

Microorganisms isolated from cultures and infection focus and antibiotic treatments in febrile neutropenic children from Şanlıurfa, Turkey

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Chemotherapy induced febrile neutropenia predisposes patients to life threatening infections. We aimed to determine the causative microorganisms, infection focus and antibiotic treatment success in febrile neutropenic children with leukemia. A total of 136 febrile neutropenic episodes in 48 leukemic children were reviewed retrospectively from records. Among 136 febrile neutropenic episodes, 68 (50%) episodes were microbiologically documented. Methicillin sensitive coagulase (-) *Staphylococcus aureus* were the most common isolates from hemoculture (20.5%). The most frequently documented infection focus was mucositis (31.9%). Ceftazidime plus amikacin was the most commonly used antimicrobial treatment for the empirical therapy (52.9%). The overall response rates were 70.5%, 86.9%, and 66.6% of first line, second line and third line therapies, respectively.

The spectrum of isolates among febrile neutropenic children in our hematology clinic appears to be gram positive pathogens which are the most common agents. Therefore the, documentation of the flora in each unit could help to decide appropriate empirical therapy which is life saving.

Key words: child, leukemia, fever, neutropenia, empiric therapy.

Neutropenia is one of the most common complications in children with cancer, and it is the most important parameter to determine infection risk. In neutropenic patients the signs and symptoms could be scarce and in occasions fever could be the only symptom¹. Life threatening complications due to bacterial infections have been reported in 3-10% of all febrile neutropenic episodes².

Recent studies have found that 29-60% of neutropenic patients who become febrile have bacterial infections, of which 16-25% have bacteremias and gram (+) bacteremia has increased up to 60-70% of all microorganisms identified^{3,4}. Several studies suggest that a causative agent could not be documented in almost two-thirds of infectious episodes⁵. Presumably because immediately administration of empirical therapy masks documentation of infection.

The selection of empirical therapy should be based on a variety of factors such as a patient's infectious risk, potential sites, causative organisms and sensitivity of those organism to antibiotics⁶. In addition, individual centers should aim to describe the epidemiology of bacteremia to guide empiric antibiotic treatment among children with neutropenia. We aimed to determine the infection focus, causative organisms and efficiency of antibiotic treatment in our pediatric hematology clinic.

Material and Methods

In total, 48 leukemic children admitted to Pediatric Hematology Clinic of Harran University Faculty of Medicine between January 2008- June 2010 were evaluated in this study. Sixteen episodes were excluded from the study. These episodes had no complete clinical and laboratory evaluation. A hundred thirty six

Table I. Characteristic of Children and Febrile Episodes

Mean age (year)	7.20 ± 3.81 (1.5-16.5)
Mean duration of neutropenia (day)	7.67 ± 4.1 (2-23)
Mean number of febrile episodes	2.56 ± 1.93 (1-11)
Microbiologically documented infection	68 (50%)
Clinically documented infection	47(35%)
Fever unknown origin	21 (15%)

febrile episodes were analysed retrospectively. Neutropenia was defined as an absolute neutrophil count of < 500 cells/mm³ or a count of < 1000 cells/mm³ with a predicted decrease to < 500 cells/mm³. Fever was defined as a single tympanic temperature ≥38.3 °C or a temperature of ≥38°C at least 1 hour⁷. A blood culture was considered to be contaminated if coagulase-negative staphylococci, micrococcus species, corynebacterium species in a single bottle and were excluded from this analysis. Patients were included more than once in the analysis for separate episodes of bacteremia⁸. A urine culture was considered contaminated when it had a bacterial count greater than 100,000 colonies/ml⁹.

Febrile neutropenic episodes were classified as fever of unknown origin (FUO), clinically or microbiologically documented infection. FUO was defined as fever without any focus or etiology identified by clinical history, physical examination, radiological or microbiologic testing¹⁰. The diagnosis of microbiologically documented infection was based on both isolation and a causative organism from body fluids. Clinically documented infection was defined as there was evidence of focal inflammation on physical examination but without microbiological confirmation¹¹.

The first line antibiotic (empirical) treatments were started at the beginning of fever period in all children. First line antibiotic treatment included; cefepim or ceftazidime alone, cefepim, ceftazidime or cefaperazon-sulbactam with amikacin or carbapenem alone. If the fever persist after ≥ 48-72 hours of empirical treatment, or children had gram (+) bacteria isolated from hemoculture, glycopeptid was started as a second line treatment. After 4-5 days, if fever did not settle then either glycopeptid was added or if there was suspicion of fungal infection, antifungal therapy was started as a third line therapy.

Results

A total of 136 episodes were documented in 48 leukemic children. Forty children with acute lymphoblastic leukemia (83.3%), 8 children with acute myeloblastic leukemia (16.7%). There were 27 males (56.3%) and 21 females (43.8%) whose age ranged from 1.5-16.5 years (mean age 7.2±3.81). The episodes were classified as such: 68 (50%) of febrile episodes were documented microbiologically, 47 (35%) episode were clinically documented infections and 21 (15%) episodes were classified as FUO. Characteristics of children and febrile episodes are summarized in Table I.

Table II. Clinically Documented Infection Focus of Febrile Episodes

Infection focus	n	%
Oral mucositis	15	31.9
Upper respiratory tract*	14	29.7
Pneumonia	5	10.6
Enterocolitis	5	10.6
Soft tissue	4	8.5
Labial herpes	4	8.5
Total	47	35

*Otitis media, sinusitis, tonsillitis, pharyngitis

Clinical infection focus was documented in 47 (35%) of febrile episodes. Oral mucositis (31.9%) and upper respiratory tract (29.7%) were the most common identified infection foci (Table II).

Sixty eight (50%) of febrile episodes were documented microbiologically. Bacterial documentation was made by hemoculture in 44 (32.4%), by urine culture in 14 (10.3%), by skin lesion culture in 10 (7.4%) of febrile episodes. In 28 (63.8 %) of the 44 febrile episodes gram (+) bacteria were isolated in hemoculture. Gram (-) bacteria were isolated in 9 episodes (20.5%), and fungus were isolated in 7 episodes (15.9%). The distribution of bacteria isolated from hemoculture were shown in Table III.

Skin lesion culture were made in 13 of febrile episodes. Microorganisms were isolated in 10 of these cultures. Microorganism isolated from skin lesion cultures and infection focus presented in Table IV.

In 14 (10.3%) of febrile episodes microorganism were isolated by urine culture. *E.coli* (7), *Enterococcus spp* (2), *Klebsiella pneumonia* (2), *Klebsilla oxytaca* (1), *Proteus mirabilis*(1) and *Methicillin-resistant Staphylococcus aureus (MRSA)* (1) were isolated in urine culture. Pyuria was detected in 5, and positivity of nitrite in 2 of them. Normal results was detected in 7 of urinalysis.

Antibiotic treatments and outcomes

Of the 136 febrile episodes, 96 (70.5%) episodes improved with first line therapy, while modification of first line antibiotic therapy was required in 38 (27.9%) episodes as second and third line therapy. Twenty-three episodes were improved with second line therapy while 15 episodes were improved third line therapy.

As first line treatment, 73 (75%) children received cephalosporins with amikacin. Ceftazidime+amikacin, cefepim+amikacin, cefaperazon-sulbactam+amikacin were given in 56 (76.7%), 9 (12.3%), 8 (11%) of febrile episodes, respectively. Ten (10%) children received carbapenem. Fifteen (15%) children received cephalosporins alone. Ceftazidime and cefepime were given in 9 (60%) and 6 (40%) of febrile episodes, respectively. Two child died while under the first line therapy (Table V).

Second line therapy was used in 23 of febrile episodes. Glycopeptide (teicoplanin) agent combination with ceftazidime+amikacin in 9 (1 child died), combination with cefepime+amikacin in 3, combination with carbapenem in 11 (2 children died) of febrile episodes (Table VI).

Third line therapy was used in 15 of febrile episodes. Antifungal agent (amphotericin B) combination with ceftazidime+amikacin in 7 (1 child died) and combination with carbapenem in 8 (4 children died) of febrile episodes (Table VI). In this study, antibiotic treatment outcomes in overall treatment

Table III. The Distribution of Bacteria Isolated From Hemoculture.

Gram (+) bacteria	n	%	Gram (-) bacteria	n	%
MSSA	9	20.5	G (-) agents*	3	6.8
Corynebacteria spp.	5	11.4	Enterobacter spp.	2	4.5
Streptococcus spp.	5	11.4	<i>P. aeruginosa</i>	1	2.3
Enterococcus spp.	4	9.1	<i>S. maltophila</i>	1	2.3
MRSA	2	4.5	Enterobacteraerogenes	1	2.3
<i>S. aureus</i>	1	2.3	<i>K. pneumoniae</i>	1	2.3
<i>S. pneumoniae</i>	1	2.3	Total	9	20.5
MSSA and <i>S. pneumoniae</i>	1	2.3			
			Fungus <i>C. albicans</i>	6	13.6
			Aspergillus	1	2.3
Total	28	63.8		7	15.9

MSSA: Methicillin sensitive coagulase (-) staphylococcus aureus, MRSA: Methicillin resistant coagulase (-) staphylococcus aureus, *S. aureus*: Staphylococcus aureus, *S. pneumoniae*: Streptococcus pneumoniae, *P. aeruginosa*: Pseudomonas aeruginosa, *K. pneumoniae*: Klebsiella pneumoniae, *C. albicans*: Candida albicans.*Not identified

Table IV. Microorganism Isolated From Skin Lesions Cultures and Infection Focus.

Infection focus	Microorganisms (each patient)
Catheter-related*	MSSA
Buccal abscess	MSSA <i>E. Coli</i>
Soft tissue	Enterobacter <i>P. aeruginosa</i>
Lip abscess	Enterobakter
Necrotic tissue	<i>P. aeruginosa</i> Acinetobacter
Maxillary sinus	Streptococcus spp.
Decubitus ulcer	<i>C. albicans</i>

*Catheter was removed, MSSA: Methicillin sensitive coagulase (-) *staphylococcus aureus*, *P. aeruginosa*: *Pseudomonas aeruginosa*, *E. coli*: *Escherichia coli*, *C. albicans*: *Candida albicans*.

were 96/136 (70.5%), 20/23 (86.9%), 10/15 (66.6%) of first line, second line and third line therapy, respectively. Treatment failed in 10 (7.4%) of febrile neutropenic children. Two children were AML, eight children were ALL, two of them were relapse ALL. All ten deaths occurred during the febrile neutropenic episode. Three were from septic shock (two children in first line treatment, one child in second line treatment), three were from pneumonia and acute respiratory distress syndrome (two children in second line treatment, one child in third line treatment), three were from fungal sepsis and multiple organ dysfunction (all in third line treatment), one was from massive pulmonary hemorrhage (in third line treatment). Types of antibiotic treatment and outcomes were described as shown in Tables V and VI.

Discussion

Febrile neutropenia is a common complication associated with cancer and its treatment. Infections remain a major cause of morbidity in children with cancer, although mortality from infectious complications has diminished significantly^{12,13}. Bacteria are the major causes of initial infection at early phase of febrile neutropenia. Pathogens have evolved over time. Today gram-positive bacteria are the predominant cause of infections in granulocytopenic cancer patients Coagulase (-) staphylococci, *Staphylococcus aureus*, *Streptococcus viridans* and Enterococcus are the most common gram (+) pathogens⁴.

Many reports from Turkey and other countries found different information related to isolated pathogens ratio with febrile neutropenia. Güneş

Table V. First Line Antibiotic Treatment and Outcomes

Antibiotic	First line treatment		Treatment outcome	
		n	n	%
Ceftazidime	(9)	9	9	100
Cefepime	(6)	6	6	100
Ceftazidime+amikacin	(72)	56	54	96.4
Cefepime+amikacin	(12)	9	9	100
Cefaperazon-sulbactam+amikacin	(8)	8	8	100
Carbapenem	(29)	10	10	100
Total	136	98	96	70.5

Table VI. Second and Third Line Antibiotic Treatment and Outcomes.

Second and third line treatment		Treatment outcome	
		n	%
Ceftazidime+amikacin+teicoplanin	(9)	8	88.8
Ceftazidime+amikacin+teicoplanin+amphotericin B	(7)	6	85.7
Cefepime+amikacin+teicoplanin	(3)	3	100
Carbapenem+teicoplanin	(11)	9	81.8
Carbapenem+teicoplanin+amphotericin B	(8)	4	50
Total	38	30	78.9

et al.¹¹, Hamidi et al.¹⁴, Akan¹⁵, Sanboonrat et al.¹⁶ had all found gram (-) bacteria in about 85%, 73%, 56,8%, 50% respectively. Also Jeddi et al.¹⁷ found that gram (-) bacteria are predominant. Conversely, Düzova et al.¹⁸ 67%, Kobayashi et al.¹⁹ 61%, Paganini et al.²⁰ 47 % reported positive hemocultures for gram (+) bacteria . Also Oguz et al.²¹ showed that gram (+) bacteria are more frequently causative agents. In the present study the most commonly isolated agents were gram (+) bacteria (63.8%). Among the gram positives Methicillin-sensitive *Staphylococcus aureus* (MSSA) were the predominant pathogens (20.5%) of febrile episodes (Table III).

In our study, we found the most common infection site was oral cavity and catheter entry site infections of which documented gram (+) bacteria by hemoculture. These results may be related to inadequate care and hygienic problems of our patients. According to the literature, such things as growing use of indwelling venous catheters and oral mucositis are risk factors for gram (+) infections in febrile neutropenic patients^{22,23}. Our data also supported these investigations.

Several studies have reported that 24% to 55% of febrile episodes are fever of unknown origin^{24,25}. International Antimicrobial Therapy Cooperative Group–European Organization for Research and Treatment of Cancer (IATCG-EORTC) have reported microbiological documentation in about 27% of the febrile patients²⁶. In our study, 68 (50%) of febrile episodes were microbiologically documented which causes infection in neutropenic children. About 44 (32.4%) of these episodes were associated with bacteremia. We were able to find that microbiologically documentation in this study may be associated with several

factor, such as, their parents have low levels education, majority of parents could not make the measurement of fever and not admitted the hospital early time and our patients do not receive of antibacterial prophylaxis.

In our study 47 (35%) of febrile episodes were clinically documented infections. The findings about source of infection seemed to be various. Some studies reported that most common site was respiratory tract^{27,28}. Güneş et al.¹⁰ and Saanboonrat et al.¹⁶ found that the most common infection source was oral cavity. Oral mucositis and respiratory tract infections have similar proportions as the most frequent foci of infection were identified in our study (Table II).

With improved treatment and better survival from bacterial infections in febrile neutropenic patients, prevention and treatment of fungal infections have assumed greater importance, especially in patients with prolonged neutropenia. These infections tend to occur as secondary infections, rarely being identified at the onset of a febrile episode. Most fungal infections in children with cancer are caused by *C. albicans* accounting for most isolates. In recent years, an increase in prevalence of other *Candida* species such as *C. glabrata*, and *C. crusei* have become more common. However, *C. albicans* are still more frequent in many institutions²⁹. In our study the incidence of microbiologically proven fungal infections were found in 15.9%, although most isolated fungal agents were *C. albicans*.

In our study, the response rate was comparable to those of other beta-lactam-aminoglycoside regimens tested in such a pediatric population. In a prospective non-comparative open study of piperacillin plus gentamicin for the treatment

of 239 febrile episodes in neutropenic children, Fleischhack et al.³⁰ reported an overall response rate of 55.2%. In a prospective, open-labeled, single-center study of single-daily dose of ceftriaxone plus amikacin for the treatment of 191 febrile episodes in neutropenic children, Ariffin et al.³¹ reported an overall response rate of 55.5%.

In our study, an overall response rate of 70.5% was achieved by the first-line treatment. These results suggested that ceftazidim plus amikacin therapy is effective in our neutropenic patients.

In conclusion, we suggest that complete physical examination which skin, mucous membranes, and sinuses should be done. Recommended initial treatment should be considered as guidelines, but alterations could be based on the predominant organisms isolated from patient population of each hospital. In this study we report the frequency of isolated microroganisms and infection site in our hematology clinic. Our study to was the first study to evaluate febrile episodes in neutropenic children in Southeast Anatolia.

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