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Bacteremia in Pediatric Cancer Patients : Causative Organisms and Antibiotic Sensitivities

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Purpose : Bacteremia in immunocompromised pediatric cancer patients can lead to high morbidity and mortality, if not treated early and properly. The incidence and antibiotic sensitivities to common pathogens of bacteremia in pediatric cancer patients are liable to change, according to region and time. We investigated the causative organisms and antibiotic sensitivities of bacteremia in pediatric cancer patients to assess the adequacy of empiric antimicrobial therapy.

Methods : From September 1995 to August 2003, we retrospectively evaluated 58 episodes in 39 pediatric cancer patients with bacteremia treated at the Pediatric Department of Yeungnam University Hospital. We investigated and analyzed the causative organisms and the antibiotic sensitivity test results by reviewing the records of the microbiologically proven positive blood culture results.

Results : The incidence of bacteremia in pediatric cancer patients in this study was 5.7 percent (58 episodes out of 1,022 occasions of blood cultures). Gram-positive organisms were isolated more often than gram-negative organisms (63.8 percent vs 36.2 percent) in the following order : *Staphylococcus epidermidis* (37.9 percent), *Staphylococcus aureus* (17.3 percent), *Escherichia coli* (12 percent), *Streptococcus* (8.6 percent), *Enterobacter* (6.9 percent), *Klesiella* (6.9 percent), *Serratia* (3.5 percent), *Acinetobacter* (3.5 percent), *Proteus* (1.7 percent) and *Morganella morganii* (1.7 percent). In antibiotic sensitivity tests, only six of 37 isolates (16 percent) of gram positive bacteria were sensitive to penicillin and 15 of 37 isolates (40 percent) were sensitive to oxacillin. All except one *Staphylococcus aureus* were sensitive to vancomycin and all except one *Staphylococcus epidermidis* were sensitive to teicoplanin among 37 isolates of gram positive bacteria. In the case of gram negative bacteria, two of 21 isolates (10 percent) and four of 21 isolates (19 percent) were sensitive to cefotaxime and ceftazidime, respectively. Only six of 21 isolates (29 percent) were sensitive to aminoglycoside, but all 21 isolates (100 percent) were sensitive to imipenem. All seven isolates tested after the year 2000 were sensitive to meropenem.

Conclusion : In conclusion, we should choose the proper antimicrobials in treating pediatric cancer patients with suspected bacteremia, reflecting the increasing episodes of gram positive bacteremia and polymicrobial resistance of gram positive and negative organisms. **(Korean J Pediatr 2005;48: 619-623)**

Key Words : Bacteremia, Gram-positive bacteria, Gram-negative bacteria, Antibiotic sensitivities

Introduction

Pediatric cancer is the second most common cause of death following accident in children and the most common cause of death from pediatric diseases[1]. Although the potent anticancer therapy increased survival rates or cure rates of pediatric cancer patients, the risk of infection became even higher due to profound and protracted neutropenia[2].

Infection and hemorrhage are the important complications in the treatment of pediatric cancer patients. Especially, infections in neutropenic pediatric cancer patients lead to the high morbidity or mortality if not treated promptly with proper antimicrobials[3, 4]. In acute lymphoblastic leukemia (ALL), Lee et al.[5] reported the incidence of infections occurring during the period of remission induction, remission and relapse as 40.6%, 22.7% and 8.6%, respectively.

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And Rahiala et al.[6] reported the incidence of infections occurring during the course of anticancer chemotherapy in children with ALL was about 50%. But fever is occasionally associated with non-infectious causes such as malignancy, chemotherapeutic agents, and transfusion[7]. Therefore infection-associated fever and non-infectious fever need to be differentiated.

In the beginning of cancer therapy, infection could be caused by bacteria or viruses, but in a later stage of cancer therapy it could be associated with resistant bacteria, fungi, protozoa or viruses. The incidence of bacteremia in pediatric cancer patients was reported as about 20%[8]. Although in the past, the major pathogen was reported to be gram negative bacteria (*E. coli*, *K. pneumoniae* and *P. aeruginosa*, etc), recently infections of gram positive bacteria (*Staphylococci* and *streptococci*, etc) are increasing and polymicrobial resistant bacteria (vancomycin resistant enterococci, etc) is emerging[9]. Among the viruses, herpes group viruses (herpes simplex virus, cytomegalovirus, varicella-zoster virus, Epstein-Barr virus, etc) are prevalent in cancer patients. Among the fungi, *Candida* spp. (*C. albicans*, etc) and *Aspergillus* spp. are prevalent[10]. The infections in pediatric cancer patients are different from those in non-immunocompromised children. The infection caused higher morbidity (6.3-28%) and mortality (10-14%)[2, 4-7, 11] in pediatric cancer patients compared to the morbidity (2.7 %) and mortality (8%) from severe sepsis in non-immunocompromised children[12]. Therefore pediatric cancer patients need to be treated early and promptly with proper antibiotics until the blood culture results are available if bacteremia is suspected.

The regional centers caring for pediatric cancer patients need to monitor the prevalent microorganisms of bacteremia with antibiotic sensitivities as this could be liable to change according to the region and time. Thus initiating the proper and prompt empirical antibiotics prior to the blood culture and sensitivity test results would be possible for these high risk patients population. We investigated causative organisms of bacteremia and antibiotic sensitivity test results in pediatric cancer patients for the last 8 years.

Materials and Methods

1. Materials

We retrospectively evaluated the results of the blood cultures and the antibiotic sensitivities of 1,022 samples of blood cultures taken from 91 pediatric cancer patients who were admitted to the pediatric department of the Yeungnam University Hospital for suspected bacteremia from September 1995 to August 2003. Fifty eight episodes of proven bacteremia in 39 patients were analyzed. There were 39 episodes of bacteremia in leukemia patients (21 episodes in ALL and 18 in acute myeloid leukemia), 2 episodes in myelodysplastic syndrome (MDS) patients and 17 episodes in solid tumor patients. Median age at diagnosis was 5.5 years (1.2-18.3 years) and 46 episodes occurred in male and 12 episodes occurred in female populations (Table 1).

2. Methods

Blood cultures were taken before the antibiotics treatment in pediatric cancer patients with fever (over 38.3℃) but without localized clinical signs of infection and blood samples were immediately implanted on the media (BD BACTEC, Becton, Dickinson, USA) and incubated (BACTEC 9240, Becton, Dickinson, USA) at 35℃ for over 120 hours.

In antibiotic sensitivity tests we put cultured bacteria with the antibiotics discs into the media and interpreted as sensitive to antibiotics if no bacterial growth surrounding the index antibiotic discs was noted.

Antibiotics used in sensitivity tests were penicillin, oxacillin, amikacin, cefotaxime, ceftazidime, vancomycin, teico-

Table 1. Characteristics of Pediatric Cancer Patients with Bacteremia

Characteristics	No.
Episodes	58
Age at diagnosis	
mean (years)	5.5
range	1.2-18.3
Male/Female	46/12
Diagnosis	
Leukemia	39
ALL	21
AML	18
MDS	2
Solid tumors	17
Lymphoma	3
Brain tumor	3
Sarcoma	3
Neuroblastoma	2
Others*	6

*Others : hepatoblastma, pineoblastoma, Wilms' tumor, hemangiopericytoma, retinoblastoma (2)
Abbreviations : ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome

planin, imipenem and meropenem.

We retrospectively investigated and analyzed etiologic pathogens and their antibiotic sensitivities of pediatric cancer patients with bacteremia by reviewing the medical records, laboratory results and microbiological results.

Results

There were 1,022 episodes of fever in 91 patients with cancer for whom blood cultures were taken for suspected bacteremia. The incidence of bacteremia in pediatric cancer patients of this study was 5.7% (58 episodes of bacteremia out of 1,022 of blood culture samplings).

The most common pathogens identified were gram positive bacteria (37 out of 58 isolates, 63.8%). *Staphylococcus epidermidis* (22 isolates, 37.9%) was the most common isolates, followed by *Staphylococcus aureus* (10 isolates, 17.3 %) and *Streptococcus* (5 isolates, 8.6%). Gram negative bacteria (21 out of 58 isolates, 36.2%) such as *Escherichia coli* (7 isolates, 12%), *Enterobacter* (4 isolates, 6.9%), *Klebsiella* (4 isolates, 6.9%), *Serratia* (2 isolates, 3.5%), *Acinetobacter* (2 isolates, 3.5%), *Proteus* (1 isolate, 1.7%) and *Morganella morganii* (1 isolate, 1.7%) were following in decreasing order (Table 2).

In antibiotic sensitivity tests, only 6 of 37 (16%) gram positive bacteria were sensitive to penicillin and 15 of 37 (40%) were sensitive to oxacillin. Twelve of 32 (37%) *Staphylococci* and 3 of 5 (60%) *Streptococci* were sensitive to oxacillin and 1 of 5 (20%) *Streptococci* was sensitive to cefotaxime. All *Staphylococcus aureus* except one were sensitive to vancomycin and all *Staphylococcus epidermidis* except one were sensitive to teicoplanin. One patients with vancomycin-resistant *S. aureus* (VRSA) and another patient with teicoplanin-resistant *S. epidermidis* (TRSE) bacteremia did not have past medical history of therapy with vancomycin or teicoplanin (Table 3).

In case of gram negative bacteria, only 2 of 21 isolates (10%) and 4 of 21 isolates (19%) were sensitive to cefotaxime and ceftazidime, respectively, thus 19 of 21 (90%) and 17 of 21 (81%) were resistant to cefotaxime and ceftazidime, respectively. Only 6 of 21 isolates (29%) were sensitive, thus 15 of 21 (71%) were resistant to aminoglycoside. But all 21 gram negative bacteria (100%) were sensitive to imipenem. All 7 isolates tested after the year 2000 were sensitive to meropenem. Among *E. coli* (1 isolate), *Enterobacter* (1 isolate), *Klebsiella* (1 isolate) and *M. morganii* (1 isolate) sensitive to ceftazidime, only *E. coli* (1 isolate) and *Enterobacter* (1 isolate) were also sensitive to cefotaxime. All *Serratia* (2 isolates), *Acinetobacter* (2 isolates) and *Proteus* (1 isolate) were resistant to penicillin, aminoglycoside, cefotaxime and ceftazidime (Table 4).

Table 2. Isolated Organisms of Bacteremia in Pediatric Cancer Patients

Organisms	Cases (%)
Gram positive	37 (63.8)
S. epidermidis	22 (37.9)
S. aureus	10 (17.3)
Streptococcus	5 (8.6)
Gram negative	21 (36.2)
E. coli	7 (12.0)
Enterobacter	4 (6.9)
Klebsiella	4 (6.9)
Serratia	3 (3.5)
Acinetobacter	2 (3.5)
Proteus	1 (1.7)
M. morganii	1 (1.7)

Abbreviations : *S. epidermidis*, *Staphylococcus epidermidis*; *S. aureus*, *Staphylococcus aureus*; *E. coli*, *Escherichia coli*; *M. morganii*, *Morganella morganii*

Table 3. Antibiotic Sensitivities of Gram Positive Organisms Causing Bacteremia in Pediatric Cancer Patients

Organisms (No.)	Sensitivity (No.)				
	Pen	Oxa	Cefo	Vanco	Teico
S. epidermidis (22)	1	4	–	22	21
S. aureus (10)	4	8	–	9	10
Streptococcus (5)	1	3	1	5	5
Total (%)	6 (16)	15 (40)	1 (20)	36 (97)	36 (97)

Abbreviations : Pen, penicillin; Oxa, oxacillin; Cefo, cefotaxime; Vanco, vancomycin; Teico, teicoplanin

Table 4. Antibiotic Sensitivities of Gram Negative Organisms Causing Bacteremia in Pediatric Cancer Patients

Organisms (No.)	Sensitivity (No.)					
	Pen	Ami	Cefo	Cefta	Imi	Mero
E. coli (7)	1	2	1	1	7	3/3
Enterobacter (4)	3	2	1	1	4	–
Klebsiella (4)	1	1	0	1	4	2/2
Serratia (2)	0	0	0	0	2	–
Acinetobacter (2)	0	0	0	0	2	1/1
Proteus (1)	0	0	0	0	1	–
M. morganii (1)	1	1	0	1	1	1/1
Total (%)	6 (29)	6 (29)	2 (10)	4 (19)	21 (100)	7/7

Abbreviations : Pen, penicillin; Ami, aminoglycoside; Cefo, cefotaxime; Cefta, ceftazidime; Imi, imipenem; Mero, meropenem; *E. coli*, *Escherichia coli*; *M. morganii*, *Morganella morganii*

Discussion

Infection is one of the important causes of high morbidity and mortality encountered during the treatment of pediatric cancer patients[11]. As newly developed more potent chemotherapeutic agents are widely used and the use of central venous catheter and broad-spectrum antibiotics are increased, the trends of infections in immunocompromised pediatric cancer patients are changing[13, 14]. In the 1970's gram negative bacteria were thought to be the major pathogens of bacteremia in pediatric cancer patients. But with the introduction of the Broviac catheter in 1972 and the Hickmann catheter in 1979, gram positive bacteria were recognized to be the major pathogens of bacteremia in pediatric cancer patients in the 1980's[15, 16]. The recent reports, although made by different study groups, have been focusing on the gram positive bacteria such as *S. aureus*, *S. epidermidis*, and *Streptococcus*[7, 11, 13, 14, 17-23]. But it is also emphasized to recognize the importance of bacteremia due to the organisms such as *E. coli*, *P. aeruginosa* and *Klebsiella* spp. as they caused higher mortality than bacteremia due to gram positive organisms[13, 14].

In this study the incidence of gram positive bacteremia was higher than gram negative bacteremia. The gram negative bacteremia encountered was only about a third of total bacteremia. High incidence of gram positive bacteremia seems to be associated with the increased use of the central venous catheter[11, 14]. Actually 18 of 37 episodes (49 %) of gram positive bacteremia were associated with the use of the central venous catheter in this study.

Recently, the use of empirical antibiotics led to the decrement in the morbidity and mortality associated with the bacterial infections but led to the emergence of the resistant bacteria[9, 20, 23]. In this study the resistance of cultured gram positive and negative organisms from the pediatric cancer patients with bacteremia was prominent in the conventional antibiotics of longstanding use, although these organisms were sensitive to the most recently developed antibiotics. Fortunately, the incidence of recently reported vancomycin resistant gram positive bacteria was low in this study. Among gram positive bacteria, only 6 of 37 isolates (16%) were sensitive to penicillin. Twelve of 32 isolates (38%) of *Staphylococci* were sensitive to oxacillin and 3 of 5 isolates (60%) of *Streptococci* were sensitive to oxacillin. Among gram negative bacteria, 2 isolates sensitive to cefotaxime were also sensitive to ceftazidime but 2 other isolates resistant to cefotaxime were sensitive to ceftazidime. But these results showed no statistical significance because of the small numbers of cases.

Because this study was done in one institution with small numbers of cases, only limited conclusions could be elucidated. It seems to be important to select the proper empirical antibiotics prior to the blood culture and antibiotic sensitivity test results if bacteremia is suspected in pediatric cancer patients by monitoring continuously and analyzing periodically the isolated pathogens with antibiotic sensitivity test results of the institutions. We propose a prospective multicenter study on this subject.

한글 요약

소아 암 환자에서 발생한 균혈증 : 원인균과 항생제 감수성

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목 적 : 면역 저하된 소아 암 환자에서 균혈증은 조기에 적절한 치료를 하지 못하면 이환율과 사망률이 높아 질 수 있는 질환으로서 호발 원인균의 발생 빈도 및 항생제에 대한 감수성은 지역적 · 시기적으로 변화하는 경향이 있으므로 이를 조사하여 경험적 항생제 선택에 도움을 주고자 하였다.

방 법 : 1995년 9월부터 2003년 8월까지 영남대학교 의과대학 부속병원 소아과에 입원한 소아 암 환자를 대상으로 병력지와 혈액배양검사 결과를 조사하여 균혈증이 확진된 39명, 58례를 대상으로 원인 균의 종류 및 항생제 감수성을 조사 · 분석하였다.

결 과 : 소아 암 환자에서 균혈증의 발생빈도는 균혈증이 의심되어 혈액배양을 시행한 1,022례 중 58례로 5.7%였다. 균혈증을 일으킨 가장 흔한 원인 균은 그람양성균으로 총 37례(63.8%)였고 그람음성균은 총 21례(36.2%)였다. 그람양성균의 경우 *Staphylococcus epidermidis* (22례, 37.9%), *Staphylococcus aureus* (10례, 17.3%), *Streptococcus* (5례, 8.6%) 순이었고, 그람음성균의 경우 *Escherichia coli* (7례, 12%), *Enterobacter* (4례, 6.9%), *Klebsiella* (4례, 6.9%), *Serratia* (2례, 3.5%), *Acinetobacter* (2례, 3.5%), *Proteus* (1례, 1.7%), *Morganella morganii* (1례, 1.7%) 순으로 나타났다. 항생제 감수성 검사에서는 그람양성균 37례 중 6례(16%)에서만 penicillin 감수성을 나타내었고, 15례(40%)에서 oxacillin 감수성을 나타내었다. *Staphylococcus aureus*는 1례를 제외한 모든 예에서 vancomycin에, *Staphylococcus epidermidis*는 1례를 제외한 모든 예에서 teicoplanin에 감수성을 나타내었다. 그람음성균의 경우, 21례 중 2례(10%)만이 cefotaxime에, 4례(19%)에서만 ceftazidime에

감수성을 나타내었다. Aminoglycoside에는 21례 중 6례(29%)에서만 감수성을 나타내었으며, 21례 모두에서 imipenem에 감수성을, 2000년 이후부터 감수성 검사를 시행한 meropenem에도 모든 예에서 감수성을 나타내었다.

결 론 : 균혈증이 의심되는 소아 암 환자에서 그람양성균에 의한 균혈증이 증가하는 점과 그람양성균과 그람음성균 모두 항생제 다제내성 빈도가 증가하고 있음을 유념하여 적절한 항생제를 선택해야 할 것이다.

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