PIDSP Journal, 2005 Vol. 9 No. 2

A FIVE-YEAR RETROSPECTIVE STUDY ON THE COMMON MICROBIAL ISOLATES AND SENSITIVITY PATTERN ON BLOOD CULTURE OF PEDIATRIC CANCER PATIENTS ADMITTED AT THE PHILIPPINE GENERAL HOSPITAL FOR FEBRILE NEUTROPENIA

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ABSTRACT

Rationale: Febrile neutropenia is a common clinical problem among pediatric cancer patients. This often necessitates hospitalization and immediate empiric broad spectrum antimicrobial therapy. In selecting the initial antibiotic regimen, the type, frequency and antibiotic susceptibilities of the microbial isolates should be considered.

Objective: To determine the bacterial blood isolates and antimicrobial sensitivity pattern of pediatric cancer patients admitted at the Philippine General Hospital for febrile neutropenia.

Methods: Retrospective study of all pediatric patients diagnosed with a hematologic or oncologic malignancy admitted at the Philippine General Hospital from January 1999 to December 2003 for febrile neutropenia.

Results: A total of 90 patients were included in the study. Sixty two per cent (62%) of the subjects were diagnosed to have hematologic malignancy while 38% are oncologic cases. Only 7% of the patients had growth in the blood culture while 93% had no growth in the blood culture. Causative organisms isolated were *Streptococcus viridans*, Gram negative bacilli, *Staphylococcus epidermidis*, *Candida* sp., *Salmonella sp.* and *Haffnea alveii*. All patients received Ceftazidime as empiric antimicrobial therapy in combination with Netilmycin for patients admitted in 1999 or Amikacin for patients admitted from January 2000 to December 2003. *S. viridans*, G(-) bacilli, *Salmonella sp*. and *H. alveii* showed sensitivity to Ceftazidime. All patients given Ceftazidime with Netilmycin/Amikacin became afebrile on the 3rd day of antibiotics with increasing absolute neutropenic count except for patients who developed nosocomial infections causing delay in recovery and prompting shift of antibiotics.

Conclusion: Majority of pediatric cancer patients with febrile neutropenia yielded no growth in blood culture. However, most cases responded well with the empiric antibiotic combination of Ceftazidime and Amikacin. Few cases with isolates were also sensitive to the current antibiotic regimen. The microbiological laboratory should also act in consultation with the clinician to determine the optimal approach for blood cultures in the immunocompromised patients.

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Keywords: febrile neutropenia, malignancy, granulocytopenia, absolute neutrophil count, blood culture

INTRODUCTION

Infection and its complications were the main causes of morbidity and mortality among pediatric patients receiving chemotherapy for malignant diseases.[9] Granulocytopenia carries the risk of bacterial infection. If prolonged, this can lead to fungal infection. As the neutrophil count decreases below 500 cells/cu.mm, the risk of infection increases proportionately.[3] Hence, antimicrobials play a major role in the management of patient with febrile neutropenia.

International trend shows that gram-positive bacteria account for 60-70% of microbiologically documented infections. Some of these are methicillin resistant. However, gram-negative bacilli especially *P. aeruginosa, E. coli* and *Klebsiella* sp. remain prominent causes of infection. Fungal infections on the other hand, are usually superinfections. In some cases, *Candida* sp. or other fungi can cause primary infection.[6]

It is therefore important in the selection of the initial antibiotic regimen for febrile neutropenia to consider the type, frequency of occurrence and antibiotic susceptibility of bacterial isolates recovered from other patients at the same hospital. Current recommendation in the empiric antibiotic management of febrile neutropenia at the Philippine General Hospital is based on the 1997 Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer prepared by the Infectious Diseases Society of America (IDSA) Fever and Neutropenia Guidelines Panel. This recommends the use of Vancomycin plus Ceftazidime (or Cefepime) or a carbapenem or combination therapy with an aminoglycoside plus an anti-pseudomonal beta-

lactam as initial intravenous therapy.[7] This is based on international trend of microbiologic growth and sensitivity pattern.

This study was conceived to determine whether bacterial blood isolates among pediatric patients with febrile neutropenia at the Philippine General Hospital is comparable with the international trend. It aims to provide local data on the bacterial blood isolates and antimicrobial sensitivity patterns. This study also hopes to provide valuable information that will aid in the decision-making and improvement in the care of pediatric patients with febrile neutropenia especially in the selection of initial antibiotic regimen.

DEFINITION OF TERMS

Febrile neutropenia – a single temperature measurement of >/= 38.3 C in the absence of obvious environmental causes or temperature of >/= 38.0 C for>/ = 1 hour and granulocytopenia by routine complete blood count determination Granulocytopenia – absolute neutrophil count of </= 500 cells/cu.mm.

REVIEW OF RELATED LITERATURE

Children with cancer can be severely compromised. This can be due to immunodeficiency secondary to malignancy, the therapy or both. Most chemotherapeutic agents also inhibit the inflammatory response to invading microbes. In these patients, the physical signs and symptoms are not reliable in predicting infection.[3] The neutrophil count on the other hand, is important in predicting risk and response to infection. As the absolute neutrophil count goes down, the patient's immunological status becomes compromised and the risk of infection is greater. In such patients with impaired inflammatory response coupled with granulocytopenia, fever most of the time is the only sign of infection. This demands urgent empirical antibiotic therapy with broad spectrum coverage. This is to decrease the risk of septic shock, ARDS, hypotension, renal and other organ dysfunction and death.[2]

For febrile neutropenia cases, the Infectious Diseases Society of America (IDSA) recommends a thorough physical examination, complete blood count, blood urea nitrogen, creatinine and transaminase level determination and blood cultures as part of initial management. Sample for blood culture is drawn from a peripheral line including a set from central venous access device. Urinalysis and urine culture is warranted if the patient has symptoms of urinary tract infection or has a chronic urinary catheter. Chest radiograph is indicated when the patient has respiratory symptoms. High resolution chest computed tomography is requested in the presence of respiratory symptoms and normal chest radiographic findings.[6]

According to the 2002 Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer published by IDSA, the bacterial causes of febrile episodes in neutropenic patients are as follows:

Gram-positive cocci and bacilli
- *Staphylococcus* species *
  - Coagulase-positive (*Staphylococcus aureus*)
  - Coagulase-negative(*Staphylococcus epidermidis* and others)
- *Streptococcus* species *
  - *Streptococcus pneumoniae*
  - *Streptococcus pyogenes*
- Viridans group
- *Enterococcus faecalis/faecium* *
- *Corynebacterium* species *

Gram-negative bacilli and cocci
- *Escherichia coli* *
- *Klebsiella* species *
- *Pseudomonas aeruginosa*
- *Enterobacter* species

Anaeorobic cocci and bacilli
- *Bacteroides* species
- *Clostridium* species
- *Fusobacterium* species
- *Propionibacterium* species
- *Peptococcus* species
- *Veillonella* species
- *Peptostreptococcus* species

The 2002 Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer published by IDSA provided the following algorithm in the management of cancer patients with febrile neutropenia:

Factors that favor a low risk for severe infection among patients with neutropenia are absolute neutrophil count >/= 100 cells/cu.mm, absolute monocyte count of .>/= 100 cells/cu.mm, normal findings on chest radiograph, nearly normal results of hepatic and renal function tests, duration of neutropenia of less than 7 days, resolution of neutropenia expected in less than 10 days, no intravenous catheter-site infection, early evidence of bone marrow recovery, malignancy in remission, peak temperature of less than 39 C, no neurological and mental changes, no appearance of illness, no abdominal pain and no comorbidity complications.[6]

* the most common cause of bacteremia

PIDSP Journal, 2005 Vol. 9 No. 2

OBJECTIVES

General objectives:

To determine the bacterial blood isolates and antimicrobial sensitivity pattern of pediatric cancer patients admitted at the Philippine General Hospital for febrile neutropenia.

Specific objectives:

1. To determine the bacterial blood isolates of pediatric cancer patients admitted at the Philippine General Hospital for febrile neutropenia.
2. To determine the antimicrobial sensitivity patterns of bacterial blood isolates of pediatric cancer patients admitted at the Philippine General Hospital for febrile neutropenia.
3. To determine whether the current empiric antibiotics given to pediatric cancer patients admitted at the Philippine General Hospital for febrile neutropenia are effective.

METHODOLOGY

Study Design

Retrospective, descriptive study

Study Population

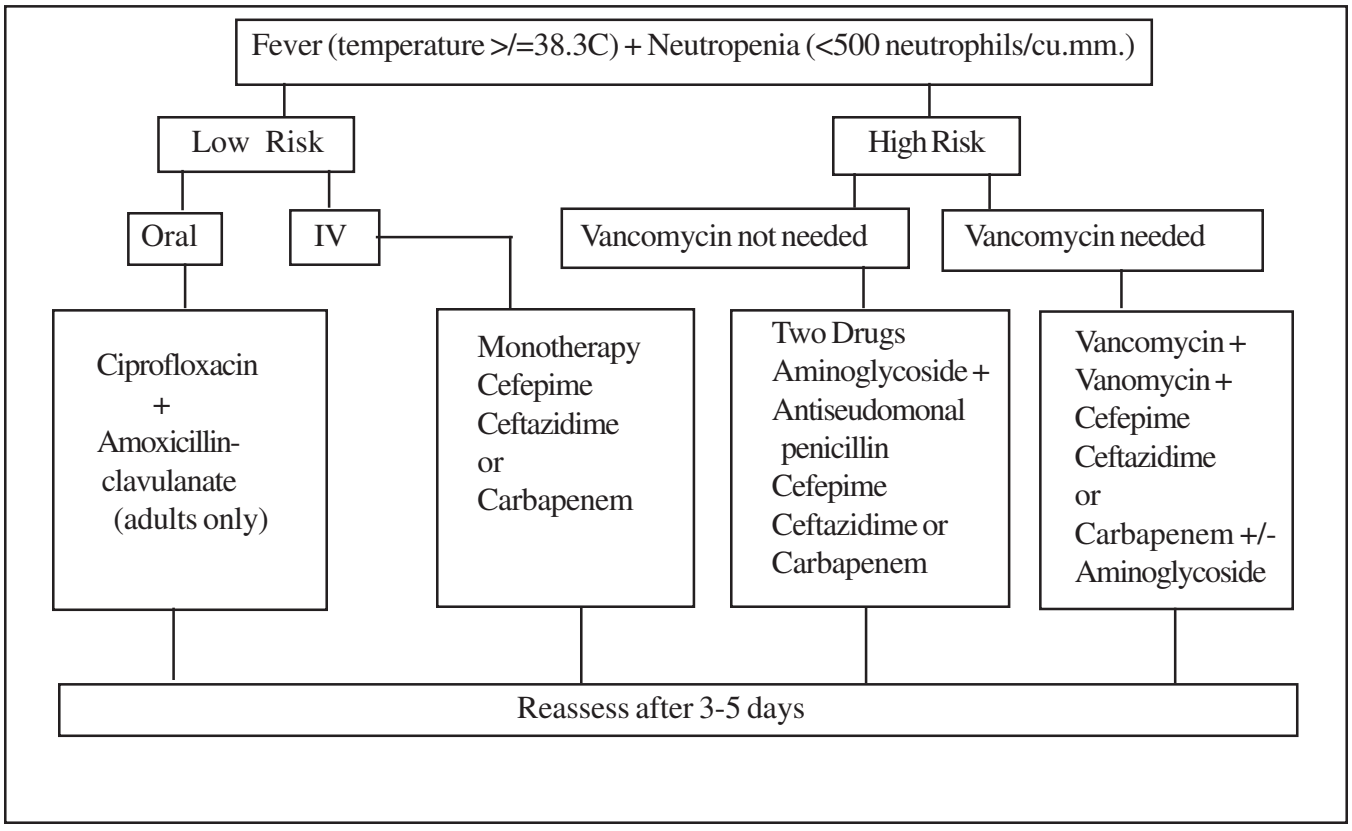
The study involved chart review of all pediatric cancer patients admitted at the Philippine General Hospital from January 1999 to December 2003 selected on the basis of the following inclusion criteria: Pediatric patients aged 1-19 years old diagnosed with oncologic or hematologic malignancy documented to have granulocytopenia (neutrophil count </= 500 cells/cu.mm) by routine complete blood count determination. A single temperature measurement of >/=38.3 C in the absence of obvious environmental causes or temperature of >/= 38.0 C for >/= 1 hour no overt site or focus of infection at the time of admission

DATA COLLECTION

Charts of patients who fulfill the criteria for the study were retrieved and reviewed. The final blood culture results prior to the start of any antibiotic regimen was recorded including the antimicrobial sensitivity patterns.

OUTCOMES MEASURED

The outcome of interest was the determination of the common bacterial blood isolates and antimicrobial



sensitivity pattern of pediatric cancer patients with febrile neutropenia at the Philippine General Hospital.

ANALYSIS

Descriptive analysis was done on the data collected.

RESULTS

From January 1999 to December 2003, there were a total of 90 febrile neutropenia cases. 56% of the subjects were male while 44% were female. 56% of the subjects belong to the 0-6 years of age.

Among the 90 subjects, 62% had hematologic malignancy i.e. acute lymphocytic leukemia, acute myelogenous leukemia. 38% were oncologic cases comprising of osteosarcoma, embryonal carcinoma, neuroectodermal sinus tumor, nasopharyngeal carcinoma, Wilm's tumor, Ewing's sarcoma, rhabdomyosarcoma, malignant mixed germ cell tumor and malignant peripheral nerve sheath tumor.

Only 7% of the patients had growth in the blood culture. 93% had no growth. Table 4 and 5 indicates the blood microbial isolates and antimicrobial sensitivity patterns of these isolates. Among the patients who had growth in the blood culture, 50% grew Gram-negative bacteria, 33% had Gram-positive bacteria and 17% had fungal isolate.

All patients received Ceftazidime as empiric antimicrobial therapy in combination with Netilmycin for patients admitted in 1999 or Amikacin for patients admitted from January 2000 to December 2003. Majority patients given Ceftazidime with Netilmycin/Amikacin had lower temperature and less febrile episodes on the third day of antibiotics with increasing absolute neutrophil count except for patients who developed nosocomial infections causing delay in recovery and prompting shift of antibiotics.

Table 1. Age Distribution of Study Population

Age Group (Years)	N	%
0-3	25	28
4-6	25	28
7-9	3	3
10-12	18	20
13-15	16	18
16-18	3	3
>18	0	0
Total	90	100

Table 2. Gender Distribution of Study Population

Gender	N	%
Male	50	62
Female	40	38
Total	90	100

Table 3. Frequency Distribution of Study Population According to Nature of Malignancy

Nature of Malignancy	N	%
Hematologic	56	62
Oncologic	34	38
Total	90	100

Table 4. Frequency Distribution of Study Population According to Blood Bacterial Isolates

Blood Bacterial Isolates	N	%
Streptococcus viridans	1	1
Gram-negative bacilli	1	1
Staphylococcus epidermidis	1	1
Candida sp.	1	1
Salmonella sp.	1	1
Haffnea alveii	1	1

Table 5. Sensitivity Pattern of Blood Microbial Isolates

Anti-*biotic*	S. *viridans*			G(-) bacilli			S. *epider midis*			*Candida sp. sp.*			*Salmo-nella*			H. *alveii*		
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
Ceftazidime				+									+					
Amikacin						+												
Meropenem													+					
Piperacillin-Tazobactam																+		
Ciproflo-xacin	+												+					
Netilmycin	+																	
Co-amoxy-clav																+		

DISCUSSION

Bacteremia is detected in only a handful of pediatric cancer patients with febrile neutropenia. Studies done by Mahmud, Latiff, Celiken, Ariffin and Muller had growth in blood culture in only 25%, 24%, 27% 35.4% and 24% of their subjects respectively.[10,8,4,2,11] This is comparable with the blood culture results of pediatric cancer patients with febrile neutropenia at the Philippine General Hospital. In terms of major etiologic agents, the trend varies per institution. Although Gram-positive bacteria accounts for 60-70% of microbiologically documented infections based from the IDSA data, this is not so in other institutions. In a study done by Mahmud among pediatric cancer patients with febrile neutropenia in Riwalpindi 51.7% of his subjects grew Gram-positive bacteria in their blood culture.[10] This is similar to the study done by Celkan in Istanbul, Turkey where 60% of the isolated bacteria were coagulase-negative *Staphylococcus* sp. and *Staphylococcus aureus*.[4] 63.4% of the subjects in a study done by Kern grew coagulase-negative *Staphylococcus* sp.[7]. Gram-negative bacteria on the other hand, was the predominating isolates in the studies done by Latiff and another one by Ariffin with yield of 64% and 62% respectively.[8,2] While the international trend shows that gram-positive bacteria is the predominant isolate, the 2002 Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer published by IDSA still recommends the use of broad-spectrum antibiotics that would cover for both gram-positive and gram-negative bacteria. Hence, most patients respond well to the empiric antibiotics given.[10, 8,4,2,11]

CONCLUSION

Majority of pediatric cancer patients with febrile neutropenia yielded no growth in blood culture. However, most cases responded well with the empiric antibiotic combination of Ceftazidime and Amikacin. The predominant pathogen isolated were Gram-negative bacteria which is in contrast with the international trend. These are also sensitive to the current antibiotic regimen. The empiric antibiotic therapy are effective and well tolerated in febrile neutropenia.

RECOMMENDATION

The types of microbial isolates and sensitivity patterns should be continuously monitored to identify trends and to gauge the suitability of antibiotics chosen for empirical therapy. The microbiological laboratory should also act in consultation with the clinician to determine the optimal approach for blood cultures in the immunocompromised patients.

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