Fever and granulocytopenia in children with Acute Lymphoblastic Leukemia under induction therapy

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ABSTRACT

Objective: Infection is one of the most serious complications of cancer therapy. The rationale of using broad spectrum antibiotics prophylactically has led to a great change in the causative organisms. The aim of the present study is to review retrospectively the type and sequence of infectious complications among Saudi children with acute lymphoblastic leukemia.

Methods: A total of 233 febrile episodes were observed in 137 children with acute lymphoblastic leukemia under induction therapy using modified BFM protocol were studied.

Results: Profound neutropenia (Absolute Neutrophil count $\leq 100/mm^3$) was encountered in 72 episodes (31%). Clinical signs and symptoms suggestive of infection were evident in 39% of the neutropenic episodes. The respiratory system was the most frequently affected site encountered in 17% of the episodes. Microbiologically documented infection was recorded in 59% (n=137) of the fever and granulocytopenia episodes. In 96 episodes (41%), there was neither clinical nor microbiological evidence of infection fever of unknown origin. Out of the 932 cultures, positive isolates were detected in 346 cultures (37%). Gram positive cocci were the most frequently organisms (54%) followed by gram negative bacilli (39%). In the current study, 7 patients (3%) died because of direct or indirect consequences of infection.

Conclusion: The current study stresses the importance of frequent reviewing of the type, frequency, severity and outcome of infection complications over years to detect changing epidemiological patterns.

Keywords: Febrile neutropenia, childhood acute lymphoblastic leukemia.

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The association between malignancy, the immunocompromised host and infectious morbidity and mortality is well established. With the use of more intensive and potentially curative treatment regimens, a larger number of children are being rendered immunocompromised. Despite the great progress in the treatment of infectious complications in neutropenic patients, infection-related morbidity and fatality continues to be of great significance. Moreover, the rational of using broad spectrum antibiotics prophylactically has led to a great change in the causative organisms.[1,2] The aim of the present retrospective study was to review the type and frequency of infectious complications among children with acute lymphoblastic leukemia (ALL) referred to King Abdulaziz Hospital and Oncology Center, Jeddah, Saudi Arabia during the period between 1993-1998. Isolated bacterial microorganism in positive cultures and the in-vitro sensitivity test to the most commonly used

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antimicrobial agents were analyzed.

Methods. Febrile neutropenic episodes occurred in 137 children with ALL under induction therapy using modified BFM protocol, were reviewed. Fever defined as a single episode of body temperature of 38.5°C or higher or as a temperature between 38°C and 38.4°C persisting for at least 6 hours. Neutropenia was defined as an absolute neutrophil count (ANC) < 500 x 10^6/L. All patients performed baseline laboratory and radiologic investigations. Clinical samples (blood, sputum, throat swab, urine and stool) were collected and subjected to routine cultures for bacterial growth and candida species using different media. Aspirate or biopsy culture from any accessible sites suggesting infection were also taken. Identification of the isolates was confirmed using standard microbiological methods.[3] Empiric antibiotic therapy was administered (mostly 3rd generation cephalosporin in addition to aminoglycoside). Then evaluation of the patients as regards fever and granulocyte count was performed. Response to empiric therapy was classified by using the following criteria.

Fever and granulocytopenia. 1. Improvement: If there was a lasting return of temperature, signs, and symptoms to normal or to pre-infectious state. 2. Partial improvement: Significant decrease of temperature but not to normal. 3. Failure: If there was no or minimal response to antibiotics. For patients showing partial improvement or failure, modification of therapy was performed according to the results of cultures or clinical status. If patients showed clinical signs of anaerobic infection (periodontal gingivitis, intra-abdominal infection), metronidazole was added. Systemic antifungal therapy was added if the patient was still febrile and neutropenic with no clinical or bacteriologic evidence of infection.

Table 1 - Demographic characteristics of 137 acute lymphoblastic leukemia patients with 233 febrile neutropenic episodes.

Demographic characteristics	Number	%
Sex		
Male	162	74
Female	35	26
Male:Female	2.9:1	
Age in years	2 - 18	
Range	9.5	
Median	8.7 + 5.6	
Mean	8.7 + 5.6	
Degree of neutropenia		
ANC ≤ 100/mm³	72	31
ANC > 100-500/mm³	161	69
Duration of neutropenia (ANC < 500mm³)		
≤ 7 days (low-risk)	131	56
>7 days (high risk)	102	44

ANC = absolute neutrophil count

Table 2 - Incidence of clinically and microbiologically documented infection in 137 children with acute lymphoblastic leukemia (233 febrile neutropenic episodes).

Incidence of infection	Number of episodes	%
Clinically documented infection	91	39
Respiratory system	40	17
GIT tract	26	11
Urinary Tract	16	7
Soft tissue	9	4
Absent signs and symptoms of infection	142	61
Microbiologically documented infection	137	59
Fever of unknown origin	96	41

GIT = gastrointestinal tract

Results. ***Febrile episodes.*** A total of 233 febrile episodes were observed in the 137 children with ALL under induction therapy using modified BFM protocol. Thirty-three patients (24%) had only one episode; 53 patients had 2 episodes (39%) and 51 patients (37%) had 3 or more episodes. The clinical characteristics of the patients included in the current study are illustrated in Table 1. Colony-stimulating factors (CSF) were used in only 22 episodes (9%). The impact of their effect on the fate of the febrile episodes was not included in the analysis. Profound neutropenia (ANC < 100/mm³) was encountered in 72 episodes (31%). In our study, 102 episodes (44%) were considered to be high-risk, as neutropenia (ANC < 500/mm³) persisted for more than 7 days (Table 1). Clinical signs and symptoms suggestive of infection were evident in 39% of the neutropenic episodes. The respiratory system was the most frequently affected site encountered in 17% of the episodes. Microbiologically documented infection was recorded in 59% (n = 137) of the episodes. In 96 episodes (41%), there was neither clinical nor microbiological evidence of infection. These episodes can be grouped under the category of fever of unknown origin Table 2.

Table 3 - Distribution and frequency of isolated bacteria according to the site of culture.

Organism Isolated	Blood culture %	Throat swab %	Ear swab %	Wound swab %	Urine culture %	Stool culture %	Sputum culture %	Cerebrospinal fluid culture %
Staphylococcus aureus	17	16	40	14	4	-	-	-
Staphylococcus epidermidis	11.5	-	-	-	2	-	-	-
Staphylococcus pneumoniae	6	-	-	-	-	-	-	33
Staphylococcus group A	3	8	20	-	-	-	40	67
Staphylococcus group C	-	8	20	-	-	-	-	-
Staphylococcus group D	6	3	-	-	6	-	-	-
Klebsiella pneumoniae	14.5	10	-	29	30	-	-	-
Haemophilus influenza	-	-	-	-	-	-	60	-
Pseudomonas aeruginosa	14.5	29	-	28	12	-	-	-
E. coli	6	5	20	-	18	60	-	-
Enterobacter spp.	9	8	-	-	12	-	-	-
Citrobacter spp.	3	3	-	-	6	-	-	-
Acinetobacter spp.	-	8	-	29		-	-	-
Proteus spp.	-	3	-	-		-	-	-
Aeromonas spp.	9	-	-	-	-	-	-	-
Salmonella spp.	3	-	-	-	-	40		-
Other gramnegativebacteria	-	-	-	-	12	-	-	-

E. = escherichia
% = percentage

Table 4 - Results of antimicrobial sensitivity for isolated gram positive bacteria.

Antibiotic Agent	S. aureus %	S. epidermidis %	Strept. Group A %	Strept. Group B %	Strept. Group C %	Strept. Group D %	Pneumoniae %
Penicillin	0	4	26	81	49	55	54
Erythromicin	46	16	28	58	51	-	49
Tetracycline	20	32	43	-	22	51	63
Co-Trimoxazole	33	24	-	-	12	-	-
Gentamicin	26	56	28	-	22	-	-
Vancomycin	100	100	100	100	100	100	100
Clindamycin	53	52	57	-	63	25	91
Oxacillin	74	32	28	91	53	-	94
Cephalothin	67	64	43	84	88	52	71
Amoxicillin	33	12	14	-	38	-	68
Amikacin	6	40	-	-	-	-	-
Ceftiaxone	-	4	-	-	-	-	-
Cefotaxime	13	4	19	-	53	-	-
Chloramphenicol	6	4	16	-	22	-	79
Fucidic Acid	13	8	28	-	52	-	-
Cefoxitin	13	-	-	-	-	-	-
Tobramycin	6	-	14	-	-	-	-
Ampicillin	-	-	14	-	38	-	-
Piperacillin	-	-	14	-	36	22	-

Strept. = streptomycin
S. = staphlycoccus
% = percentage

Table 5 - Results of antimicrobial sensitivity for isolated gram negative bacteria

Antibiotic	Ps. aeruginosa %	E coli %	Kleb. spp %	Acinetobacter %	Enterobacter %	Citrobacter %	Salmonella %
Amickacin	72	40	22	45	33	29	68
Imiponem	36	81	56	82	44	32	31
Gentamicin	68	51	53	45	44	100	100
Piperacillin	59	10	33	36	-	-	65
Azotronem	31	49	26	27	-	37	93
Cephalothin	-	40	20	-	-	-	32
Ceftriaxone	18	-	18	-	-	-	31
Tetracycline	14	-	6	27	11	-	98
Colistin	31	-	-	-	-	-	-
Ceftazidime	36	-	18	18	-	31	64
Co-Trimox.	-	20	33	27	33	-	33
Amoxicillin	-	30	20	9	21	31	68
Cefoxitin	-	-	-	-	24	65	52
Tobramycin	64	30	26	45	34	67	71
Cabramycin	36	-	-	-	-	-	-
Netilimicin	55	-	-	-	-	-	-
Ciprofloxacin	14	29	20	36	21	-	62
Cefoxitin	-	65	47	-	28	100	30
Cefotaxime	-	83	61	9	-	-	-
Nalidixic Acid	-	22	26	-	12	42	-
Nitrofurantoin	-	31	21	-	10	48	-
Norfloxacin	-	10	27	19	-	-	-
Chloramphenicol	-	-	-	-	13	30	96

Ps = pseudomonas, E = escherichia, kleb = klebsiella, spp = species, % = percentage

Isolated micro-organisms and antimicrobial treatment. Out of the 932 cultures, positive isolates were detected in 346 cultures (37%). Gram positive *cocci* were the most frequently isolated organisms (54%) followed by gram-negative *bacilli* (39%). Fungal infection was detected in 24 isolates (7%). Table 3 shows the spectrum of the isolated microorganisms. *Staphylococcus aureus* was the most commonly encountered bacterium in positive blood cultures. About 2/3 of the isolated *staphylococcus aureus* was MRSA that is known to be very resistant to most antibiotics. Only a few of the bacteria isolated from throat swab cultures are pathogenic *(Streptococcus A and C)*. The other organisms had heavy growth in culture. Gram-negative bacteria form about 88% of all bacteria causing urinary tract infections. Only 6% of stool cultures revealed to be positive. Enteropathogenic *Escherichia coli* (*E coli*) constituted 40% of positive isolates from stool cultures which indicates the growing significance of these special types of (*E. coli*) (i.e. EPEC, EIEC, ETEC). Tables 4 and 5 illustrate the results of in-vitro sensitivity to the most commonly used anti-microbial agents. Analysis of our data shows that isolated gram positive bacteria are sensitive to vancomycin, cephalothin, oxacillin, clindamycin and gentamicin. Gram negative bacteria are sensitive to impimen, gentamicin, piperacillin, tobramycin and azotronem.

Fate of febrile episodes. Clinical and microbiological assessment of the patients 48-72 hours after starting empiric antibiotics, showed complete resolution (improvement) of signs and symptoms in 151 episodes in (65%) while, partial response and treatment failure were encountered in 51 episodes (22%) and 31 episodes (13%). Modification of therapy in the form of addition of antifungal therapy or metronidazole for anaerobic infection was performed. In the current study, 7 patients (3%) died because of direct or indirect consequences of infection. The final response to treatment after modification was raised to 97%.

Discussion. The diagnosis and management of cancer in children poses many challenges to the multidisciplinary care team. The unique problems associated with the delivery of aggressive and potentially toxic treatment are further magnified in the management of children with cancer. With cancer chemotherapy, infectious complications are life threatening and may limit the benefits of the antineoplastic therapy. The duration and severity of neutropenia, the presence of indwelling catheters, and mucosal damage produced by cytotoxic drugs are all correlated with the incidence of infectious complications.[4] Clinical signs or symptoms of infection, except for fever, were documented by Jansen et al,[4] and Petrilli et al [5] in 58% of their study group, whereas De Pauw et al[6] reported clinically documented infections in 11% of their studied febrile neutropenic episodes. In the study carried out by Bow et al,[7] clinically documented infection was reported in 22% of the neutropenic episodes. In our

study, clinical signs or symptoms of infection were documented in 39% of the neutropenic episodes and the most common site of infection was the respiratory system encountered in 17% of the episodes. The absence of clinical signs or symptoms of infection in a great proportion of neutropenic episodes does not exclude its presence, and this may be due to the fact that granulocytopenia markedly alters the host's inflammatory response making the classic signs and symptoms of infection undetectable. In the last 2 decades, major shifts have occurred in the distribution of the pathogens causing infections in neutropenic cancer patients. Infections due to gram-negative bacilli have virtually decreased while, those caused by gram-positive bacteria are rapidly increasing, however, the latter infections are most often only minor.[8,9] In the current study, microbiologically or clinically documented infection, or both were reported in 59% of the neutropenic episodes where the gram-positive *cocci* were responsible for 54% of the positive cultures and gram-negative *bacilli* were isolated in 39% of positive cultures. These results are comparable with the results of the study carried out by De Pauw et al[10] who reported microbiologically documented infection in about 41% of the neuropenic episodes. Gram-positive *cocci* and gram-negative *bacilli* were responsible for 42% and 24% of the positive cultures. However, Kojima et al[11] reported a higher incidence of the isolated gram-negative organisms (62%) than gram-positive organisms (33%) in their studied neutropenic episodes. The current study included 96 (41%) episodes where neither clinical nor microbiological evidence of infection was detected. Comparable figures were reported by Petrilli et al.[5] These episodes can be grouped under the category of FUO. However, the use of more sophisticated techniques for isolation of the causative organisms (bacteria or fungi or both) was well as estimation of rising titres for various expected viruses may lower the percentage of patients with FUO.[8,9] In children with cancer under treatment by chemotherapeutic agents, the spectrum of the pathogenic micro-organisms causing febrile episodes, as well as the resistance pattern to commonly used antibiotics has changed markedly over the years. This necessitates adequate modifications of the empiric first-line antimicrobial regimen approximately every 3 years.[2] The current study analyzed the type and frequency of bacterial infection and their in-vitro sensitivity pattern during the last 5 years in a pediatric oncology unit in Saudi Arabia. Comparison of our results with those published by other centers in the world has shown many similar, and a few different findings.[10-12] From the current study, we should stress the importance of frequent reviewing of the type, frequency, severity and outcome of infectious complications, in such critically ill patients over the years in order to detect changing epidemiologic patterns. Based on this data, empiric therapy should be continuously modified.

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