 0.3 |
| | *Candida krusei* | 1 | 0.3 |
| Gram-positive bacilli | | 3 | 0.9 |
| | *Bacillus ceieus* | 1 | 0.3 |
| | *Colynebacterium* spp. | 1 | 0.3 |
| | *Listeria* spp. | 1 | 0.3 |
| Mixed isolates | | 45 | 13.7 |
| | Fungi and Gram +ve cocci | 12 | 3.7 |
| | Fungi and Gram −ve organisms | 9 | 2.7 |
| | Mix of Gram +ve cocci | 7 | 2.1 |
| | Gram +ve cocci and −ve organisms | 15 | 4.6 |
| | Gram +ve cocci and +ve bacilli | 1 | 0.3 |
| | Gram −ve and +ve bacilli | 1 | 0.3 |
| Other | | 6 | 1.8 |
| Total | | 328 | 100.0 |

Gram +ve: Gram-positive organisms; Gram −ve: Gram-negative organisms.

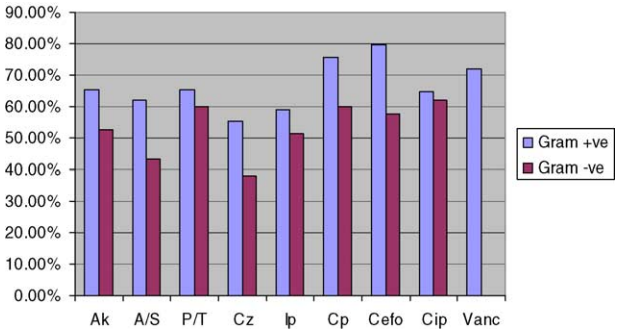


**Figure 1** The in-vitro antibiotic susceptibility (%) of Gram-positive ($n = 168$) and Gram-negative bacteria ($n = 97$) isolated from blood cultures of pediatric cancer patients with BSI during one year at National Cancer Institute, Cairo University. Ak: amikacin, A/S: ampicillin/sulbactam, P/T: piperacillin/tazobactam, Cz: ceftazidime, Ip: imipenem, Cp: cefepime, Cefo: cefoperazone, Cip: ciprofloxacin, and Vanc: vancomycin.

episodes; mucositis being the most frequent site. Lower respiratory tract infections were recorded in 127 (38.7%) of the occurrences. Gastroenteritis manifested by diarrhea, with or without vomiting, and abdominal pain was present at the time of BSI in 67 (20.4%) episodes. Other sites of infection included the skin (perianal cellulitis or ulcers, facial cellulitis, skin abscesses, infected bed sores and others) and catheter-related infections and were found in 49 (14.9%) and 45 (13.7%) episodes respectively. Urinary tract infections were recorded least often, in six (1.8%) patients.

## Neutrophils and fever

At the onset of febrile episodes, ANC was below $1.0 \times 10^9$/L in 287 (87.5%) episodes and in 77.2% the count was $<0.5 \times 10^9$/L. At day four and day seven of evaluation, 68.3% and 54.8%, respectively, of episodes were associated with ANC below $0.5 \times 10^9$/L. Persistent fever at day four was encountered in 53% ($n = 174$) and after a week in 30.25% ($n = 99$). Fever at day seven was not found to be related to neutropenia at the onset of fever ($p = 0.92$) whereas it was significantly related to reduced ANC ($<0.5 \times 10^9$/L) at day four ($p = 0.001$) and day seven ($p = 0.001$).

## Microbiologic pattern

As a single isolate, Gram-positive cocci were the most frequently observed cause of BSI, accounting for 168 (51.2%) of the total number of BSI. Gram-negative organisms accounted for 97 (29.6%) of the total number of BSI. Mixed infections were detected in 45 of the episodes (13.7%); micro-organisms isolated were 35 Gram-positive cocci, 25 Gram-negative bacilli, 21 fungal isolates and two Gram-positive bacilli. Fungi constituted 30 of the isolates and were obtained from a localized site in 12 patients (i.e. catheter site sample) and from a peripheral blood sample (fungemia) in 18 patients. Results of the etiologic agents of the 328 episodes of BSI are summarized in Table 1 and results of antibiotic sensitivity for Gram-positive, Gram-negative and mixed organisms are illustrated in Figure 1. Methicillin-resistant *Staphylococcus aureus* accounted for 41.7% (18 out of 44) *S. aureus* isolates. Forty of the organisms isolated as causes of bacteremia were resistant to all used antibiotics, but this multi-resistance was not significantly associated with persistence of fever at day seven, nor with an unfavorable outcome, $p = 0.28$ and 0.20 respectively.

**Table 2** Risk factors attributed to the persistence of fever on day seven.

| | Febrile $N = 99$ | | Afebrile $N = 229$ | | $p$-value* |
|---|---|---|---|---|---|
| | No. | % | No. | % | |
| Disease type | | | | | |
| Hematological | 84 | 84.8 | 158 | 69.0 | 0.003 |
| Solid tumor | 15 | 15.2 | 71 | 31.0 | |
| Chemotherapy | | | | | |
| None | 7 | 7.1 | 19 | 8.3 | <0.001 |
| Standard | 52 | 52.5 | 157 | 72.9 | |
| Intensive | 40 | 40.4 | 43 | 18.8 | |
| Focus of infection | | | | | |
| Mucositis | 51 | 51.5 | 100 | 43.7 | 0.19 |
| Skin infection | 17 | 17.2 | 32 | 14.0 | 0.46 |
| Catheter-related | 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 | |
| Single isolate | 69 | 69.7 | 214 | 93.4 | <0.001 |
| Polymicrobial | 30 | 30.3 | 15 | 6.6 | |
| Fungemia | 13 | 13.1 | 5 | 2.2 | <0.001 |
| Neutrophils | | | | | |
| Day 7 neutrophil count $<0.5 \times 10^9$/L ($n = 170$) | 71 | 77.2 | 99 | 45.4 | <0.001 |
| Day 7 neutrophil count $\geq 0.5 \times 10^9$/L ($n = 140$) | 21 | 22.8 | 119 | 54.6 | |
| Outcome of episode | | | | | |
| Death | 31 | 31.3 | 20 | 8.7 | <0.001 |
| Survival | 68 | 68.7 | 209 | 91.3 | |

* $p$-value is significant at 0.05 level; Gram +ve: Gram-positive organisms; Gram −ve: Gram-negative organisms.

**Table 3** Outcome of bloodstream infections in relation to different risk factors studied.

| | Favorable (survival) $N = 277$ | | Unfavorable (death) $N = 51$ | | $p$-value* |
|---|---|---|---|---|---|
| | No. | % | No. | % | |
| Disease type | | | | | |
| Hematologic | 199 | 71.8 | 43 | 84.3 | 0.063 |
| Solid tumor | 78 | 28.2 | 8 | 15.7 | |
| State during episode | | | | | |
| Complete remission | 120 | 46.9 | 5 | 10.4 | <0.001 |
| Relapse | 87 | 34.0 | 27 | 56.3 | |
| New/induction | 49 | 19.1 | 16 | 33.3 | |
| Chemotherapy | | | | | |
| None | 19 | 6.9 | 7 | 13.7 | 0.03 |
| Standard | 193 | 69.7 | 26 | 51.0 | |
| Intensive | 65 | 23.5 | 18 | 35.3 | |
| Focus of infection | | | | | |
| Mucositis | 129 | 46.6 | 22 | 43.1 | 0.65 |
| Skin infection | 39 | 14.1 | 10 | 19.6 | 0.31 |
| Catheter-related | 37 | 13.4 | 8 | 15.7 | 0.66 |
| Lower respiratory tract | 94 | 33.9 | 33 | 64.7 | <0.001 |
| Bacteremia | | | | | |
| Polymicrobial | 20 | 7.2 | 25 | 49.0 | <0.001 |
| 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 |
| Neutrophils | | | | | |
| Day 7 neutrophil count $<0.5 \times 10^9$/L ($n = 170$) | 138 | 52.5 | 32 | 68.1 | 0.05 |
| Day 7 neutrophil count $\geq 0.5 \times 10^9$/L ($n = 140$) | 125 | 47.5 | 15 | 31.9 | |

* $p$-value is significant at 0.05 level; Gram +ve: Gram-positive organisms; Gram −ve: Gram-negative organisms.

## Response to empirical therapy

The majority of the episodes ($n = 208$, 63.4%) responded to first-line empirical antibiotic therapy. The two regimens used as first-line empirical antibiotic therapy did not show significant differences with respect to the persistence of fever or the outcome, $p = 0.30$ and 0.46 respectively.

## Morbidity and mortality

Age and gender were not found to be contributors to either morbidity or mortality. Factors related to morbidity and mortality are listed in Tables 2 and 3 respectively. In 37/51 (72.5%) deaths occurring in the 328 infectious episodes, BSI was judged to have either contributed to or caused the terminal event

**Table 4** Stepwise logistic regression results of the variables that significantly correlated to persistence of fever on day seven.

| Variables | B | S.E. | $p$-value | Odds ratio (OR) | 95% C.I. for (OR) | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| Hospitalization | 0.762 | 0.309 | 0.014 | 2.142 | 1.170 | 3.921 |
| Intensive chemotherapy | 1.148 | 0.304 | <0.001 | 3.153 | 1.737 | 5.725 |
| Polymicrobial episode | 2.030 | 0.426 | <0.001 | 7.614 | 3.307 | 17.532 |
| Lower RT infection | 1.449 | 0.313 | <0.001 | 4.261 | 2.307 | 7.869 |
| Neutrophils at Day 7 $>0.5 \times 10^9$ K | −1.002 | 0.330 | 0.002 | 0.367 | 0.192 | 0.701 |
| Constant | −3.211 | 0.540 | <0.001 | 0.040 | | |

OR: the odds of persistence of fever on day seven.

**Table 5** Stepwise logistic regression results of the variables that significantly correlated to an unfavorable outcome of bloodstream infections.

| Variables | B | S.E. | *p*-value | Odds ratio (OR) | 95% C.I. for (OR) | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| Hospitalization | 1.208 | 0.450 | 0.007 | 3.346 | 1.386 | 8.075 |
| Disease in remission | | | | | | |
| (Relapsed) | 1.505 | 0.618 | 0.015 | 4.502 | 1.340 | 15.126 |
| (Induction) | 1.953 | 0.650 | 0.003 | 7.048 | 1.972 | 25.193 |
| Polymicrobial episode | 2.447 | 0.542 | 0.000 | 11.556 | 3.996 | 33.420 |
| Lower RT infection | 1.094 | 0.445 | 0.014 | 2.987 | 1.249 | 7.144 |
| Fungemia | 1.537 | 0.801 | 0.055 | 4.649 | 0.967 | 22.353 |
| Constant | −4.930 | 0.649 | 0.000 | 0.007 | | |

OR: the odds of death.

through septicemia. The other causes of death were relapsing or resistant malignant disease ($n = 11$), intra-cranial hemorrhage ($n = 2$) and disseminated intravascular coagulation ($n = 1$). Although Gram-negative bacteremia was observed more frequently among patients with continuous fever and in deceased patients than Gram-positive bacteremia, the differences were not statistically significant.

### Multivariate analysis

The co-morbid conditions found after multivariate analysis correlated to persistence of fever after the first week are shown in Table 4. Odds ratio or risk of death along with its confidence intervals for the presence of these risk factors are shown in Table 5.

## 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 clinical or laboratory predictors of causes of morbidity and mortality in febrile patients with cancer is crucial to early treatment.[11] It was previously reported that an organism was isolated in 10—20% of pediatric cancer patients with febrile neutropenia.[2] Elting and his colleagues have reported an overall rate of bacteremia of 22% from the results of several European studies in febrile neutropenic pediatric oncology patients.[12] In a single pediatric oncology unit, bacteremia was reported in 35.4% of febrile neutropenic episodes over a five-year period.[13] In the present study BSI accounted for 328 of 1135 febrile episodes occurring in 250 patients and constituted 29% of total febrile episodes over a one-year period. This prevalence is comparable to other series.

Trends in the bacterial isolates found in cancer patients have varied over the past few decades. The results of this study are consistent with the changing epidemiology of infections in patients with neutropenia and cancer towards a predominance of Gram-positive organism predominance.[3] As was documented in the studies of the International Antimicrobial 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 BSI with a single organism are due to Gram-positive cocci.[14] It was previously demonstrated that Gram-positive cocci were the predominant cause of BSI in pediatric cancer patients at the National Cancer Institute at Cairo University, constituting 68.9% of organisms isolated over a six-month study period.[15] In the present study, over a longer period, Gram-positive cocci were found to account for 61.9% of the total isolates (either single or mixed with other isolates) and 51% of the single isolates caused BSI. This drop between the two studies could be explained by the increase in mixed and fungal infections compared to that previously recorded at the National Cancer Institute. This is most probably due to the use of more intensified chemotherapeutic protocols used in the management of pediatric cancer patients and also due to better detection after using the Bactec® system.

The most common single causative agents of bloodstream infections in this study were coagulase-negative staphylococci (16.2%), *Staphylococcus aureus* (13.4%), *Streptococcus* spp. (12.1%) followed by *Acinetobacter* spp. (6.7%) and *Pseudomonas* spp. (5.5%). 13.7% of the episodes were polymicrobial. Similar trends have been documented in other studies. Of the 399 episodes of BSI occurring among 273 patients with neutropenia in a one-year study, Gram-positive organisms were

isolated in 221 (55%) of the BSI, Gram-negatives in 161 (40%) and *Candida* spp. in 17 (5%). Overall, the common pathogens isolated were *S. aureus* (18%), coagulase-negative staphylococci (16%), *Klebsiella* spp. (10%), *E. coli* (10%), *Enterococcus* spp. (8%) and *Pseudomonas* spp. (6%).[16]

In a multi-center study, carried out to determine the causative agents of bacteremia in children with cancer, the most frequently isolated pathogens were coagulase-negative staphylococci (43%), *S. aureus* (16%), *E. coli* (9%), *Klebsiella* spp. (8%), *Pseudomonas* spp. (5%) and *Candida* spp. (4%).[17] In another multi-center surveillance study conducted in 18 pediatric hematology centers over a one-year period, Gram-positive cocci caused 45% (85/191) of the episodes, Gram-negative rods 41% (78/191) and fungi 9%; whereas 5% of the episodes were polymicrobial infections.[18]

In the present study, risk factors contributing to a more serious bloodstream infection were prolonged neutropenia (i.e. ANC $0.5 \times 10^9$/L at day four and seven) rather than ANC at the onset of fever, hematological malignancies, hospitalization at time of diagnosis of febrile episode, intensified protocols of chemotherapy and lower respiratory tract infection as a co-morbid condition.

This study related morbidity (due to infection) to persistent fever, whether continuous or intermittent, at day seven. Fever at day seven was reported in 99 (30.2%) of the BSI episodes; while an unfavorable outcome was reported in 15.5% (51/328). In a multi-center surveillance study, the overall mortality rate from any cause within 30 days of the first positive blood culture was 11% and was higher among patients who were neutropenic at the onset of infection than among those who were not neutropenic (15 vs. 4%, $p = 0.03$). In addition, the mortality was significantly higher among fungemia and polymicrobial infections than in single Gram-positive or Gram-negative bacteremia.[18] In this study, polymicrobial infections were significantly associated with a higher mortality rate.

In a study carried out to investigate the etiologic organisms, risk factors and other infectious features of septic shock in hematology oncology patients with neutropenic fever, Gram-negatives were isolated significantly more frequently than Gram-positive bacteria — they accounted for 78.3% of isolates in 39 patients with septic shock, $p \leq 0.001$.[19] On multivariate analysis, leukocyte count at the onset of fever was the only significant risk factor for septic shock in febrile neutropenic cancer patients.[19] Furthermore, Alexander and coworkers found that febrile neutropenia in children with cancer with an anticipated duration of neutropenia of over seven days, with or without a significant co-morbidity, showed a significantly higher frequency of bacteremia, other documented infections and serious medical complications than those with a shorter duration of neutropenia (41% versus 4%).[6] On the other hand, febrile children with lower risk neutropenia (i.e. expected duration of neutropenia less than a week), were found to survive pass their febrile episodes with no major complications or death.[8] Rapid neutrophil recovery was associated with good prognosis in 762 consecutive episodes of febrile neutropenia over a five-year period in a single pediatric oncology unit.[13]

Immunocompromized febrile cancer patients are often characterized by the lack of an evident focus of infection accompanying BSI, perhaps because of the inability to mount an adequate inflammatory response.[2] Nonetheless, a potential or documented focus of infection frequently accompanied BSI in this study.

Upper respiratory tract infection, mainly mucositis, was the most common documented site of infection in our patients (46.0%), followed by lower respiratory tract infections (38.7%), diarrhea (20.4%) and then catheter-related infections (13.7%). A significant association of RT infections with BSI has previously been observed. Paganini and his coworkers found clinical evidence of infection in 47% of episodes of pediatric febrile neutropenia during anticancer therapy; 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.[18] In the present study, lower RT infection proved to be a co-morbid condition and was significantly associated with a prolonged course of the BSI episode and an unfavorable outcome. In agreement with the findings here, the most common infection sites in a two-year study in hematology oncology patients with neutropenic fever were the respiratory and gastro-intestinal tracts. Respiratory tract infection was significantly more frequent in patients who developed septic shock, $p = 0.038$.[19]

Resistance patterns of pathogens isolated from febrile neutropenic patients have emerged as a significant challenge. It is clear from data presented in Figure 1 that pathogens causing bacteremia in pediatric cancer patients at this institution show high resistance rates to many antimicrobial agents. Methicillin-resistant *S. aureus* accounted for 41.7% of staphylococcal isolates. In a similar study, a significant increase in Gram-positive antibiotic resistance was noted: 55% of coagulase-negative staphylococci were resistant to methicillin, 44% of *S. aureus* were resistant and the resistance of *Streptococcus* spp. to penicillin reached 50%.[17]

In this study, very high resistance rates were reported for Gram-negative pathogens, reaching 60% for ceftazidime, 50% for amikacin and imipenem and 40% for piperacillin-tazobactam, cefoperazone, cefepime and ciprofloxacin. The most probable explanation for these findings is the increased use of antibiotics in the hospital, as evidenced by a more profound resistance to both amikacin and ceftazidime, which have been used extensively as first-line empirical therapy. Fortunately, this pattern of high resistance was not significantly associated with either the persistence of fever at day seven or the outcome. Likewise, the antibiotic regimen used in this study did not significantly affect either the persistence of fever or the outcome. The discrepancy between in vitro susceptibility and clinical response suggests that, in the neutropenic patient, outcome is a function of a combination of the host and microbial factors. However, the high antibiotic resistance rates encountered necessitate the investigation of a link between antimicrobial prescribing behavior and antimicrobial resistance.

From the results of this study, factors can be identified that may serve as determinants for more serious bloodstream infections in pediatric oncology patients. These include: hospitalization at the time of diagnosis of the febrile episode, intensified chemotherapeutic protocols, prolonged neutropenia, lower respiratory tract infections and multiple coexisting organisms. The same criteria can be used as prognostic features of the outcome of bloodstream infections with the addition of fungemia and state of underlying disease, as uncontrolled cancer and the induction phase of acute leukemia were found to be more hazardous.

Further research at the National Cancer Institute is needed to evaluate empirical antibiotic regimens using these risk criteria. In addition, better surveillance of antimicrobial prescribing practice is necessary to control the high rates of antibiotic resistance.

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## References


1. Alexander S, Walsh T, Freifeld A, Pizzo P. Infectious complications in pediatric cancer patients. In: Pizzo P, Poplack D, editors. *Principles and practice of pediatric oncology*. Philadelphia: Lippincott Williams and Wilkins; 2002. p. 1239—83.
2. McCullers J, Shenep J. Assessment and management of suspected infection in neutropenic patients. In: Patrick C, editor. *Clinical management of infections in immunocompromised infants and children*. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 413—49.
3. Hughes WT, Armstrong D, Bodey GP, et al. Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. *Clin Infect Dis* 1997;**25**:551—73.
4. Simon A, Fleischhack G, Hasan C, Bode U, Engelhart S, Kramer MH. Surveillance for nosocomial and central line-related infections among pediatric hematology-oncology patients. *Infect Control Hosp Epidemiol* 2000;**21**:592—6.
5. Giamarellou H, Antoniadou A. Infectious complications of febrile leucopenia. *Infect Dis Clin North Am* 2001;**15**:457—82.
6. Alexander SW, Wade KC, Hibberd PL, Parsons SK. Evaluation of risk prediction criteria for episodes of febrile neutropenia in children with cancer. *J Pediatr Hematol Oncol* 2002;**24**:38—42.
7. Kock A, Pizzo PA. Empirical oral antibiotic therapy for low risk febrile cancer patients with neutropenia. *Cancer Invest* 2002;**20**:420—33.
8. Paganini HR, Rodriguez Brieshcke T, et al. Criteria of low risk of mortality in children with neutropenia and fever during cancer chemotherapy. *Medicina B Aires* 2001;**61**:63—6.
9. Calandra T, Zinner S, Viscoli C, et al. Efficacy and toxicity of single daily doses of amikacin and ceftriaxone versus multiple daily doses of amikacin and ceftazidime for infection in patients with cancer and granulocytopenia. *Ann Intern Med* 1993;**119**:584—93.
10. Centers for Disease Control and Prevention. Recommendations for preventing the spread of vancomycin resistance: recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC). *MMWR Recomm Rep* 1995; **44**(RR-12):1—13.
11. Aledo A, Heller G, Ren L, et al. Septicemia and septic shock in pediatric hematology-oncology service. *J Pediatr Hematol Oncol* 1998;**20**:215—21.
12. Elting L, Rubenstein E, Rolston K, Bodey G. Outcomes of bacteremia in patients with cancer and neutropenia: Observations from two decades of epidemiological and clinical trials. *Clin Infect Dis* 1997;**25**:247—59.
13. Ariffin H, Navaratnam P, Lin HP. Surveillance study of bacteremic episodes in febrile neutropenic children. *Int J Clin Pract* 2002;**56**:237—40.
14. Hann I, Viscoli C, Paesmans M, Gaya H, Glauser M. A comparison of outcome from febrile neutropenic episodes in children compared with adults: results from four EORTC studies. *Br J Haematol* 1997;**99**:580—8.
15. El-Mahallawy HA, Attia IA, Aly El-Din NH, Moneib N. Risk factor evaluation and prognosis of bacteremia in children with cancer. *J Egypt Nat Cancer Inst* 1999;**11**:299—305.
16. Alangaden GJ, Cutright J, Chandrasekar P. Pathogens causing bloodstream infections in hospitalized cancer patients. *Int J Infect Dis* 2002;**6**:64.
17. Paya E, Alvarez AM, Aviles C, et al. Causative agents of bloodstream infections in children with neoplasm, in 5 hospitals of Santiago. *Rev Med Chil* 2001;**129**:1297—304.
18. Viscoli C, Castagnola E, Giacchino M, et al. Bloodstream infections in children with cancer: a multicentre surveillance study of the Italian Association of Pediatric Haematology and Oncology. Supportive Therapy Group-Infectious Diseases Section. *Eur J Cancer* 1999;**35**:770—4.
19. Cho SM, Lee DG, Choi JM, Yoo JH, Sin WS, Kim C-C. Septic shock in hematology oncology patients with neutropenic fever. *Int J Infect Dis* 2002;**6**(S2):531—2.