J Microbiol Immunol Infect
2003;36:197-202

Bacteremia in hematological and oncological children with febrile neutropenia: experience in a tertiary medical center in Taiwan

Hsin-Pao Lai[1], Po-Ren Hsueh[2,3], Yee-Chun Chen[2], Ping-Ing Lee[4], Chun-Yi Lu[4], Meng-Yao Lu[4], Wen-Chuan Lin[4], Yu-Chia Hsieh[4], Chin-Yun Lee[4], Kai-Hsin Lin[4], Li-Min Huang[4]

[1]Department of Pediatrics, God's Help Hospital; Departments of [2]Internal Medicine; [3]Laboratory Medicine; and [4]Pediatrics, National Taiwan University Hospital and Natioal Taiwan University College of Medicine, Taipei, Taiwan, ROC

Received: August 3, 2002 Revised: September 7, 2002 Accepted: September 28, 2002

A retrospective study of bacteremia in children with febrile neutropenia admitted to a medical center in Taiwan from January 1999 to December 1999 was performed. There were 190 episodes of febrile neutropenia during this period and 46 pathogens were isolated from blood specimens in 38 bacteremic episodes (7 mixed infections). *Pseudomonas aeruginosa* (17.4%), *Staphylococcus aureus* (10.9%), *Klebsiella pneumoniae* (10.9%), and *Enterobacter cloacae* (10.9%) were the most common isolates. Three of the 5 isolates of *S. aureus* were resistant to methicillin. Twenty-three episodes of bacteremia (four mixed infections) were associated with recent antibiotic use. Of the 23 bacteremic episodes with recent antibiotic use, *P. aeruginosa* (20%), methicillin-resistant *S. aureus* (10%), *K. pneumoniae* (10%), *Escherichia coli* (10%), and *E. cloacae* (10%) were isolated most often. Relapsed leukemia (odds ratio 3, 95% confidence interval 1.4-6.5) and recent antibiotic therapy (odds ratio 3.4, 95% confidence interval 1.7-7.7) were the independent risk factors of bacteremia. There were 9 mortality cases in patients with bacteremia, including 4 cases with mixed infections, and 5 cases with *P. aeruginosa*, *E. coli, Klebsiella oxytoca, S. aureus*, and *Streptococcus mitis*, respectively. Broad-spectrum antibiotics were necessary in febrile neutropenic children because of the high percentage of mixed infection.

Key words: Bacteremia, children, neutropenic fever

Infection is a common cause of morbidity and mortality in patients with neoplastic disease, particularly those receiving cytotoxic chemotherapy. Between 48% and 60% of neutropenic patients who become febrile have an established or occult infection, and 16% to 20% of patients with neutrophil counts of <100 /mm^3 have bacteremia [1-3]. Gram-positive organisms account for 60% to 70% of microbiologically documented infections in most reports [3-5]. However, gram-positive organisms accounted for only 24.1% in Taiwan in the period between 1994 and 1995 [6]. Infection in neutropenic patients is a major event and the etiologic pathogen is hard to predict. Thus, it is standard practice to begin empiric broad-spectrum antibiotic therapy in neutropenic patients with fever while awaiting the results of cultures [5]. However, there are scant data addressing the characteristics of febrile neutropenia in children because most publications address the condition in adult patients.

Corresponding author: Dr. Li-Min Huang, Department of Pediatrics, National Taiwan University Hospital, 7, Chung-Shan South Road, Taipei, Taiwan, 100, ROC. E-mail: lmhuang@ha.mc.ntu.edu.tw

The purpose of this study was to evaluate the spectrum of infectious complications in febrile neutropenic children, especially the organisms associated with these infections and the risk factors and outcome of bacteremia.

Materials and Methods

The records of children admitted to the pediatric oncology ward of the National Taiwan University Hospital due to febrile neutropenia between January 1, 1999 and December 31, 1999 were retrospectively reviewed.

Definitions

Neutropenia was defined as an absolute neutrophil count (ANC) of less than 500/μL. Fever was defined as a single temperature of ≥38.5°C or 2 separate temperatures of ≥38°C more than 1 hour apart [5]. Profound neutropenia was defined as having an ANC of less than 100 /mm^3 [1]. Recent antibiotic therapy was defined as any antibiotic therapy within the previous 2 weeks [6]. Patients with solid tumors and lymphoma were considered to have a refractory neoplasm if they failed to achieve complete remission

or were in relapse. Remission was defined in leukemia patients as having 5% blasts or less in the bone marrow aspirate closest in time to the date of fever.

The following data were collected: age, sex, dates of admission and discharge, diagnosis, disease status, initial and nadir ANC, patient characteristics, duration of fever, duration and severity of neutropenia, initial antibiotic regimen, culture results, Pediatric Risk of Mortality (PRISM) score II [7], and outcome.

Microbiologically documented infections

Bacteremia was considered in the case of any organism isolated from blood or, in case of coagulase-negative *Staphylococci*, from 2 separate isolations. Other microbiologically defined sites of infection were considered in cases of clinical evidence of focal inflammation as well as a positive culture.

Clinically documented infections

Clinically documented infections were considered when there was a focus of infection on physical examination, but a microbiologic diagnosis was not confirmed. Upper respiratory infection was diagnosed in patients with rhinorrhea and cough without signs of sinusitis, pneumonia, or other infection. Pneumonia was diagnosed in patients having positive findings on physical examination and an infiltrate on chest radiograph. Perianal infection was defined as erythema/induration in the perianal area. Patients were considered to have fever without a source if there was no microbiologic or clinical evidence of infection on physical examination.

Clinical managements

Initial treatment consisted of piperacillin and gentamicin or ticarcillin/clavulanate and gentamicin, which were then changed according to the drug susceptibility of the isolated organism or changed to ceftazidime and amikacin empirically if the fever persisted for more than 2 to 3 days. Amphotericin-B was added empirically if the fever persisted for 5 to 7 days. All patients with leukemia or lymphoma received trimethoprim/sulfamethoxazole 3 times per week for *Pneumocystis carinii* prophylaxis. Otherwise, patients did not receive other antimicrobial prophylaxis.

Statistical analysis

Univariate analysis was carried out separately for each of the potential risk factors using chi-square test or Fisher's exact test. After identifying potential risk factors from the univariate analysis, a multivariate analysis was conducted by a stepwise logistic regression model to identify the set of independent risk factors that together best predicted the event of bacteremia.

Results

The characteristics of patient are summarized in Table 1. There were 91 patients with 179 admissions and 190 episodes of neutropenic fever (mean number of episodes per person, 2.1), representing 20.7% of the total pediatric admissions in 1999. Acute leukemia (61.6%, 117/190) was the leading underlying disease, followed by solid tumor. The median patient age was 8 years (range, 0.2-19.1 years), and the male-to-female ratio was 1:1.5. Venous catheter was in place in the vast majority (90.5%, 172/190) of patients. Granulocyte-colony stimulating factor or granulocyte-macrophage colony stimulating factor was given to roughly 3 quarters of patients during the course of their hospitalization. The median duration of hospitalization was 23.5 days (range, 2-277 days), and neutropenia

Table 1. Underlying disease of children with febrile neutropenia in National Taiwan University Hospital, 1999

Diagnosis	No. of patients	No. of episodes		
		Total	Bacteremia	%
AML				
Relapse	11	26	9	34.6
Remission	7	25	3	12.0
ALL				
Relapse	13	32	10	31.3
Remission	22	34	6	17.6
CML	1	1	0	0
Lymphoma	6	10	2	20
Aplastic anemia	7	13	3	23.1
Myelodysplasia	2	4	0	0
Solid tumor	22	45	5	11.1
Total	91	190	38	20

Abbreviations: ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CML = chronic myeloid leukemia

Table 2. Infection focus of childhood febrile neutropenia in National Taiwan University Hospital in 1999

Infection focus	No. of infection episodes[a]	
	Total	Bacteremia
Catheter-related infection	7	4
Endocarditis	2	2
Sinusitis	10	4
Otitis media	3	1
Upper respiratory infection	6	1
Pneumonia	36	13
Enterocolitis	32	10
Perianal infection	4	0
Soft tissue infection	27	5
Urinary tract infection	5	0
Viral infection	21	6
No identified focus	73	7
Total	190	38

[a]A patient may have more than one identified infection focus.

persisted for a median of 10 days (range, 1-120 days). Intravenous antibiotics were instituted for a median duration of 14 days (range, 0-123 days).

Table 2 outlines the focus of infection in the 190 episodes of fever and neutropenia. Pneumonia, enterocolitis, and soft tissue infection were the most commonly identified infection foci, representing 18.9% (36/190), 16.8% (32/190), and 14.2% (27/190) of the total episodes, respectively. Patients with bacteremia were more likely to have pneumonia (p=0.011) and less likely to have no identified focus of infection (p=0.005).

About one-fifth (20%) of the total episodes of febrile neutropenia were associated with bacteremia. Thirteen (6.8%) episodes were microbiologically documented infections without bacteremia, while 74 (39%) episodes were clinically documented infections, in which there was evidence of focal inflammation on physical examination but without microbiological confirmation. There was no clinical or microbiologic evidence of infection in 65 (34.2%) of these episodes.

Table 3 outlines the 46 microbial isolates from the 38 episodes of bacteremia in this study. Seven (18.4%) of septic episodes were polymicrobial, in which 85.7% of the isolates were gram-negative and *Enterobacter cloacae* was most commonly isolated. Of the 7 polymicrobial infections, infection foci were identified in 4 cases, including 2 catheter-related infections, 1 lung abscess, and 1 pneumonia. All had relapsed or refractory malignancy except one patient with severe aplastic anemia who received bone marrow transplant during admission. Most of these polymicrobial bacteremia were nosocomial infections. Prolonged steroid use and recent antibiotic therapy before the febrile episode were documented in 5 of these 7 patients.

Gram-positive organisms comprised only 29% (9/31) of the episodes in which single organism was isolated, with *Staphylococcus aureus* (5 isolates) and *Streptococcus mitis* (2 isolates) being isolated most frequently. Gram-negative organisms comprised 71% of single organism sepsis, and *Pseudomonas aeruginosa* (7 isolates), *Escherichia coli* (4 isolates), and *Klebsiella pneumoniae* (3 isolates) were the most common isolates. Recent antibiotic use preceded 23 episodes of bacteremia, with *P. aeruginosa* (20%, 6/30), methicillin-

Table 3. Organisms isolated from blood in children with febrile neutropenia in National Taiwan University Hospital, 1999

Organism	No. of isolates (%)	No. with recent antibiotic treatment (%)
Gram-positive	11 (23.9)	6 (20.0)
Staphylococcus aureus	5 (10.9)	3 (15.0)
Streptococcus mitis	3 (6.5)	2 (6.7)
Enterococcus spp.	2 (4.3)	1 (3.3)
Group G *Streptococcus*	1 (2.2)	0
Gram-negative	34 (73.9)	24 (76.7)
Pseudomonas aeruginosa	8 (17.4)	6 (20.0)
Enterobacter cloacae	5 (10.9)	3 (10.0)
Klebsiella pneumoniae	5 (10.9)	3 (10.0)
Escherichia coli	4 (8.7)	3 (10.0)
Burkholderia pickettii	2 (4.3)	2 (6.7)
Salmonella spp.	2 (4.3)	0
Aeromonas hydrophila	2 (4.3)	2 (6.7)
Stenotrophomonas spp.	2 (2.2)	2 (6.7)
Campylobacter sp.	1 (2.2)	0
Acinetobacter baumannii	1 (2.2)	1 (3.3)
Klebsiella oxytoca	1 (2.2)	0
Morganella morganii	1 (2.2)	1 (3.3)
Candida tropicalis	1 (2.2)	1 (3.3)
Total	46 (100)	30 (100)

resistant *S. aureus* (MRSA, 10%, 3/30), *K. pneumoniae* (10%, 3/30), *E. coli* (10%, 3/30), and *E. cloacae* (10%, 3/30) as the most common isolated pathogens.

All of the patients received either ticarcillin/clavulanate and gentamicin or pipercillin and gentamicin as initial empirical therapy, but antibiotic modification was done in 81.6% (31/38) of the bacteremic episodes and 42.1% (64/152) of the nonbacteremic ones. There were 170 episodes in which patients did not have hypotension or require fluid resuscitation at admission. Of these episodes, 26 (15.3%) were associated with positive blood cultures and the case fatality rate was 4.1% in this group. A total of 20 episodes developed hypotension. Of these 20 episodes, 12 (60%) were associated with positive blood cultures. Among these hypotensive patients, there were 9 ICU transfers and 10 respiratory failures with the case fatality rate of 55% (11/20).

Table 4 summarizes the presenting features of these patients and their outcomes, and compares these characteristics of patients with and without bacteremia. Relapsed leukemia, nosocomial infection, prolonged steroid therapy (>3 weeks) and recent antibiotic therapy, profound neutropenia, and duration of neutropenia were all associated with bacteremia. Using multivariate analysis, only relapsed leukemia (odds ratio 3, 95% confidence interval 1.4-6.5) and recent antibiotic therapy (odds ratio 3.4, 95% confidence interval 1.7-7.7) were the independent risk factors.

Table 5 summaries the hospital course of the study patients. The case fatality rate was 23.7% (9/38) in the bacteremic group and only 5.9% (9/152) in the nonbacteremic one. Empirical amphotericin-B use was given to 55.3% (21/38) of the bacteremic patients and to 22.4% (34/152) of the nonbacteremic ones. Bacteremic episodes also were associated with longer fever and more hypotension and respiratory failure when compared with the nonbacteremic ones. Of the 9 infection-related mortality cases, 4 cases were due to mixed infections while 5 cases were due to *P. aeruginosa*, *E. coli*, *Klebsiella oxytoca*, *S. aureus*, and *S. mitis*, respectively.

Table 4. Clinical features of children with febrile neutropenia in National Taiwan University Hospital, 1999

	No. of episodes	Positive blood culture (%)	*p*
Relapsed leukemia			
Yes	58	19 (32.7)	0.02
No	132	19 (14.4)	
Allogeneic bone marrow transplant			
Yes	15	5 (33.3)	NS
No	175	33 (18.9)	
Graft-versus-host disease			
Yes	6	2 (33.3)	NS
No	184	36 (19.6)	
Central venous catheter			
Yes	172	36 (20.9)	NS
No	18	2 (11.1)	
Nosocomial infection			
Yes	88	24 (27.3)	0.02
No	102	14 (13.7)	
Mucositis			
Yes	56	11 (19.6)	NS
No	134	27 (20.1)	
Prolonged steroid therapy >3 weeks			
Yes	47	15 (31.9)	0.03
No	143	23 (16.1)	
Recent antibiotic used in 2 weeks			
Yes	65	22 (33.8)	0.001
No	125	16 (12.8)	
Profound neutropenia (<100 /mm^3)			
Yes	107	28 (26.2)	0.02
No	83	10 (12.0)	
Duration of neutropenia			
>10 days	89	25 (28.1)	0.01
<10 days	101	13 (12.9)	

Abbreviation: NS = not significant

Table 5. Hospital course and outcome of children with febrile neutropenia in National Taiwan University Hospital, 1999

	All episodes	With bacteremia	Without bacteremia	*p*
Respiratory failure, n (%)	15 (7.9)	9 (23.7)	6 (3.9)	<0.001
Hypotension, n (%)	20 (10.5)	12 (31.6)	8 (5.3)	<0.001
ICU transfer, n (%)	11 (5.7)	9 (23.7)	2 (1.3)	<0.001
Antibiotic change, n (%)	55 (28.9)	21 (55.3)	34 (22.4)	<0.001
PRISM-II score[a]	1 (0-32)	5 (0-32)	1 (0-25)	<0.001
Highest CRP (mg/dL)[a]	5.58 (0.01-53.6)	14.3 (0.92-46.9)	4.90 (0.01-53.6)	0.001
Duration of antibiotic, days[a]	14 (0-123)	20.5 (10-123)	12 (0-120)	
Duration of fever, days[a]	4 (0-122)	9 (1-122)	3 (0-119)	0.009
Duration of admission, days[a]	23.5 (2-277)	37 (10-277)	18.5 (2-164)	0.005
Case fatality rate (%)	9.5	23.7	5.9	0.001
Total number	190	38	152	

[a]Data are presented as median (range).
Abbreviations: CRP = C-reactive protein; ICU = intensive care unit; PRISM-II = Pediatric Risk of Mortality score II

Discussion

Gram-negative organisms accounted for 73.9% of the blood isolates in 1999 in this study. Previous data on bacteremia complicating neoplastic or hematologic diseases between 1994 and 1995 [6], during which period piperacillin and gentamicin were the first-line antimicrobial regimen for neutropenic fever, also showed a preponderance of gram-negative (76%) organisms in bacteremia of neutropenic children. The present data is different from the reports from western countries, where gram-positive organisms account for 60% to 70% of microbiologically documented infections [3-5], even though over 90% of the patients in this study group have a Port-A catheter implanted surgically. Why gram-negative organisms predominate in febrile children with neutropenia in Taiwan is unclear.

K. pneumoniae (27.8%), *E. coli* (10.1%), *S. aureus* (10.1%), and *P. aeruginosa* (7.6%) were the leading blood pathogens in children with febrile neutropenia in Taiwan in the period between 1994 and 1995 [6]. In 1999, *P. aeruginosa* (17.4%), *E. cloacae* (10.9%), *K. pneumoniae* (10.9%), and *S. aureus* (10.9%) became the predominant isolates. Two notable changes were the increase of polymicrobial infection from 10% to 18.4% (p=0.22, not significant) and *E. cloacae* from 0% to 10.9% (p=0.008). *Enterobacter* spp. still constituted 5.2% of the 58 blood isolates from Janunary 2000 to May 2001 (unpublished data).

The reasons why *P. aeruginosa* emerges as the leading pathogen and why *E. cloacae* and polymicrobial infections increased remain unclear. One possible explanation is the stronger chemotherapeutic regimen and better supportive care kept children with relapsed or refractory malignancy survive longer than before. These children would have protracted granulocytopenia and thus, more polymicrobial infections and opportunistic pathogens like *P. aeruginosa* due to reasons such as infiltration of bone marrow and receiving more intensive chemotherapy.

In the present study, relapsed malignancy, fever occurring in the hospital, prolonged steroid therapy (> 3 weeks), recent antibiotic use, and profound and prolonged neutropenia were associated with more bacteremia. The risk factors that were identified were largely consistent with previous reports. The observation made by Bodey *et al* [1] indicated that the risk and severity of infection were greatest in patients with profound neutropenia (<100 /mm^3) and prolonged (>14 days) neutropenia. Patients with prolonged neutropenia, hematologic malignancy, or allogeneic bone marrow transplantation, substantial comobidity, clinically unstable condition, and slow response to initial therapy were considered to be at high risk for complications. On the other hand, patients with short-lived neutropenia (≤7 days), solid tumor with conventional chemotherapy without comobidity, and clinically stable condition at onset of the febrile episodes were considered to be at low risk for complications [11]. Talcott *et al* also included disease status as an indicator for likelihood of complications [12].

Prolonged steroid therapy was associated with bacteremia in febrile neutropenic children in this study, which was not an important factor in the similar reports pertaining to adults. The most common form of acute leukemia in children, acute lymphoblastic leukemia (ALL), is treated with corticosteroid and cytotoxic chemotherapy that are clearly different than that for acute myeloid leukemia (AML), the most common form of acute leukemia in adults (corticosteroids are not used in the treatment of AML). This may be the reason why prolonged steroid therapy is significantly associated with bacteremia in febrile neutropenic children.

Recent antibiotic therapy was also identified as an independent risk factor for bacteremia in children. One explanation is that recent antibiotic use is a marker for a protracted immunocompromised state, which carries a higher risk of infection. Another explanation is that antibiotics selectively eliminate endogenous bacterial flora to permit the overgrowth of resistant bacteria.

From this study, febrile neutropenic children who have relapsed leukemia and recently received antibiotic therapy are at higher risk of bacteremia, with higher risk of mortality, hospital stay, and complications including hypotension, respiratory failure, and intensive care unit stay. Because of the increased likelihood of polymicrobial infection, broad-spectrum antimicrobial therapy is necessary in pediatric febrile neutropenia.

References

1. Bodey GP, Buckley M, Sathe YS, Freireich EJ. Quantitative relationship between circulating leukocytes and infections in patients with acute leukemia. Ann Intern Med 1996;64:328-40.
2. Schimpff SC. Empiric antibiotic therapy for granulocytopenic cancer patients. Am J Med 1986;80(Suppl 5c):S13-20.
3. Lucas KG, Brown AE, Armstrong D, Chapman D, Heller G. The identification of febrile, neutropenic children with neoplastic disease at low risk for bactetermia and complications of sepsis. Cancer 1996;77:791-8.
4. Marie JP, Vekhoff A, Pico JL, Guy H, Andremont A, Richet H. Neutropenic infections: a review of the French Febrile Aplastic Study Group trials in 608 febrile neutropenic patients. J Antimicrob Chemother 1998;41(Suppl D):S57-64.
5. Hughes WT, Armstrong D, Bodey GP, Brown AE, Edwards JE, Feld R, Pizzo P, Rolston KV, Shenep JL, Young LS. 1997 guidelines for the use of animicrobial agents in neutropenic patients with unexplained fever: Infectious Diseases Society of America. Clin Infect Dis 1997;25:551-73.
6. Chiu HH, Huang LM, Lee PI, Lee CY. Bacteremia and fungemia in hematological and oncological children with neutropenic fever: two-year study in a medical center. J Microbiol Immunol Infect 1998;31:101-6.
7. Pollack MM, Ruttimann UE, Getson PR. Pediatric Risk of Mortality (PRISM) score. Crit Care Med 1988;16:1110-6.
8. Herbrecht R, Damonte JC, Bergerat JP, Jehl F, Liu KL, Prevost G, Dufour P, Duclos B, Oberling F. Piperacillin and netilmicin combination therapy for febrile episodes in neutropenic patients. Infection 1990;18:310-3.
9. Yu LC, Shaneyfelt T, Warrier R, Ode D. The efficacy of ticarcillin-clavulanate and gentamicin as empiric treatment for febrile neutropenic pediatric patients with cancer. Pediatr Hematol Oncol 1994;11:181-7.
10. Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG. Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. Am J Med 1982;72:101-11.
11. Rolaton KVI. New trend in patient management: risk-based therapy for febrile patients with neutropenia. Clin Infect Dis 1999;29:515-21.
12. Talcott JA, Siegel RD, Finberg R, Goldman L. Risk assessment in cancer patients with fever and neutropenia: a prospective, two-center validation of a prediction rule. J Clin Oncol 1992; 10:316-22.