CEFOPERAZONE/SULBACTAM PLUS AMIKACIN FOR EMPIRICAL THERAPY OF FEBRILE NEUTROPENIC PATIENTS

Esin ŞENOL, M.D., Gülsan TÜRKÖZ SUCAK*, M.D., Funda ERGİN**, M.D., Rauf HAZNEDAR*, M.D.

Gazi University, Faculty of Medicine, Departments of Infectious Diseases and Clinical Microbiology and Hematology*, Ankara-Turkey
Başkent University, Faculty of Medicine Infectious Diseases and Clinical Microbiology, Ankara-Turkey**
Gazi Medical Journal 2001; 12: 165-172

ABSTRACT

Purpose: *The aim of the study was to evalute the efficacy of cefoperazone-sulbactam plus amikacin for initial therapy of febrile neutropenic patients with hematological malignancies.The overall efficacy and the need for modifications were also determined.* ***Methods:*** *72 neutropenic patients with various hematological malignancies who developed 97 febrile episodes were included in the study. They received cefoperazone 2g-sulbactam 1g every 8h and amikacin 15mg/kg single daily. The study design was in accordance with that described by the Immunocompromised Host Society.* ***Results:*** *29 episodes were excluded from the study leaving a total of 68 episodes in 50 patients for the evalution. 55% of the febrile episodes were documented as fever of unknown origin. At the initial evaluation 29% of the episodes responded to therapy. At the end of the therapy, success rates were 49% and 70% without and with modification, respectively. Most of the failures were due to adjustments in therapy accounting for 81% of the failures.* ***Conclusion:*** *This protocol is considered be a successful one with regard to the study population and strict criteria used for assessments. Although frequent modifications were needed to ensure patient survival, the protocol was efficacious in preventing early death within 72 hours and in improving the outcomes at the end of the therapy.*

Key Words: *Fever, Neutropenia, Cefoperazone-Sulbactam, Efficacy, Empirical Treatment.*

INTRODUCTION

The importance of prompt initiation of empirical antibiotic therapy for febrile episodes in neutropenic patients is well recognized and is the current standard practice. However, there is still contraversy about the selection of the optimum scheme. Several different regimens including monotherapeutic and multidrug regimens have been evaluated in this setting and have been demonstrated to be effective but there is no clear evidence that one regimen is superior to another (1).

Although there is no single best regimen, there are several appropriate options for the empirical treatment of febrile neutropenic patients. It is necessary to continually reevaluate these options because of the changing epidemiology of organisms and growing emergence of resistance (2). Thus the selection of the ideal empirical antibiotic regimen in an institution must be based on the microbiological data of that institution (3). In our center, most of the microbiologically documented infections of cancer patients are caused by resistant Gram-

negative bacilli part of which resistance has been demonstrated to be mediated with extended-spectrum beta-lactamases (4,5). The highest susceptibility rates were recorded for cefoperazone/sulbactam and carbapenems whereas it was documented that there was an increase in resistance to ceftazidime and to other beta-lactam antibiotics (4). Because of the consideration that the widespread use of ceftazidime for many years at this institution has resulted in the emergence of resistance, we decided to change the beta-lactam part of our combination therapy to cefoperazone/sulbactam in order to improve the efficacy of our empirical regimen.

Cefoperazone is a broad-spectrum cephalosporin which has been used successfully for the treatment of infections in neutropenic cancer patients (6). However it is susceptible to inactivation by the beta-lactamases of some Gram-negative bacilli. Sulbactam is a chemically stable irreversible inhibitor of many beta-lactamases and, when combined with cefoperazone, it expands the spectrum of the activity to include some anaerobes and many beta-lactamase producing Gram-negative bacilli (7). Therefore we are interested in evaluating the combination of cefoperazone-sulbactam plus amikacin as an empirical regimen for febrile neutropenic patients with various hematological malignancies.

PATIENTS AND METHODS

The trial was conducted as an open, prospective study between the years 1997 and 1999. All adult patients with various hematological malignancies admitted to the Hematology Unit of the Gazi Medical School, presenting with fever and neutropenia, were enrolled in this study. The study design was in accordance with that described by the Immunocompromised Host Society (IHS) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) (8, 9).

Fever was defined as a single axillary reading of a temperature > 38.5° C or > 38° C on two or more occasions during a 12-h period. Neutropenia was defined as a neutrophil count< 500/mm^3 or <1000/mm^3 that was rapidly falling. Patients were excluded for the following reasons; previous anaphylactic reaction to cefoperazone or other beta-lactam antibiotics, pregnancy or nursing, age <18 years, renal impairment (evidenced by creatinine clearance of <15 mL/min) or the previous administration of parenteral antibiotic therapy during the same neutropenic episode. Patients were entered only once during the same neutropenic episode and at least one week had to pass between the neutropenic episodes before a patient could be included again. None of the patients were receiving any prophylactic antibiotics.

Antimicrobial Therapy

Treatment was initiated immediately after completion of a comprehensive physical examination and samples of blood and appropriate specimens determined by clinical signs had been obtained for microbiological assesments. Patients recived a fixed combination of 2g of cefoperazone and 1 g of sulbactam every 8 hours and amikacin 15 mg/kg/day in a single daily dose by the intravenous route.The minimum duration of the treatment with the initial regimen was 7 days.Therapy was continued until all signs and symptoms of infection had resolved for at least 2 days when the neutrophil count exceeded 500/mm^3 or 5 consecutive days when the count remained below 500/mm^3. Patients with neutrophil counts below 100/mm^3 and/or unstable clinical vital signs received therapy throughout the course of neutropenia. Modifications or changes of therapy were allowed for one of the following reasons: if a pathogen which was resistant to the empirical regimen was isolated, if a patient was not responding to treatment and deteriorating clinically after 72 hours of initial therapy, if only fever persisted without clinical deterioration after 7 days of therapy, if there was recurrence of fever or if there was a serious adverse event related to therapy. The choice of the agent for modification was directed by the microbiological data when available although vancomycin administration was based on specified criteria: persistant fever with progressive disease or severe mucositis after 72-96 hours of initial therapy, isolation of a pathogen resistant to study therapy (e.g methicillin resistant staphylococci) and definition of an obvious catheter-related infection. Also it was our general policy to give amphotericin B to patients either with evidence of fungal infection or unexplained fever

persisting for 7 days during neutropenia. Otherwise therapy was continued without any modification or change in the primary antibiotic regimen for at least 7 days and the patients were reviewed daily.

Clinical and Laboratory Investigations

After taking complete histories from all the patients, physical examinations with special attention to skin, oral cavity, perirectal area and indwelling catheter sites were also performed. Clinical assessments were carried out daily during the study. Routine chest X-rays, a complete battery of laboratory tests including serum chemistries, complete blood count, urine analysis , at least two sets of cultures from blood (from indwelling catheters and venipunctures at 30-minute intervals) from urine, throat and swabs from possible sites of infection were also performed and examined before initiating antibiotic therapy. Blood cultures were further taken daily if a patient's temperature stayed above 38° C, after 48-72 hours of treatment and before any change in antibiotic therapy. Biochemical and hematologic profiles were done once and three times weekly, respectively.Appropriate follow-up cultures, radiologic examinations and invasive procedures were performed during the course of therapy if indicated.

Classification of Febrile Episodes

Febrile episodes were classified as microbiologically documented, clinically defined and fever of unknown origin (FUO) using the criteria of IHS (8). Briefly, a microbiologically defined infection (MDI) was indicated by one or more blood cultures positive for any organism (except for the same strain of a coagulase-negative staphylococcus or a Corynebacterium sp. was isolated from at least two sets of blood cultures) or a microbiologically defined site of infection (e.g pneumonia, cellulitis, urinary tract infection) without concomittant bacteremia. An infection was designated as clinically defined when a site of infection was detected but its microbiological origin could not be proven or was inaccessible for examination. All the other episodes were regarded as FUO.

Evaluation of Results of Therapy

Febrile episodes were evaluated after 72h (early evaluation), if only fever persisted without clinical improvement and treatment was continued without a change in the assigned regimen after 5 and 7 days, and at the end of the febrile episode (late evaluation). Each treatment episode was assessed according to guidelines proposed by the IHS (8). Briefly; success was achieved if all signs and symptoms and microbiological evidence of infection were eradicated without modification of the initial regimen and no recurrence was found for at least a week after discontinuation of the initial therapy. Initial response but regimen modified was present when the initial infection/fever was resolved with the initial regimen but it was necessary to add antiviral or antifungal agent for a new infection. Failure was designated when any addition of antibacterial agents to, modification of, or change in the primary antibiotic regimen was needed to eradicate the primary infection. Death due to infection was also counted as failure. If treatment was discontinued for reasons unrelated to infection such as allergy or sudden death due to hemorrhage, if the patient received other antibiotics earlier than specified in the protocol or if there was violation of the protocol due to inapproprite addition to or change in antibiotic therapy the episode was considered non evaluable for efficacy. The primary aim was to assess the clinical efficacy of the study drugs for the first 72 hours of a febrile neutropenic episode in patients with hematological malignancies. The overall efficacy and the need for modification of the initial regimen were also determined.

RESULTS

During the 2 year study period, 97 episodes occurring in 72 patients were entered into the study. Twenty-nine of the episodes were excluded from the study for the following reasons: ten patients did not receive the study drugs, ten patients received concurrent antibiotics, five received therapy for less than 24 hours, two had protocol violations due to inappropriate addition to or change in therapy, two had sudden death due to hemorrhage. So totally, 68 episodes occurring in 50 patients were evaluated for efficacy. The clinical characteristics of 68 episodes are summarized in Table 1.

It was noteworthy that all patients had hematological malignancies with acute leukemia

Table - 1: Clinical characteristics of evaluable episodes.

Characteristics	
No.of episodes	68
No.of patients	50
Age (years) (mean ±SD)	42.5±13.4
Sex (M/F)	34/16
Underlying Disease	
Acute leukemia	49(72%)
Non-Hodgkin's lymphoma	15(22%)
Chronic leukemia	2(3%)
Myelodysplastic syndrome	2(3%)
No.with central venous catheter	7(10%)
Neutrophil count at inclusion	
< 100/mm³	13(19%)
< 500/mm³	21(31%)
> 500/mm³	34(50%)
Duration of neutropenia (days) (mean±SD)	13.8±6.9

predominating. At study entry, half of the patients had neutrophil counts below 500/mm³ and the duration of neutropenia was long with a median of 13 days, ranging from 6 to 19 days. In 44/68 (65%) episodes the duration was longer than 10 days. The patients who had neutrophil counts above 500/mm³ at inclusion developed severe neutropenia within 24-48 hours of admission with rapidly falling neutrophil counts.

Categorization and details of the evaluable 68 episodes are shown in Table 2. Totally, microbiologically and clinically defined infections together accounted for 45 percent of episodes. The sites of microbiologically defined infections were upper respiratory tract (two patients), urinary tract (four patients), lower respiratory tract (two patients), and catheter exit site infections (two patients). Of the isolates associated with microbiologically documented

Table - 2: Documentation of infection in the 68 evaluable episodes.

Type of infection			No. of episodes
MDI			11(16 %)
	Bacteremia only		1
	Localized infection with bacteremia		2
	Localized infection without bacteremia		8
		Gram-positive pathogen	5
		ß-hemolytic streptococci	2
		Staphylococcus aureus	2
		Corynebacterium spp.	1
		Gram-negative pathogen	5
		Pseudomonas aeruginosa	1
		Escherichia coli	3
		Klebsiella spp	2
CDI			20 (29%)
	sites of infection		
		upper respiratory tract	4
		lower respiratory tract	11
		skin and soft tissues	4
		more than one site of infection[a]	1
FUO			37(55%)

a.lower respiratory tract and perirectal abscess at the same time.

infections, only 2 were resistant to cefoperazone/sulbactam. One of the resistant isolates was a strain of coagulase-positive staphylococcus and the other was a strain of Corynebacterium spp. both of which were isolated from blood cultures of patients with catheter exit site infections. The strain of coagulase-positive staphylococcus was also resistant to methicillin. The most frequently implicated site of clinically defined infections was lower respiratory tract. In 5 of the 20 febrile episodes defined as CDI, microbiological documentation could not be done in spite of obtaining appropriate specimens while in 15 of them, specimens could not be obtained. Notably FUO accounted for more than half of the episodes in this study.

Results of Therapy

Study drugs were administered for a median of 16 days (range 8-24 days). The median duration of fever was 13 days, ranging from 5 to 21 days.The results of therapy related to site of infection at the initial evaluation (at 72 h) and at the final evaluation are shown in Table 3.

At the initial evaluation, considering episodes with persistent fever as treatment failures, 20/68 (29%) episodes responded to therapy. The response rates were highest for FUO and lowest for CDI. Notably approximately three quarters of episodes were still febrile after 3 days of therapy, but none of the patients died within 72 hours of the trial. Some of the patients failing on initial treatment at the first evaluation became afebrile by the fifth and seventh days of therapy. It was observed in 6 (9%) and 7 (10%) episodes by the fifth and seventh days, respectively. At the final evaluation, 33/68 (49%) episodes responded to therapy without modification and 14/68 (21%) responded to a modified regimen.

Antifungal agents were administered as first modifications of the empirical regimen in 11 episodes and acyclovir was commenced for 3 episodes. Consequently, taking into account all cases successfully treated with the initial regimen with or without modification, the overall response rate of the antiinfective strategy was 70%, giving the failure rate of 30%. At the late evaluation, the highest and lowest response rates were again documented for FUO and CDI, respectively.

The reasons for failures were distributed as follows; antibiotics were added for 13 episodes, treatment was changed in 4 episodes and 4 patients died from infection, giving the mortality rate of 8%. All the 13 episodes in which antibiotics were added included additions of glycopeptides alone or concurrently with antifungals or antiviral agents. Thus, the most important reason for failures was modification of or change in therapy which accounted for 81% of episodes. The majority of patients failing on initial treatment became afebrile after changes in antibiotic treatment except for 4 deaths from infection despite several changes in treatment.

Types of modications and the most frequent reasons prompting modifications are shown in Table 4 and 5. There were 31/68 (46%) modifications and glycopeptide addition accounted for 42% of all modifications. Most of the modifications were made according to clinical judgement except for two episodes for which there was documentation of resistance of the initial pathogen to cefaperazone/sulbactam.

Of the 50 patients treated in this study 43 survived their febrile episodes. Thus the study drugs were effective as the initial empiric treatment in 86% of patients if survival is used as a critereon for success. Totally, seven patients died during the study, giving an overall mortality

Table - 3: Response rates by site of infection.

	% Response at 72 h		%Response at the end of the therapy		
Infection category	**Success**	**Failure**	**Success**	**Success with modification**	**Failure**
MDI	3 (27%)	8 (73%)	6 (55%)	1 (9%)	4 (36%)
CDI	2 (10%)	18 (90%)	6 (30%)	2 (10%)	12 (60%)
FUO	15 (41%)	22 (59%)	21 (57%)	11 (29%)	5 (14%)
Total	20 (29%)	48 (71%)	33 (49%)	14 (21%)	21 (30%)

Table - 4: Documentation of all modifications and changes in study therapy.

Type of modification	No.of episodes
Vancomycin (alone) 5	
Vancomycin + Fluconazol	2
Vancomycin+Amphotericin B	4
Vancomycin+ Amphotericin B +Acyclovir	2
Fluconazol	5
Amphotericin B	6
Acyclovir	3
Carbapenems	4

Table - 5: Documentation of reasons for modification.

Reasons prompting modification	No.of episodes
Persistent fever	11
Initial microorganism resistant	2
Progression of primary infection	4
Suspected nonbacterial infection	14

of 14%. Three of these deaths were from non-infectious causes (2 from hemorrhagic complications,1 from pulmonary embolism). Three of the infectious deaths were from pneumonia and one from multiple organ failure (none with microbiologic documentation).

DISCUSSION

Combination therapy with an antipseudomonal beta-lactam drug plus an aminoglycoside has been widely adopted as standard practice for many years especially for those with profound long-lasting neutropenia (10). The use of a combination regimen is conceptually attractive for reasons which include extended coverage, synergism and a reduced probability of the development of resistance (11). A number of combination regimens were studied for the treatment of febrile neutropenic episodes, and most were associated with success rates of 50-70% (12) .

Cefoperazone-sulbactam is an antimicrobial agent with a wide spectrum and more potent, especially to gram-negative infections than existing agents for empirical treatment of fever in neutropenic patients (13). Clinical experience with cefoperazone-sulbactam seems to be promising but has been limited. Bodey et al. reported a response rate of 76% but this study included cancer patients with adequate neutrophil counts (6). In another clinical trial the efficacy was 74% in neutropenic cancer patients but it was combined with vancomycin and the patients evaluated in this study were a group with solid tumors (7). Horuichi et al. reported a 53% response rate in patients with hematological malignancies (14).

The main reason directing us to design a combination of an antipseudomonal beta-lactam plus an aminoglycoside was the patient population in this study, which consisted of hematological malignancies. The microbiological data of our institution prompted us to choose cefoperazone-sulbactam as the beta-lactam agent. The primary aim of the study was to evaluate the efficacy of the study drugs for the first 72 hours of the febrile neutropenic episode, which could be accepted as the true empirical therapy period and the secondary aims were to evalute the efficacy at the end of the treatment period and to determine the need for modification of the initial therapy.

The patient population in this study was a high risk group, considering the underlying disease, the severity and duration of neutropenia (12,15). All patients included in this study had hematological malignancies with acute leukemia predominating. In 65% of the episodes the duration of neutropenia was longer than 10 days. In fact profound neutropenia is expected in patients with hematological malignancies (16). Also it must be emphasized that for the design and analysis of this study we used the recommended criteria from the IHS and ESCMID, according to which every addition to, modification of and change in initial therapy is considered as a falure (8, 9).

We found a high incidence (55%) of FUO. Although the policy of prompt institution of antimicrobial therapy has reduced the early morbidity and mortality, antibiotics may be the factor mainly responsible for the decreased rate of infectious etiology (17). This is mostly the problem of such studies especially in patients with prolonged and profound neutropenia where it is mostly reported that FUO accounted for 60-70 % of episodes (3, 18, 19).

Regarding the primary aim of the study the efficacy of the study drugs was 29% at the initial evaluation. The relatively low response rates were thought to be related to stringent definitions of failure used in this study which are supported

by the IHS consensus. All the episodes with fever lasting for more than 3 days were considered as treatment failures. However none of the patients died within 72 hours which is certainly more important than the resolution of fever, because most of the deaths related to the initial infective episode occurs early.The response rates for episodes classified as FUO were found to be 41% as the highest at the initial evaluation. It is reported that 40-50% of fevers classified as FUO appears to resolve within two to three days of therapy (18, 20) .

Regarding the secondary aims of study, before documenting the response rates at the late evaluation, adjustments of therapy were evaluated. In this study all the adjustments allowed during the study period were clearly specified in the protocol which was supported by the suggestions of guidelines for antimicrobial therapy published by the Infectious Society of America (IDSA) in 1997 (21). However there were still some protocol violations which were excluded from the study. According to the specified criteria for adjustments, some of the patients who continued on initial regimen alone for up to 5-7 days resolved their fevers. Totally, 19 percent of the episodes became afebrile by the seventh day of therapy without adjustment of the initial therapy. This supported the suggestion that changing or modifying therapy in a case of unexplained fever alone of less than five days duration would not be permitted (2, 20, 21).

At the late evaluation the overall success rate of 70% achieved seems comparable to the results of 50-70% obtained with other commonly recommended combinations (9,12). At the end of therapy, in 21% of episodes a modification of empirical therapy was required. The modifications were mainly with antifungal agents (11/14 episodes). The response rates without modification (49%) seemed to be relatively lower and this again was thought to be related to the stringent definitions and to the characteristics of the study population and was not associated with high mortality. A significantly lower response rate has been reported for patients with profound and protracted neutropenia than for patients with less severe and short term neutropenia (22).

The overall mortality rate was 14%. Thus the study drugs were effective if the ultimate goal was to ensure patient survival. The infection related mortality was 8%. Considering the duration of neutropenia and the underlying hematological disease of the patients evaluated in this study this was not higher than expected (2, 23). The most important reasons of failure was the adjustment of therapy which was documented for 17 of 21(81%) episodes. As noted in other trials adjustment of therapy has become a common clinical practice in patients with fever and neutropenia, especially in high risk patients despite the absence of a documented microbiologic pathogenesis (24). There were a total of 31 (46%) modifications and the most frequent modification was the addition of a glycopeptide which accounted for 42% of all modifications. However it was justified by microbiological data only in two of the episodes. Thus glycopeptide was added empirically in most of the episodes. It could therefore not be suggested that the modifications were needed because the efficacy of study drugs in gram-positive infections was suboptimal. The frequency and types of modification and the reasons prompting these modifications documented in the present study are comparable to other studies dealing with high-risk patients (20, 25, 26).

Finally, before coming to the conclusion of this study, it should be emphasized that this study has three important features. First of all this is one of a few where only hematological malignancies are included. This results in a very homogeneous population of patients and duration of neutropenia leading to a powerful validation of the efficacy of therapy. Second, in categorizing the febrile episodes a high percentage of FUO was documented. Because some of them might be the results of nonmicrobial processes this makes the efficacy of study drugs less impressive. Third, all definitions and assessments were done according to the criteria described by the IHS .

In conclusion, although the relatively small number of patients included in our study makes it diffucult to decide whether this regimen is as effective as the others, cefoperazone-sulbactam plus amikacin appears to be comparable to other presently recommended regimens for empirical therapy in febrile neutropenic patients with hematological malignancies according to the results of this study. Although it seems that

modifications are frequently required to achieve success as the main objective of empirical antibiotic protocols is to prevent early mortality, in our opinion modifications show the limitation of the treatment protocol rather than failure of it. This is the main reason for us to consider our protocol a successful one in spite of the low response rates at the initial evaluation and frequent modifications.

Correspondence to: Esin ŞENOL, M.D.
Çankaya Evleri F-Blok No: 28
Çankaya
06550 ANKARA - TÜRKİYE
Phone : 312 - 440 20 44
E-mail : senole @ med.gazi .edu.tr

REFERENCES

1. Martino P, Micozzi A. Controversies in the therapy of fever in neutropenic patients. Current Opinion in Infectious Diseases 1995; 8: 415-419.
2. Hathorn JW, Lyke K. Empirical treatment of febrile neutropenia: evaluation of current therapeutic approaches. Clin Infect Dis 1997; 24 (Suppl. 2.): 256-265.
3. Pizzo PA. Management of fever in patients with cancer and treatment-induced neutropenia. N Engl J Med 1993; 328: 18: 1323-1332.
4. Senol E, Yetkin A, Sucak G, Akçalı Z, Ergin F, Dizbay M, Karakuş R, Haznedar R, Günel N, Arman D, Aktaş F. Classification of microorganisms isolated from immunocompromised host. The Journal of Hospital Infection. Abstracts presented at the 4th International Congress of Hospital Infection Society, 13-17 September 1998, W.B.Saunders Company Ltd. P.6.1.1.6.
5. Arman D, Yetkin A, Maral I. Detection of extended-spectrum beta-lactamases in clinical and outpatient isolates of Klebsiella pneumonia. Antiinfective Drugs and Chemotherapy 1998; 16 (Suppl 1):87.
6. Bodey GP, Elting LS, Narro J, Koller C, O'Brien S, Estey E, Benjamin R. An open trial of cefoperazone plus sulbactam for the treatment of fever in cancer patients. J Antimicrob Chemother 1993; 32: 141-152.
7. Bodey G, Abi-Said D, Rolston K, Raad I, Whimbey E. Imipenem or cefoperazone-sulbactam combined with vancomycin for therapy of presumed or proven infection in neutropenic cancer patients. Eur J Clin Microbiol Infect Dis 1996; 15:625-634.
8. The Immunocompromised Host Society. The design, analysis, and reporting of clinical trials on the empirical antibiotic management of the neutropenic patient .Journal of Infect Dis 1990; 161: 397-401.
9. Hughes WT, Pizzo PA, Wade JC, Armstrong D, Webb CD, Young LS. General guidelines for the evaluation of new anti-infective drugs for the treatment of febrile episodes in neutropenic patients. In European Guidelines for the Clinical Evaluation of Anti-Infective Drug Products (ESCMID) 1993; 221-227.
10. The Meropenem Study Group of Leuven, London and Nijmegen.Equivalent efficacies of meropenem and ceftazidime as empirical monotherapy of febrile neutropenic patients. J Antimicrob Chemother 1995; 36: 185-200.
11. Bodey GP. Infection in cancer patients. Am J Med 1986; 81 (suppl 1A): 11-26.
12. Lee JW, Pizzo PA. Management of cancer patients with fever and prolonged neutropenia. Hematol Oncol Clin N Am 1993; 75: 937-965.
13. Giamarellou H. Empiric therapy for infections in the febrile neutropenic, compromised host. Med Clin N Am 1995; 79:3: 569-580.
14. Horiuchi A, Hasegawa H, Kageyama T, Yonezawa T, Kitani T, Masaoka M, Yasunaga K, Kawagoe H, Nagai K. Efficacy of sulbactam/cefoperazone for the treatment of infections in patients with hematologic diseases. Diagn Microbiol Infect Dis 1989; 12: 215-219.
15. Pizzo PA. Empirical Therapy and Prevention of Infection in the immunocompromised host. In. Gl Mandell, JE Bennett, R Dolin (ed) Principles and Practice of Infectious Diseases, Fourth Edition.New York, Churchill Livingstone 1995; 2686-2696.
16. Brown AE. Neutropenia, fever and infection. Am J Med 1984; 76: 421-428.
17. Pizzo PA, Rubin M, Freifeld A, Walsh TJ. The child with cancer and infection: empiric therapy for fever and neutropenia, and preventive strategies. J Pediatr 1991; 119: 679-694.
18. Donnelly JP, De Pauw BE. Diagnosis and treatment of infection. Curr Opin Infect Dis 1992; 5: 415-421.
19. Samuelsson J, Lönnovist B, Palmblad J, Grimfors G, Jarnmark M, Lerner R, Ljungman P, Nyström-Rosander C, Berg G and the Leukemia Group of Middle Sweden. Ceftazidime as initial therapy in febrile patients with acute leukemia during induction chemotherapy. Scand J Infect Dis 1992; 24: 89-96.
20. Donnelly JP. Assessment and reporting of clinical trials of empirical therapy in neutropenic patients. J Antimicrob Chemother 1991; 27: 377-387.
21. Hughes WT, Armstrong D, Bodey GP, Brown AE, Edwards JE, Feld R, Pizzo P, Rolston KVI, Shenep JL, Young LS. 1997 Guidelines for the use of Antimicrobial Agents in Neutropenic Patients with Unexplained Fever. Clin Infect Dis 1997; 25: 551-573.
22. Talcott JA, Finberg R, Mayer RJ, Goldman L. The medical course of cancer patients with fever and neutropenia: clinical identification of a low-risk subgroup at presentation. Arc Intern Med 1988; 148: 2561-2568.
23. Rukonen P. Imipenem compared with ceftazidime plus vancomycin as initial therapy for fever in neutropenic children with cancer. Pediatr Infect Dis J 1991; 10: 918-923.

24. De Pauw BE, Deresinski SC, Feld R, Lane-Allman EF, Donnelly JP and the Intercontinental Antimicrobial Study Group. Ceftazidime compared with piperacillin and tobramycin for the empiric treatment of fever in neutropenic patients with cancer. Ann Intern Med 1994; 120: 834-844.
25. Cometta A, Calandra T, Gaya H, Zinner H, Bock R, DelFavero A, Bucanneve G, Croakert F, Kern WV, Klastersky J, Langenaeken J, Micozzi A, Padmos A, Paesmans M, Viscoli C, Glauser MP. Monotherapy with meropenem versus combination therapy with ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. Antimicrob Agents Chemother 1996; 40: 1108-1115.
26. Ramphal R, Gucalp R, Rotstein C, Cimino M, Oblon D. Clinical experience with single agent and combination regimens in the management of infection in the febrile neutropenic patient. Am J Med 1996; 100: 83-89.