RESPIRATORY VIRAL INFECTIONS IN PEDIATRIC ACUTE LEUKEMIA PATIENTS PRESENTING WITH FEBRILE NEUTROPENIA IN A TERTIARY HOSPITAL IN ANKARA, TURKEY

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Abstract

Background: The prevalence and roles of respiratory viral pathogens in pediatric acute leukemia patients with febrile neutropenia is not well understood and laboratory tests to detect viral agents are not a routine practice in the investigation of these patients.

***Patients and methods*:** The medical records of 50 neutropenic episodes in pediatric acute leukemia patients in the Hacettepe University Children's hospital, Ankara-Turkey, were reviewed. Blood samples were obtained for blood culture, aspergillus antigen and other routine tests. Nasopharyngeal aspirate samples were collected and transferred to the laboratory in a viral transport medium. Therapy for febrile neutropenia was initiated according to our institution's protocols.

Results: Fifty (50) consecutive febrile neutropenic episodes in 44 pediatric ALL and AML patients were included in the study between 1st October 2009 and 31st August 2010.

Microbiologically documented infections were found in 36% of the episodes, clinically documented infections in 16% of the episodes and 48% of the episodes were accepted as Fever of Unknown Origin. Twenty-two percent (22%) of the microbiologically documented infections were due to viral agents, 56 % were due to Gram positive bacteria, 21% were due to Gram negative bacteria (*E. coli)* and only one episode of fungemia was documented.

***Conclusions*:** Fever of Unknown Origin constituted nearly 50% of the febrile neutropenic episodes in this study despite the availability of advanced laboratory diagnostic methods. Among the episodes with microbiologically documented infections, bacterial pathogens were especially common. Presenting complaints like cough and rhinorrhea are not specific to a viral etiology and care should be taken not to miss potentially threatening bacterial pathogens in such episodes.

Key Words: Acute leukemia, febrile neutropenia, children, nasopharyngeal aspirate, Polymerase Chain Reaction

Introduction

Acute leukemia is the most common cancer encountered in children and is a leading cause of death in this population [1,2]. One of the severe complications encountered during the management of acute leukemia in children is febrile neutropenia (FN) which often leads to delay and or suspension of much needed chemotherapy protocols [3]. This is due in part to the ever-emerging new and potent chemotherapeutic agents, which, while bringing the primary disease under control, also lead to severe and prolonged suppression of the bone marrow. Patients with hematological malignancies frequently develop fever associated with neutropenia, which is a leading cause of morbidity and mortality in these groups of patients [4]. Previous reports on this topic show that about 30 – 60% of febrile neutropenic episodes have an infectious etiology, with the focus mostly on bacterial and fungal pathogens and very little on viral pathogens [5-7].

Respiratory viruses are a common cause of morbidity in children[8] and thus may be significantly involved in the pathogenesis of FN among this group. Previous studies using real time Polymerase Chain Reaction (PCR) analyses have reported the detection of respiratory viruses in the nasopharynx in 44 – 57% of childhood febrile neutropenia cases [9,10].

Although respiratory viruses are a common cause of self-limiting febrile infections in healthy children, their frequency and significance in the neutropenic child with fever is not well appreciated [11]. Very few studies have explored the viral etiologies of FN [11,12] while much more research studies rather focused on the bacterial etiologies within this setting [13].

This prospective study was conducted to evaluate the frequency of respiratory viral pathogens and their roles in FN encountered in pediatric acute leukemia patients managed in a tertiary institution.

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Patients and Methodology

Study Group

Children 18 years old or younger who were diagnosed of Acute Lymphocytic Leukemia (ALL) or

Acute Myeloid Leukemia (AML) and routinely received chemotherapy and other immunosuppressive agents at the Pediatric Hematology Division of the Children's Hospital, Hacettepe University Faculty of Medicine, were evaluated for inclusion into the study when they developed FN. Patients who developed FN while on admission in the hospital were excluded from the study because of the risk of pathogen exposure and change in flora. The study was conducted between 1st October 2009 and 31st August 2010 and it was approved (approval number: 09/123-22) by the Internal Reviews Board of Hacettepe University Faculty of Medicine, Ankara, Turkey. Consent to participate was obtained from parents and/patients.

The hospital records of all patients were reviewed for demographic information, underlying malignancy, duration of follow-up, stage of chemotherapy protocol, relapse of disease, duration of neutropenia, interval since the last chemotherapy, number of previous neutropenic episodes and Granulocyte- Colony Stimulating Factor (G-CSF) use. Detailed history of the current febrile neutropenic episode including duration of fever before presentation to hospital, maximum temperature, associated respiratory symptoms like cough, runny nose, eye discharge and rashes and a family member with symptoms of upper respiratory tract infection in the last week was documented. All FN episodes were managed as inpatients according to standard guidelines and the study institution's protocols.

Data Collection techniques

Peripheral and central line blood cultures were collected into BACTEC PED. Plus^{R} bottles following standard sterilization precautions and incubated in BACTEC^{R} automatic reading machines in the central microbiology laboratory of the study institution. Samples that did not produce a positive signal at the end of the tenth day of incubation were considered negative for microbial agents. Nasopharyngeal aspirates were obtained by placing a thin nasogastric tube into the patient's nostril and irrigating with normal saline. Samples were transferred to the laboratory in a viral transport medium within 48 hours according to manufacturer's guidelines, where the Seeplex^{R} Respiratory Pathogen 18-plex kit was used for detection of viral pathogens by the multiplex PCR method. Aspergillus galactomannan antigen was detected using the Platelia^{R} Enzyme Immunoassay. The Cut-off value was 0.5 ng/ml.

The vital signs of the patients and complications due to infection or antibiotic therapy were monitored after admission, per inpatient management guidelines of the study institution, and further laboratory analysis such as repeat blood cultures were performed based on clinical course of individual patients.

Definitions

For this study, **neutropenia** was defined as Absolute Neutrophil Count (ANC) of < 1000/mm^3 or between 1000-1500/mm^3 but expected to fall below 1000/mm^3 within 48 hours [14]; and **fever** was defined as a single axillar measurement of 38.5^{o}C or 2 or more measurements within 4 hours of body temperature > 38^{o}C[15,16].

Statistical analysis

The data obtained from this study was evaluated using the SPSS 15.0 for Windows (SPSS Inc, Atlanta, USA) packet program. The results were analyzed and presented in tables as counts, frequencies, means and percentages. Initially univariate analysis was used to test for significance. Non parametric variables were also evaluated with the Mann-Whitney U test. P values less than 0.05 was considered statistically significant for each of the variables analyzed.

Results

*Distribution of the study group***:**

One hundred and three (103) children with acute leukemia were managed at the Division of Pediatric Hematology of the institution during the study period. Out of these, 44 patients and 50 consecutive FN episodes were included in the study. Table 1 shows the demographic and baseline characteristics of all the episodes. The age and sex distribution of the FN episodes were similar to the general patient population managed in the division of Pediatric Hematology. 88 % of the acute leukemia patients in the division had ALL, while 68 % of the FN episodes were also ALL patients. There was an indwelling central venous line in 98 % of the episodes. Four (4) patients had 2 FN episodes and one had 3 episodes during the study period. About 90 % of the episodes developed FN within 15 days of the last chemotherapy.

Thirty-six percent (36%) of the FN episodes in this study was classified as microbiologically documented infections. Bacteremia was the cause of all the microbiologically documented infections and Gram positive bacterial pathogens constituted about 60% of the isolated pathogens. Coagulase negative *Staphylococcus spp.* were the most commonly isolated Gram positive bacteria and *E. coli* was the most common Gram negative bacteria isolated in culture-positive episodes (Table 2). Seventy-five percent (75%) of the respiratory viral agents detected by the multiplex PCR method were due to Influenza A. Twenty-six percent (26 %) of the cases were classified as clinically documented infections while 48 % were classified as fever of unknown origin (FUO). Out of the 11 FN episodes with mucositis at presentation, *E. coli* was isolated in the blood cultures of 2, *Methicillin Resistant Staphylococcus Epidermidis(MRSE)* in 1 and *Streptococcus spp.* in 1 episode.

Table 1: Demographic and baseline characteristics of patients with FN

Characteristics	Patients managed in the hematology division; n (%)	Patients with FN; n (%)
Sex Female Male	 38(37) 65(63)	 14(32) 30(68)
Mean age(years)	9,5	8,9
Underlying malignancy ALL AML	 91(88) 12(12)	 34(68) 16(32)
Central venous catheter Present Absent	 - -	 49(98) 1(2)
Relapse patients		13 (26)
Recurrent episodes of FN		5 (10)
Mean interval since last chemotherapy (days)		8,5

Table 2: Etiological classification of FN episodes.

Classification	n (%)
Microbiologically documented infection	18 (36.0)
Bacteremia	
- *MRSE*	6 (28.0)
- *MSSE*	2 (11.0)
- *Streptococcus spp.*	1 (6.0)
- *E. coli*	3 (15.0)
- *Acinetobacter spp.*	1 (6.0)
- *Salmonella spp.*	1 (6.0)
- *Candida* spp.	1 (6.0)
Viral PCR (nasopharyngeal aspirate)	
- Influenza A	3 (16.0)
- Human Rhinovirus	1 (6.0)
Clinically documented infections	13 (26.0)
FUO	24 (48.0)

Twenty-six percent (26%) of the FN episodes had runny nose and 38% had cough as an associated symptom at presentation. Mucositis was detected in 22% and respiratory distress in 4% of the episodes at initial evaluation. All the episodes for which a viral agent was detected by the multiplex PCR had at least a cough or runny nose, which are frequent in viral respiratory infections, at presentation. Among the culture-positive episodes, 8 (47 %) had at least one of these symptoms at presentation as shown in Table 3.

Table 3: Frequency of cough and rhinorrhea in viral PCR and blood culture-positive and negative episodes of FN.

	Viral PCR		Blood culture	
	(+)	(-)	(+)	(-)
Rhinorrhea (n)	2	5	6	5
Cough (n)	3	9	5	11

Statistically, there was no difference in the duration of fever (mean 12.7 versus 4.2 days, p=0.085) and the duration of antibiotic therapy (mean 22 versus 13.7 days, p=0.075) between the viral PCR positive episodes and the culture-positive episodes. However, as shown in Table 4, there was clearly a numerical difference between the 2 groups with the duration of fever and of antibiotic therapy, tending to be shorter in the culture-positive FN episodes. There were also no significant differences in mean previous neutropenic episodes (p=0.600), ANC at presentation (p=0.650), mean age (p=0.150), duration of neutropenia (p=0.100) and the frequency of antibiotic modification (p=0.240) among the group with microbiologically documented infections in a univariate analysis (Table 4).

Table 4: Comparison of FN episodes according to the microorganisms isolated

	Viral PCR positive (n=4)	Culture-positive (bacterial pathogens) (n=14)	Other (n=1)	P value
Mean neutropenic episodes (days)	4.5	2.6	2.0	0.600
Mean age (years)	10.0	7.6	7.0	0.150
Underlying malignancy				
ALL	1	10	1	NA
AML	3	4	0	NA
Central line (%)	50	100	100	NA
Symptoms at presentation(n)	2.0	4.0	1,0	0.580
ANC (/mm^3) at presentation	250	250	600	0.650
Mean CRP level (mg/L)	10.1	14.0	-	0.125
Mean duration of neutropenia (days)	3.6	6.6	5.0	0.100
Mean fever duration (days)	12.7	4.2	1.0	0.085
Antibiotic modification (n)	6.0	17.0	1.0	0.240
Mean length of stay and duration of treatment	14.5	11.8	-	0.814

Discussion

Infectious complications are an important cause of morbidity and mortality in pediatric cancer patients. It often leads to delays and/or suspension of chemotherapy protocols [3]. Despite the advancements in medicine, inpatient management is still the mainstay for acute leukemia patients with FN.

Bacteria are the most common microbial agents isolated in FN patients but with prolonged fever, the risk of fungal infections increase [17]. However, despite the advanced microbiological culture techniques available, bacterial pathogens are only isolated from 1/3 of all FN episodes and in 1/5 of episodes infections can only be documented clinically [18].

Most previous studies conducted on the etiology of FN have focused more on bacterial pathogens [19,20]. There are however, few studies in the literature investigating viral agents as an etiologic cause in FN and in most centers laboratory investigations for viral agents is not a routine practice [12,21,22].

In this study viral agents were isolated in 8% of all FN episodes and in 22% of all microbiologically documented infections. This incidence is similar to other studies in the literature [23,24]. In the study carried out by Hakim et al [24] viral agents were isolated in 33% of episodes and it was 14% in the study by Castagnola et al [23]. Differences between studies could be due to the patient population included in the study and also the methods used to detect the viral agents. Some studies, like the present one, use only the viral PCR while others use antigen detection techniques, viral culture or more than one method on different body fluids [11,24]. Beside, this study only investigated respiratory viral pathogens.

In previous studies, Respiratory Syncytial Virus (RSV) and human rhinovirus were the most common viruses that were isolated [25,26] but in this study Influenza A was the most common (2 pandemic H1N1, 1 seasonal influenza A). This result could be due to the H1N1 pandemic that was encountered in the winter of 2009 when this study was conducted. Another probable explanation may be that our patients were older (mean age 9.5 years) and the incidence of RSV infections decreases with increasing age [16]. The 2 patients with H1N1 pandemic influenza A were both treated with oseltamivir. The first patient became afebrile after the second day of treatment and was discharged on the 5th day of admission. The second patient had respiratory failure, was intubated and managed with ventilator support but he died on the 19th day of admission. Oseltamivir is a neuroaminidase inhibitor used for influenza A chemoprophylaxis and the treatment of uncomplicated infections but there are very limited second line medications for patients whose respiratory symptoms worsen [27]. There are a couple of uncontrolled studies and case reports that show that Ribavrin could be effective as a second line medication but treatment should be started early in the course of the infection to be effective [28].

Generally viral infections are considered first, as a possible diagnosis, in patients presenting with fever, cough, runny nose and rashes [16,25,26]. However, we have demonstrated in this study that these signs and symptoms may be encountered in both viral and bacterial infections or even in patients with FUO. Hence, the sensitivity of these findings is high but specificity is low and clinicians must be cautious not to miss potentially threatening bacterial infections in this setting.

Bacteremia was the single most common cause of infection in the microbiologically documented infection episodes and Gram positive bacteria were the most commonly isolated organisms from blood cultures. The pathogen shift from Gram negative to Gram positive bacteria has been demonstrated in many studies carried out in recent years [29,30]. Possible reasons cited for this shift include increased use of indwelling central venous

lines, high dose cytarabine chemotherapy protocols, use of proton pump inhibitors and wide spread use of quinolone prophylaxis [29,31]. 98% of the patients in the present study had indwelling central venous lines. The most common Gram positive and Gram negative bacteria isolated from blood cultures in this study were coagulase negative staphylococcus *and E. coli* respectively which is consistent with previous studies [32]. Blood cultures of patients with oral mucositis are more likely to yield Gram positive bacterial pathogens but in this study both pathogens were equally represented [6].

Although not pathognomonic, it is known that fever lasts longer and the C-reactive Protein (CRP) levels in viral infections are lower when compared to bacterial infections [33] but there was no significant difference between the viral PCR positive and the culture-positive bacterial infections in this study, when these two parameters were considered (mean 10.1/14.0 mg/L, p=0.125, table 4). However, it is noteworthy that CRP level was numerically higher in the bacterial episodes (14.0 mg/L as against 10.1 mg/L) and probably did not reach significance levels because of the small sample size. In our center and in many other centers, even in cases where no bacterial etiology is demonstrated, one of the most important factors determining the duration of antibiotic treatment is the duration of fever as seen clearly in this study.

The rates of FN episodes classified as FUO differ from one study to another [20,34]. In the study by Castagnola et al., 79% of the episodes were classified as FUO while in the study by Arrifin et al., 56% of episodes were classified as FUO [24,35]. In this study 48% of the episodes were classified as FUO.

Differences in given rates are due in part to the time that the diagnosis of FUO is made. Patients often present with fever as the only symptom and if diagnosis is made during the initial presentation, it might lead to increase FUO episodes [36]. Episodes of FN that are classified as FUO may be due to viral or other atypical microorganisms that are not detected with available laboratory techniques.

The duration of antibiotic treatment and hospital stay in this study was approximately 3 days longer in the FUO group (mean 14,5/11,8 days, table 4). This difference was however not statistically significant in a univariate analysis (p=0.814). We attributed this to the limited number of cases in this study but our observation is that clinicians are inclined to treating patients in the hospital until they are afebrile. It could be said that even when no focus of infection is documented, the duration of antibiotic therapy depends on duration of fever.

Conclusions

FUO constituted nearly 50% of the FN episodes in this study despite the availability of advanced laboratory diagnostic methods. Among the episodes with microbiologically documented infections, bacterial pathogens were especially common (77% as against 22% for viral agents). Wide spread use of central venous lines increases the risk of Gram positive bacterial infections. Presenting symptoms like cough, runny nose and rashes are not specific to a viral etiology and clinicians should be careful not to miss potentially threatening bacterial pathogens in this group of patients.

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