Bacteremia in Childhood Cancer

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Summary

Infection-related mortality affects the overall survival rates of children who are receiving treatment for cancer. The leading cause of mortality is bacteremia and sepsis related to it in febrile neutropenic patients. All positive blood cultures of febrile neutropenic patients treated in the Department of Pediatric Hematology-Oncology, Cerrahpasa Medical School, between January 1995 and January 2001 were reviewed. Cultures grew 159 micro-organisms, 95 (60 per cent) of which were Gram-positive bacteria, 56 (35 per cent) were Gram-negative bacteria and eight (5 per cent) were fungi. Coagulase-negative staphylococci (63, 40 per cent) and *S. aureus* (8, 5 per cent) were the most frequent Gram-positive pathogens. *Klebsiella, E. coli, Enterobacter* and *Pseudomonas* infections were the primary Gram-negative pathogens. Twenty cases were lost because of sepsis: in 11 cases (55 per cent) Gram-negative bacteria, in eight cases (40 per cent) Gram-positive bacteria, and in only one case a fungus were the causative organisms. Although vancomycin was not included in the first-line treatment, the mortality rate of Gram-positive bacteremia was 8 per cent. In Gram-negative bacteremia it was 20 per cent. Gram-negative pathogens, which were resistant to multiple antibiotics, caused the mortality. Drug resistance and mortality due to micro-organisms must be taken into consideration while febrile neutropenia protocols are prepared.

Introduction

The proportion of bacterial infections among febrile neutropenic episodes ranges between 10 and 40 per cent.[1–4] In an analysis of febrile neutropenic patients, the acute mortality rate was found to be 3.2 per cent, while the mortality rate at the end of the febrile neutropenic episode was 8.7 per cent. In another study, the overall mortality rate within 30 days after the onset of bacteremia was found to be 24 per cent.[6] Shock at the onset was the most important prognostic factor influencing mortality, which is closely related to Gram-negative bacteremia.[1,6,7] This report describes the clinical and microbiological characteristics of 159 episodes of bacteremia encountered on a pediatric hematology-oncology service during a 6-year period.

Material and Methods

Demographic and laboratory data of febrile neutropenic (the criteria of IDSA)[2] inpatients who had positive blood cultures and were treated in the Department of Pediatric Hematology-Oncology, Cerrahpasa Medical School, between January 1995 and January 2001 were reviewed. Resistance rates to selected antibiotics of isolated bacteria were evaluated.

Blood for culture was collected from each patient in two vials. The sample to be tested was inoculated into a vial which was then inserted into the BACTEC Peds plus/F brand fluorescent series instrument for incubation for a maximum of 7 days. Vials indicated as positive by the instrument were punctured to obtain blood-medium samples for Gram stain and for subcultures onto two plates of sheep blood agar, one of chocolate agar and one of sabouraud agar. We incubated the agar media for 48 h. Isolates were identified (API bio Merieux) and their antimicrobial susceptibility was determined as recommended by the National Committee for Clinical Laboratory Standards (NCCLS).[8]

'Isolate' refers to the organism recovered from the blood, which was considered to be caused by infection. Multiple blood cultures positive for the same organism during a particular episode are considered as a single isolate. An infection involving multiple organisms in which one or more isolates were Gram-negative was classified as a GN infection. Except three cases of leukemia (two acute lymphoblastic leukemia and one acute myeloblastic leukemia) patients had only one occurrence. Because a minority of patients experienced multiple episodes, we included only the first episodes for each patient.

Cultures from indwelling catheters (only 16 cases)

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TABLE 1
Underlying diagnosis in 159 positive blood cultures

	Patient no. (%)	Gram-positive bacteria			Gram-negative bacteria	Fungi
		Total	CNS	Other GP		
Hematologic malignancies	204 (43)	106 (66%)	40 (66%)	24 (75%)	36 (64%)	6 (75%)
ALL	131 (27.5)	65	24	16	21	4
AML	32 (6.7)	26	11	3	10	2
NHL	39 (8.1)	13	4	4	5	
Other	2 (0.4)	2	1	1		
Solid tumors	272 (57)	53 (33%)	23 (33%)	8 (25%)	20 (36%)	2 (25%)
CNST	51 (10.7)	1	1			
BONE	24 (5)	4	1	1	2	
HH	36 (7.5)	3	2	1		
RBS	26 (5.4)	2	1		1	
Other	135 (28.3)	43	18	6	17	2
Total	476	159	63	32	56	8

ALL: acute lymphoblastic leukemia; AML: acute myeloblastic leukemia; NHL: non-Hodgkin lymphoma; CNST: central nerve system tumors; HH: Hodgkin lymphoma; RBS: retinoblastoma; other for solid tumors: wilms, neuroblastoma, rhabdomyosarcoma, histiositosis etc; CSN: coagulase-negative staphylococci.

were also evaluated. All patients were receiving trimethoprim/sulfamethoxazole and acyclovir (after 1998) for prophylaxis. When febrile neutropenia was diagnosed, the patients received one of three empirical antibiotic regimens: piperacillin + cefazolin + netilmicin; cefoperazone/sulbactam + netilmicin; imipenem / cilastatin from January 1995 to January 1999. After 1999, a ceftazidim + amikacin combination was used as single regimen for febrile neutropenia.

Fisher's exact test and chi-squared were used as tests for significance.

Results

In a 6-year period (January 1995 – January 2001), 476 patients (187 female and 289 male; age range from 2 months to 15 years) with different malignancies who were receiving chemotherapy developed febrile neutropenia (52 per cent). The diagnoses are listed in Table 1. During the 6-year period 705 febrile neutropenic episodes were evaluated. Bacteremia occurred in 22.5 per cent (159/705). There were statistically significant differences between hematological and solid tumors for the occurrence of bacteremia ($\chi^2 = 55.27$, $p < 0.001$), for the occurrence of bacteremia due to Gram-positive micro-organisms ($\chi^2 = 29.12$, $p < 0.001$), and for the occurrence of bacteremia due to Gram-negative micro-organisms ($\chi^2 = 11.9$, $p < 0.001$). No significant difference was observed for fungi between the two groups of malignancies ($p = 0.079$).

Blood cultures grew 159 micro-organisms, 95 (60 per cent) of which were Gram-positive bacteria, 56 (35 per cent) were Gram-negative bacteria and eight (5 per cent) were fungi (Table 2). Twenty cases were lost because of sepsis: in 11 cases (55 per cent) Gram-negative bacteria, in eight cases (40 per cent) Gram-positive bacteria, and in only one case a fungus were the causative organisms for the death. Although staphylococcal infection constitutes 75 per cent of all Gram-positive infections, they were responsible for only three deaths (15 per cent). Although vancomycin was not included in the first-line treatment, the mortality rate of Gram-positive bacteremia was 8 per cent. In Gram-negative bacteremia the mortality rate was 20 per cent. The highest mortality rate was associated with pseudomonal infections (3/5). Antibiotic susceptibilities of staphylococci (*S. epidermitis* and *S. aureus*) and Gram-negative infections were documented (Tables 3 and 4).

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TABLE 2
Isolates of the bacteremia

	Total
Gram-positive	95
S. epidermitis	63
S. aureus	8
α-haem streptococci	6
S. pneumonia	6
S. oralis parasangius	4
Enterococci	6
Gram-positive bacillus	2
Gram-negative	56
Escheria spp.	5
E. coli	13
Shigella	8
Pseudomonas	5
Klebsiella	17
Stenotrophomonas maltophilia	1
Proteus	1
Enterobacter	6
Fungi	8
Candida	8

TABLE 3
Antimicrobial resistance in staphylococci infections

Resistance	*S. aureus*	Coagulase-negative staphylococci
Number of cases	8	63
Penicillin	75% (6/8)	55% (35/63)
Erythromycin	50% (4/8)	49% (31/63)
Ampicillin	37% (3/8)	41% (26/63)
Ampicillin + Sulbactam	50% (4/8)	23% (15/63)
Cefolotin	37% (3/8)	17% (11/63)
Cefuroxime	37% (3/8)	19% (12/63)
Cefotaxime	37% (3/8)	21% (13/63)
Ceftriaxone	37% (3/8)	25% (16/63)
Ceftazidime	37% (3/8)	17% (11/63)
Gentamicin	50% (4/8)	32% (20/63)
Netilmicin	0	0
Amikacin	37% (3/8)	5% (3/63)
Vancomycin	0	0
Methicillin	75% (6/8)	27% (17/63)

Discussion

A bacteremia might be fatal even in immunocompetent patients.[9] Different rates of febrile neutropenia from different centers are reported as varying between 71 and 86 per cent.[4] In our department, the incidence of bacteremia in febrile neutropenic patients with different childhood cancer was about 20.8 per cent in our previous study[10] and 11 per cent in febrile neutropenia of acute lymphoblastic leukemia patients.[11] In this study we found a bacteremia incidence of 22.5 per cent. More children with hematological malignancies suffered from bacteremia compared with solid tumors ($p < 0.0001$). Bacteremia per patient in acute lymphoblastic leukemia was 0.5; in acute myeloblastic leukemia it was 0.8. This high rate might be due to long hospitalization and aplasias in high-risk leukemic patients in our department.

Classically enteric Gram-negative rods have been the most frequent pathogens of bloodstream infections. Over the past 30 years considerable changes have occurred in the types of bacteria causing infection. Recent papers have demonstrated that Gram-positive bacteremia tended to decrease, while there has been a shift towards bacteremia due to Gram-positive cocci.[12,13] In clinical trials from four studies EORTC bacteremia due to Gram-negative organisms tended to increase from 31 to 47–59 per cent in the last 2 years.[5] We found that 60 per cent of all bacteremias were due to Gram-positive bacteria. Coagulase-negative staphylococci were the most frequent bacteria responsible for the bacteremia (40 per cent). Their role as a cause of morbidity and mortality is difficult to ascertain. Because these organisms commonly contaminate blood cultures, identifying patients with true bacteremia may be difficult. The frequency of GP infections in febrile neutropenic patients has resulted in ongoing studies to assess the appropriate use of vancomycin. In a large clinical study that included more than 300 pediatric patients, episodes of febrile neutropenia were treated successfully without the addition of vancomycin to the initial regimen.[13] We did not use vancomycin as first choice as venous access devices were seldom used in our department. As seen in Table 3, antibiotic resistance for Coagulase-negative staphylococci was not a challenge in our department, and as a result only three patients died due to bacteremia with this organism. Although the incidence of Gram-negative bacteria was lower (35 per cent), 55 per cent of deaths were in this group. Similar results have been reported in the literature.[14,15] Bacteremic infections due to *Pseudomonas aeruginosa* have been a common, difficult-to-treat complication in neutropenic children. With the use of combination therapies consisting of carbenisilin or β-lactam antibiotics with antipseudomonal activity plus aminoglycosides, cure rates increased from 50 in the 1970s to 80 per cent.[16,17] The incidence of

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TABLE 4
Antimicrobial resistance in Gram-negative infections

Resistance	*E. coli*	*Klebsiella*	*Pseudomonas*
Number of cases	13	17	5
Ampicillin	92% (12/13)	100% (17/17)	100% (5/5)
Ampicillin+Sulbactam	23% (3/13)	53% (9/17)	100% (5/5)
TMP-SMX	85% (11/13)	88% (15/17)	100% (5/5)
Gentamicin	8% (1/13)	53% (9/17)	100% (5/5)
Tobramycin	31% (4/13)	41% (7/17)	60% (3/5)
Netilmicin	0	41% (7/17)	60% (3/5)
Amikacin	0	35% (6/17)	60% (3/5)
Cefuroxime	23% (3/13)	59% (10/17)	100% (5/5)
Ceftazidime	15% (2/13)	53% (9/17)	60% (3/5)
Ceftriaxone	15% (2/13)	53% (9/17)	100% (5/5)
Imipenem	0	6% (1/17)	20% (1/5)
Meropenem	0	6% (1/17)	20% (1/5)

TMP-SMX, trimethoprin-sulfamethoxale.

P. aeruginosa bacteremia among febrile neutropenic episodes is given as 1 per cent, which is lower than our rate (5/159; 3 per cent).[18] The frequency of developing shock is 20–30 per cent in *P. aeruginosa* bacteremia.[1] We detected shock in three out of five patients who later died.

The incidence of documented fungal infections among patients with hematologic malignancies given no systemic antifungal prophylaxis is about 4–10 per cent. Our rate was 5 per cent in this range. The fatality rate due to fungemia exceeds 20 per cent in many series.[19] One patient (16 per cent) with *C. tropicalis* who had acute myeloblastic leukemia and a deep long-lasting neutropenia, died.

During the time of the study, although other antibiotic susceptibilities remained stable, penicillin, ampicillin and trimethoprin-sulfamethoxazole resistance rates tended to increase in our hospital. Although over the years susceptibility rates remain lower than desired, a promising decrease in resistance to almost all antibiotics has become apparent over the last 2 years. These favorable results may be due to changing antibiotic regimens, infection control measures, and a better understanding of the magnitude of the resistance problem. The prevalence of resistance in the cancer patient population, however, is also highly dependent on the resistance rates among isolates from the community.

The epidemiology of infections in neutropenic cancer patients is complex and undergoes periodic changes. Drug resistance and mortality due to microorganisms must be taken into consideration while febrile neutropenia protocols are prepared. The prompt detection and management of bacteremia and septicemia in childhood cancer patients is important in order to decrease mortality rates.

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Increased Heights and Weights of Isfahani Female Children and Adolescents in Iran

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Summary

Considering the different patterns of growth in various societies, an anthropometric evaluation of 6–18-year-old female students was carried out in 1997 in Isfahan, Iran with the goal of establishing height and weight values for use in clinical settings. 4638 female Isfahani students aged 6–18 years were selected by a random cluster sampling. Their height (cm) and weight (kg) were measured and the related percentiles were determined. The results were compared with previous studies in Iran using Student's *t*-test. Findings show an increase of 6–12 cm in height and of 1–4 kg in weight of Isfahani female 6–18-year-old students as compared with a similar study in 1975. The height curves can be approximately superposed on those of NCHS growth charts, but American girls are significantly heavier than Isfahani girls after the age of 14. The growth parameters among Isfahani female students have improved compared with those of their compatriots and also their fellow citizens 22 years earlier. Improvements in nutrition, health services or other unknown environmental factors may have contributed to an increase in the growth indexes.

Introduction

Height and weight are important indexes to determine the health status of children and adolescents. Special biological mechanisms regulate this growth pattern. Many genetic, systemic, endocrine and geographic factors affect the growth and it has different patterns in various societies.[1] NCHS growth charts are used in many parts of the world.[2] Some cross-sectional studies have been conducted in Isfahan, a central city of Iran (1975), Shiraz in southern Iran, and Tehran (1990–1992).[3–5] All the percentiles of generated charts were substantially below those of the NCHS charts, but the spread was similar. In 1997, an anthropometric evaluation of 6–18-year-old Isfahani female students was carried out. The goal of the study was to establish height and weight values for use in clinical settings.

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Method

Isfahan Province, located in the central part of Iran, has a total population of approximately 4 000 000 and its capital city has a total population of approximately 1 000 000. From 200 000 female Isfahani students aged 6–18 years in 1997, we selected 4638 people by a random cluster sampling. The height (cm) and weight (kg) were measured by trained health staff and their percentiles were determined by SPSS software. To compare the results with previous similar studies in Iran in 1975, and 1990–1992,[4,5] Student's *t*-test was used and *p*-values less than 0.05 were considered statistically significant.

Results

The generated centiles are shown in Tables 1 and 2.

Discussion

In this study the height and weight of 6–18-year-old female Isfahani students were measured in 1997. The generated results are eligible only to female children and adolescents of Isfahan city. A research study performed in Tehran city in 1990–1992 reported that

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