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Microbiologically Documented Infection-related Mortality in Children with Acute Leukemia: A Single-center Experience

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Abstract

Infections are a significant cause of morbidity and mortality of chemotherapy-induced neutropenia in children with acute leukemia. The aim of this study was to evaluate microbiologically documented infections (MDIs) during febrile neutropenia (FN) episodes and their relation to mortality. Four hundred eighty-seven FN episodes of 140 children were enrolled in this single-center study, and MDI in those FN episodes was retrospectively examined. Eighty-four patients (60%) had at least one positive peripheral blood, central line, or urine culture. MDIs were detected in 163 of 487 (33.4%) FN episodes of 84 children with leukemia. Gram-negative bacteria, Gram-positive bacteria, and fungal agents were isolated in 52.7%, 40.4%, and 6.9% of whole episodes. Coagulase-negative *Staphylococci* and *Enterococci* were the most detected Gram-positive bacteria. *Klebsiella* spp. and *Escherichia coli* were the most common Gram-negative bacteria isolated in the entire cohort. A central line was present in 145 MDI episodes, and catheter removal was required in 35 cases (17.7%) due to infection with Gram-negative bacteria, Gram-positive bacteria 43%, 28.5%, and fungus 28.5%, respectively. MDI-related mortality was 9.8%. The highest mortality rate (16.7%) was observed in Gram-negative bacteria and patients with relapsed and resistant leukemia. The most common infectious agent related to mortality was *Klebsiella* (31%). Resistance to third- or fourth-generation cephalosporins in Gram-negative bacteria was found to be over 50% of our cohort uri. Empirical antibiotic therapy at the onset of FN in neutropenic patients is crucial; therefore, the institution's predominant pathogens and resistance patterns should guide the choice of empirical antimicrobials. To reduce mortality and morbidity, each center should know its local epidemiological data and antibiotic susceptibility.

Keywords: Acute leukemia, febrile neutropenia, microbiologically documented infection

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Introduction

Febrile neutropenia (FN) is a severe complication of chemotherapy, classified into three groups such as *microbiologically documented infections (MDIs)*, clinically documented infections, and fever of unknown origin, and their incidences were reported as 30-40%, 20%, and 30-40%, respectively.[1-3] Bacteriemia and central line-associated bloodstream infections are the most common complications in patients receiving intensive therapy via a central venous catheter. Although mortality was reduced when using empirical broad-spectrum antibiotics, it has contributed to the evolution of resistant microbiological flora. Resistance to antibiotics is a widespread global problem with a high prevalence of mortality, and the resistance pattern varies between centers and countries.[4] Rapid clinical and microbiological assessments and appropriate antibiotic treatment initiation are the most important steps for these patients. The objective of this retrospective *study* was to appraise the etiology and frequency of *MDIs* during FN episodes in children with leukemia to determine our institutional microbiological *status,* susceptibility, and resistance patterns and to determine MDI-related mortality.

Material and Method

One hundred forty-eight pediatric patients with acute lymphoblastic leukemia (ALL) and 42 pediatric patients with acute myeloid leukemia (AML) were treated in Ankara Children's Health Hematology and Oncology Hospital between January 2012 and December 2014. In total, 487 FN episodes were detected in 140 patients (110 ALL, 30 AML), and MDIs in those FN episodes were retrospectively examined. FN episodes that occurred after hematopoietic stem cell transplantation were excluded. Patients' demographic characteristics, leukemia type, remission/relapse status, treatment protocol and treatment phase, and clinical findings were recorded from electronic files. Peripheral blood culture, port catheter and/or central venous catheter culture, urine culture results, susceptibility and resistance patterns of microorganisms, post-treatment clinical improvement, or death were documented. Analysis was conducted at both patient and episode levels. Routine antibacterial and antifungal prophylaxis except trimethoprim-sulfamethoxazole for *Pneumocystis jiroveci pneumonia* was not used.

FN is described as a single temperature of ≥38.3 °C or a temperature ≥38 °C for 1 h continually, neutropenia is described as an absolute neutrophil count (ANC) of <500 cells/mm³ or ANC expected to decline to <500 cells/mm³ during the next 48 hour.[2] MDIs were defined as positive blood, central line or urine cultures. Each new event in a prior febrile patient with documented MDI was noted as a new episode. Bacteremia was described as the presence of viable bacteria in the bloodstream that indicated a positive blood culture. The same bacterial strain was isolated in both peripheral and central-line cultures collected at the same time, and central-line culture positivity was within 2 h before blood culture positivity was defined as central-line-associated bloodstream infections. For skin flora contaminants such as *Coagulase-negative staphylococci (CoNS)*, *Corynebacterium*, or *Streptococcus* spp., clinical signs of sepsis with two positive blood cultures were considered significant.[3] Polymicrobial bacteremia is defined as more than one microorganism isolated from blood culture within 24 h of the first positive blood culture specimen.

The respiratory tract infection is described as any infectious disease of the upper or lower respiratory tract. Upper and lower respiratory tract infections include pharyngitis/tonsillitis, the common cold, acute rhinosinusitis, laryngitis, and acute otitis media and acute bronchitis, bronchiolitis, pneumonia, and tracheitis, respectively. Gastroenteritis is *inflammation of the lining of the stomach and intestines*. Urinary system (the kidneys, ureters, bladder and urethra) infection is defined as the urinary *tract infection*. Urosepsis is a term used to *describe a type of sepsis that can result from an infection in the urinary tract*.

All patients were admitted for FN episodes and remained hospitalized until antibiotic therapy was completed and neutrophil count recovered. Cultures of both peripheral blood and central line (if present) and urine cultures were collected before the start of antibiotics. Cultures from other sites, e.g., pus swabs and stool cultures, were also performed if any symptoms existed. Cefepime, piperacillin/tazobactam, and cefoperazone/sulbactam were used for the initial treatment of fever and neutropenia. Routine galactomannan antigen and beta-glucan tests for fungal infections were not performed, and empirical antifungal therapy was not administered. If the fever persisted, repeat cultures were collected and antibiotic modification was done, and/or antifungal therapy was started.

The study was approved by the Ethics Committee of Ankara Bilkent City Hospital (decision no: E2-23-5322, date: 25.10.2023).

Statistical Analysis

The IBM SPSS for Windows Version 22.0 package program was used for statistical analyses. Numerical variables were determined by mean ± standard deviation or median (minimum-maximum) values. Categorical variables were demonstrated by number and percentage. Whether there was any difference in categorical variables between the groups was investigated by the chi-square test. The Mann-Whitney U test analyzed the differences between two independent groups in terms of numerical variables. Kruskal-Wallis test was performed for the comparison of more than one independent group. The significance level was taken as $p<0.05$.

Results

Four hundred eighty-seven FN episodes of 140 children with acute leukemia (110 ALL, 30 AML) were studied. *MDIs* were detected in 163 FN episodes (33.4%) in 84 patients. Fifty-eight (69.1%) were ALL, and 26 patients (30.9%) were AML. Most of these patients were in remission (75%); 15% had relapsed or resistant disease. The mean age was 7.9±5.3 years (median:

6.6 years; 6 months-18 years). Fifty-one percent (n=43) of 84 patients with MDI were female. Forty (47.6%) of 84 patients had one MDI episode, 18 patients (21.4%) had two MDI episodes, 19 patients (22.6%) had three episodes, and seven patients (8.4%) had four or more MDI episodes during the study period. A port catheter was in 145 of the 163 MDI episodes.

Peripheral blood, central line, and urine cultures positivity was 20.5% (n=100), 25.2% (n=123), and 6.9% (n=34), respectively. 42.3% (n=69) of episodes had both positive peripheral blood and central line cultures.

Highlights

- Empirical antibiotic therapy at the onset of febrile neutropenia in neutropenic patients is crucial; therefore, the institution's predominant pathogens and resistance patterns should guide the choice of empirical antimicrobials.

Respiratory system infections (28.2%) and gastroenteritis (28.2%) were the most common clinical infection sites through MDIs. Urinary tract infection was detected in 34 cases (20.8%), and five of them had urosepsis. Thirty-three cases had mccositis, and two patients had sinusitis. Infective endocarditis, vulvovaginal abscess, staphylococcal toxic shock syndrome, and cholecystitis were detected in one. Sepsis and septic shock were noted in 13.5% and 3.7%, respectively. No clinical signs were detected in 38% of MDIs.

Gram-negative bacteria, Gram-positive bacteria, and fungal agents were isolated in 52.7% (n=138), 40.4% (n=106), and 6.9% (n=18) of whole episodes, respectively. Peripheral blood or central-line Gram-positive, Gram-negative bacteria and fungus isolations were noted in 48%, 44%, and 8% of events, respectively. The frequency of isolated microorganisms in peripheral blood or central-line cultures is shown in **Table 1**. *CoNS* and *Enterococci* were the most detected Gram-positive bacteria. *Klebsiella* spp. and *Escherichia coli (E. coli)* were the most common Gram-negative bacteria isolated in the entire cohort. Polymicrobial growth was present in 12.8% of episodes. The most frequent organisms isolated from urine culture were extended-spectrum beta-lactamases (ESBL) positive *Klebsiella* (6.7%) and ESBL-negative *E. Coli* (4.3%) and *Pseudomonas aeruginosa* (4.3%) were the other common microorganisms. The other isolated organisms in the centralline were noted as ESBL (+) *E. Coli* (2.5%), *Serratia marcescens* (1.2%), ESBL (-) *Klebsiella* (1.2%), and *Stenotrophomonas maltophilia* (0.6%).

Penicillin resistance was detected in 81.2%, and oxacillin resistance was detected in 66.7% of the Gram-positive bacteria. No glycopeptide or linezolid resistance was observed. Methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococci* were not noted. Resistance to third- or fourth-generation cephalosporins was detected in 53.7% and 51.2% of Gram-negative bacteria, respectively. Carbapenem resistance was 21.5% and quinolone resistance was 38.2%. Colistin resistance was observed in one patient. *Candida* spp. susceptibility and resistance did not analyze in our study. Antibiotic susceptibility rates of microorganisms are shown in **Table 2**.

Catheter removal for catheter-related systemic infections (the presence of bacteremia originating from an intravenous catheter) was required in 35 cases (17.7%) due to infection with Gram-negative bacteria, Gram-positive bacteria, and fungi 43%, 28.5%, respectively).

Complete recovery was observed in 77.9%, and breakthrough infection (*the development of an infection with an organism resistant to prophylaxis)* was observed in 12.3% of MDIs. *MDI*-related mortality was 9.8%. The highest mortality rate (16.7%) was observed with Gram-negative bacteria, mostly *Klebsiella pneumonia*, although it was not statistically significant (p>0.1). Mortality rates were 8.3%, both in Gram-positive and fungal infections. The characteristics of mortality associated with MDIs are shown in **Table 3**. Eighty percent of patients who had mortality had relapsed or refractory disease, and most of them had gastrointestinal infections such as gastroenteritis and thyphilitis.

Discussion

In this single-center retrospective study of MDIs in pediatric patients with leukemia, we demonstrated that 60% of the children with acute leukemia developed at least one MDI during chemotherapy. *MDI* was encountered in 33.4% of FN episodes, and most microorganisms were Gram-negative agents. Although Gram-negative bacteria were more common in the whole cohort, 49.5% of central-line culture isolates were Gram-positive organisms, mostly skin flora bacteria. *Candida* spp. was detected in 15.5% of peripheral and

Table 1.
Microbiologically documented infection agents (blood cultures)

Bacteria	Number	Frequency (%)
Gram-positive	**72**	**48**
Coagulase-negative Staphylococcus	51	34
Staphylococcus aureus	1	0.6
Streptococcus spp.	5	3.3
Enterococcus spp.	10	6.7
Micrococcus	1	0.6
Bacillus licheniformis	1	0.6
Corynebacterium spp.	3	2
Gram-negative	**66**	**44**
Escherichia coli	15	10
Klebsiella spp.	29	19.3
Pseudomonas aeruginosa	9	6
Acinetobacter baumannii	3	2
Enterobacter cloacae	3	2
Moraxella spp	1	0.6
Pantoea agglomerans	1	0.6
Burkholderia cepacia	1	0.6
Fungus	**12**	**8**
Candida albicans	5	3.3
Candida non-albicans	6	4
Trichosporon asahii	1	0.6
Total	**150**	**100**

Table 2.
Antibiotic susceptibility of microorganisms

	Gram (+) n=72		Gram (-) n=95	
	Susceptible	Resistant	Susceptible	Resistant
	n (%)	n (%)	n (%)	n (%)
Penicillin	13 (18.8)	56 (82.1)	-	-
Oxacillin	6 (33.3)	12 (66.7)	-	-
Glycopeptide	71 (100)	0	-	-
Linezolid	71 (100)	0	-	-
Aminoglycosides	-		35 (83.4)	7 (16.7)
Cefotaxime	-		20 (48.8)	21 (51.2)
Ceftazidime	-		25 (46.3)	29 (53.7)
Cephaperasone	-		12 (52.2)	11 (47.8)
Cefepime	-		27 (49.1)	28 (50.9)
Piperacillin	-		32 (55.2)	26 (44.8)
Meropenem	-		51 (78.5)	14 (21.5)
Ciprofloxacin	-		34 (61.8)	21 (38.2)
Colistin	-		14 (93.3)	1 (6.7)

catheter blood cultures, and the most common agent was nonalbicans *Candida* spp.

Studies have emphasized that there is a shift in the prevalence of microbiological infections from Gram-positive bacteria to Gram-negative bacteria, and antimicrobial-resistant strains commonly occur among Gram-negative bacteria isolated from blood.[5] Febrile neutropenic episodes due to Gram-negative organisms are still more common in centers where quinolone prophylaxis and intravenous catheterization are less.[6] Although routine quinolone prophylaxis is not used in our clinic and most of our patients had a central line, Gram-negative microorganisms were noted more frequently (52.7%) in the whole cohort, and the most common microorganisms were *Klebsiella* species (43.9%). The majority of MDIs were bacteria mostly seen in the oral cavity and gastrointestinal tract. The presence of mucositis and gastroenteritis was associated with damaged mucosal barrier integrity and a risk factor for Gram-negative bacteriemia due to the translocation of bacteria across the mucosal barriers.[7] Infectious agents vary from center to center due to the variability of microbial flora in hospitals and communities. *E. coli* and *P. aeruginosa* represent the most common species among the Gram-negatives, and an increasing frequency of *Acinetobacter* spp. and *Stenotrophomonas maltophilia* was also reported.[8]

Despite discontinuation of quinolone-based antibacterial prophylaxis, it was emphasized that the rates of multidrug-resistant Gram-negative strains increased among *Enterobacteriaceae* and nonfermenting Gram-negative rods. In addition, antimicrobial resistance and/or failure of empirical antibiotic therapy have often been associated with a poor outcome in cancer patients with bloodstream infections caused by Gram-negative isolates.[5] Resistance to third- or fourth-generation cephalosporins in Gram-negative bacteria was found to be over 50% of our cohort. Carbapenem resistance was noted in 21.5% and quinolone resistance in 38.2% of MDIs. Carbapenems are therapeutic options often used in clinically unstable patients, so it is important to monitor the colonization of these resistant pathogens. Carbapenem-producing *Klebsiella pneumoniae* is an important cause of hospital-acquired infections, which is the most common and has high mortality among carbapenemase-producing *Enterobacterales*, and this agent represents a fast-growing global threat. The use of carbapenems in patients colonized with such genotypes results in increased carbapenemase-producing *Enterobacteria* in the gastrointestinal tract, resulting in a fourfold increased risk of bloodstream infections.[9] Colistin resistance was observed in one patient. Most of resistant infections were detected in relapsed/refractory or high-risk leukemia patients who received intensive chemotherapy with prolonged neutropenia.

Untreated FN and bacteremia can be lethal within hours after the onset of fever, and fever *should* be considered infectious *until proven otherwise.*[10] Early initiation of broad-spectrum antibiotics in hospitalization and aggressive management of patients with close monitoring have reduced the mortality rates due to FN. *Treatment within the first few hours the following fever will affect success rates.*[11]

Conclusion

Empirical antibiotic therapy is crucial in neutropenic patients when fever first starts; therefore, the *institution's predominant pathogens* and their *resistance patterns should* guide the choice of *empirical* antimicrobials. Thus, patients who do not respond to initial therapy may have the chance to modify their initial empirical treatment. To reduce mortality and morbidity, each center should know its local epidemiological data and antibiotic susceptibility.

Table 3.
Microbiologically documented infections related mortality

No	Age (years)	Diagnosis/risk classification	Remission status	ANC (/mm^3)	Neutropenia duration (day)	Day of hospitalization	Sepsis/septic shock	Clinical manifestation	Microorganism	Resistance
1	5.3	Pre B ALL/ HRG	Relapse	0	3	158	Sepsis	Mucositis	*CoNS* and *Candida albicans*	
2	15.3	Pre B ALL/ HRG	Relapse	100	4	33	Septic shock	*Pneumonia* Typhlitis	*E.coli* ESBL (+)	Cephalosporin, ciprofloxacin resistant
3	0.5	Infant AML/ HRG	Non-remission	400	4	10	-	*Pneumonia* Gastroenteritis	*Micrococcus*	
4	6.7	AML/HRG	Relapse refractory	0	0	23	-	Typhlitis Gastroenteritis	*K. pneumonia* ESBL (+)	Cephalosporin, piperacillin resistan
5	2.8	Pre B ALL/ MRG	Remission	350	17	16	-	*Pneumonia* Intracranial fungal abscess	*Acinetobacter*	Cephalosporin, piperacillin, meropenem resistan
6	12.3	T-ALL/MRG	Relapse refractory	0	17	33	Septic shock	Typhlitis	*K. pneumonia* ESBL (+)	-
7	3.8	Pre B ALL/SRG	Remission	0	25	58	-	*Pneumonia* Gastroenteritis cellulitis	*S. epidermidis*	*Penicillin resistan*
8	14.5	Pre B ALL/ HRG	Relapse refractory	100	64	30	Sepsis	*Pneumonia*	*CoNS*	-
9	18	T-ALL/MRG	Remission	100	4	0	Sepsis	*Pneumonia* Gastroenteritis	*E. coli* ESBL (-)	Ciprofloxacin resistant
10	16	Pre B ALL/ HRG	Relapse refractory	0	9	92	Septic shock	*Pneumonia* Typhlitis	*Acinetobacter* + ESBL (-) *E. coli* + *Enterococcus*	Cephalosporin, piperacillin, meropenem, ciprofloxacin resistan
11	16.5	AMLal	Relapse refractory	200	142	93	-	Fungal Sinusitis *Pneumonia* Gastroenteritis	*K. pneumonia* ESBL (+)	Cephalosporin, piperacillin, meropenem, ciprofloxacin resistan
12	2.5	AML	Relapse refractory	0	7	41	Sepsis	*Pneumonia* Gastroenteritis	*S. epidermidis*	-
13	17.5	AML	Relapse	0	3	43	Septic shock	Vulvovaginal Abscess Gastroenteritis	*P. aeruginosa*	Cephalosporin, meropenem, ciprofloxacin resistan
14	10.5	AML	Non-remission	500	14	34	Septic shock	*Pneumonia* Typhlitis	*K. pneumonia* ESBL (+)	Cephalosporin, piperacillin, meropenem, ciprofloxacin resistan
15	3.5	AML	Relapse refractory	0	17	30	Sepsis	Perianal Abscess Mucositis Gastroenteritis	*K. pneumonia* ESBL (+)	Cephalosporin, piperacillin, meropenem, ciprofloxacin resistan
16	16	AML	Relapse refractory	0	32	17	-	Mucositis *Pneumonia* Gastroenteritis	*K. pneumonia* ESBL (-)	-

ANC; Absolute neutrophil count, SRG; Standard risk group, MRG; Medium risk group, HRG; High-risk group, ALL; Acute lymphoblastic leukemia, AML; Acute myeloid leukemia, CoNS; *Coagulase-negative staphylococci*, ESBL; Extended-spectrum beta-lactamases

Ethical Approval: This retrospective study was approved by the Ethics Committee of Ankara Bilkent City Hospital (decision no: E2-23-5322, date: 25.10.2023).

Informed Consent: Not necessary. Because the study was designed retrospectively no written informed consent form was obtained from the patients.

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