



The Cost Effectiveness of the Respiratory Virus Panel in Childhood Febrile Neutropenia

Çocukluk Çağı Febril Nötropenisinde Solunum Virüsü Panelinin Maliyet Etkinliği

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Abstract

Aim: The aim of this study is to analyze the clinical utility and cost of the respiratory virus panel test in the febrile neutropenia (FN) episode in children undergoing chemotherapy.

Material and Method: From 2014 to 2018, 180 episodes of FN in 93 children with cancer were retrospectively analyzed. The patients were divided into those with (Group A) and without respiratory virus panel (Group B). The demographic and clinical features and cost analysis of the groups A and B were noted.

Results: Of these FN episodes, 46 were in Group A (25.5%) and 134 were in Group B (74.5%). We found positivity in 45 (97.8%) of 46 episodes in Group A. While treatment modification was required in 14 FN episodes (30.4%) in Group A, modification was required in 35 FN episodes (26.1%) in group B. The difference was not statistically significant ($p=0.570$). In Group A, only 5 (10.8%) were modified according to the respiratory virus panel. The respiratory virus panel prices were \$72.43 (interquartile range, \$38.8). The ratio of respiratory virus panel cost to the total cost was 9.67% (interquartile range 11.6). The median total cost of group A was \$663.18 (interquartile range, 850.1), while that of group B was \$596.24 (interquartile range, 723.81). The difference was not statistically significant ($p=0.141$).

Conclusion: The respiratory virus panel may contribute to the preference of antibiotics by giving rapid results in FN attacks. However, no effect on modification rates was observed, and only a small percentage of patients underwent antibiotic modification according to respiratory virus panel.

Keywords: Febrile neutropenia, respiratory virus panel, children

Öz

Amaç: Bu çalışmanın amacı, kemoterapi alan çocuklarda febril nötropeni (FN) atağında respiratuar virüs panel testinin klinik faydasını ve maliyetini analiz etmektir.

Gereç ve Yöntem: 2014-2018 yılları arasında kanserli 93 çocukta 180 FN epizodu retrospektif olarak analiz edildi. Hastalar solunum virüsü paneli olanlar (Grup A) ve olmayanlar (Grup B) olarak ikiye ayrıldı. Grup A ve B'nin demografik ve klinik özellikleri ile maliyet analizleri not edildi.

Bulgular: Febril nötropeni ataklarının 46'sı Grup A'da (%25,5) ve 134'ü Grup B'de (%74,5) idi. Grup A'da yer alan 46 epizodun 45'inde (%97,8) pozitiflik saptadık. Grup A'da 14 FN atağında (%30,4) modifikasyon gerekirken, B grubunda 35 FN atağında (%26,1) modifikasyon gerekti. Aradaki fark istatistiksel olarak anlamlı değildi ($p=0,570$). Grup A'daki 46 FN atağından sadece 5'inde (%10,8) solunum virüsü paneline göre tedavisi modifiye edildi. Solunum virüsü paneli fiyatları 72,43\$ (çeyrekler arası aralık, 38,8). Medyan solunum virüsü paneli maliyetinin toplam maliyete oranı %9,67'dir (çeyrekler arası aralık 11,6). Grup A'nın medyan toplam maliyeti 663,18\$ (çeyrekler arası aralık, 850,1), B grubunun maliyeti ise 596,24\$ (çeyrekler arası aralık, 723,81). Fark istatistiksel olarak anlamlı değildi ($p=0.141$).

Sonuç: Solunum yolu paneli FN ataklarında hızlı sonuç vererek antibiyotik tercihi katkı sağlayabilir. Bununla birlikte, modifikasyon oranları üzerinde herhangi bir etki gözlenmedi ve hastaların sadece küçük bir yüzdesine solunum yolu paneline göre antibiyotik modifikasyonu uygulandı.

Anahtar Kelimeler: Febril nötropeni, solunum yolu paneli, çocuk



INTRODUCTION

Febrile neutropenia (FN) is one of the most common emergency in children with cancer undergoing chemotherapy.^[1] In the last two to three decades, our knowledge about antibacterial and antifungal treatments in FN has increased considerably.^[2-7] There is less experience of viral infections than with bacterial or fungal infections on FN. Unfortunately, the proven and possible infection rates in children receiving chemotherapy are low. In a study of 337 FN episodes, the proven infection rate was 25% and the probable infection rate was 22%.^[8] In this study, proven infection was detected in 86 episodes. Bacteria were detected in 41 of these, viruses were detected in 29 episodes and fungi were detected in 2 episodes. In children undergoing chemotherapy, the bacteria frequently isolated in the proven infections are viridans streptococci, *Pseudomonas* spp., and *Escherichia coli*.^[8] Virus agents constitute 34% of proven infections. The viruses that have been detected relatively frequently in children receiving chemotherapy are respiratory viruses, herpes simplex virus, and varicella-zoster virus.^[9-16]

Respiratory infections are one of the important health problems in both developed and developing countries. Particularly in children younger than five years of age, viral infections are frequent, its contribution to mortality rates due to acute respiratory tract infections and their complications was found to be 25-33%.^[17] In this study conducted in 108 pediatric cancer patients receiving chemotherapy, nasopharyngeal aspirate was analyzed with the "RNA Virus Mini Kit" in 219 episodes. Acute viral respiratory infection was detected in 39.1% of these episodes.^[17]

In this study, it was aimed to analyze the clinical utility and cost of the respiratory virus panel test in the febrile neutropenia episode in children undergoing chemotherapy.

MATERIAL AND METHOD

From 2014 to 2018, 183 episodes of FN in 93 children with cancer were retrospectively analyzed. The reason why it was preferred in this period was that the respiratory virus panel was mostly performed in this period. The written consent forms were not obtained from the guardians of all participants. The Declaration of Helsinki and principles of Good Clinical Practice was compiled in this study. Permission for this study was obtained from Selçuk University Faculty of Medicine, Local Ethics Committee with the number 2021/02 dated 27.01.2021.

The definition of febrile neutropenia was made as follows:

- Fever
 - A single oral temperature $\geq 38.3^{\circ}\text{C}$, or
 - An oral temperature $\geq 38.0^{\circ}\text{C}$ sustained for > one hour
 - An oral temperature $\geq 38.0^{\circ}\text{C}$ occurs twice within a 24-hour period
- Neutropenia
 - An absolute neutrophil count $< 500/\text{mm}^3$, or
 - An absolute neutrophil count $< 1000/\text{mm}^3$ and expected to decrease to $< 500/\text{mm}^3$ over the subsequent 48 hours

At the time of FN diagnosis, the patients were divided into those with (Group A) and without respiratory virus panel (Group B).

The patients' demographic features (age, gender, and diagnosis), clinical and laboratory findings at the diagnosis of FN episodes, preferred antimicrobial agents, whether antimicrobial agent modification was made, if it was done, which antimicrobial agent was preferred, the preferred antimicrobial advertisement respiratory virus panel were noted. Also, cost analysis of these FN episodes was made. The total cost (service + drug + material) and the price of the respiratory virus panel were recorded at the discharge of the patient's hospitalization. The total cost and the price of the respiratory virus panel were converted into US dollars at the daily rates of the Central Bank of the Republic of Turkey.

A nasopharyngeal swab sample was taken from the nostril for the respiratory virus panel. During these years, Real-Time PCR-based kits from different companies were used to detect respiratory pathogens in our hospital.

Statistical analysis

IBM Statistical Package for Social Sciences 21.0 software (IBM Corporation, Armonk, NY, USA) was used for the statistical analysis in this study. Frequency and percentage values were used for nominal variables. For continuous variables, mean and standard deviation values were given if the distribution was normal, and the median and minimum and maximum values were given if the distribution was not normal. In the comparison of nominal variables, Chi-square or Fischer-Exact tests were used depending on whether they met the necessary assumptions. The continuous variables were compared with Student's T test or Mann Whitney U test according to whether they met the necessary assumptions. A two-tailed P-value of <0.05 was considered statistically significant.

RESULTS

In this period, 180 FN episodes in 93 children with cancer were included in this study. The demographic characteristics and diagnoses of the patients are given in **Table 1**. The patients' age ranged from one month to 17 years old (median, 7 years). Considering the gender distribution of the patients, 52 patients (56%) were male and 41 patients were female (44%). The most common tumors were central nervous system tumor (n: 19, 20.4%), malignant bone tumor (n: 19, 20.4%), neuroblastoma (n: 15, 16.1%), and rhabdomyosarcoma and other soft-tissue sarcomas (n: 15, 16.1%).

Of these FN episodes, 46 were in Group A (25.5%) and 134 were in Group B (74.5%). Demographic and clinical characteristics, and cost characteristics of Groups A and B are given in **Table 2**. It was determined that 31 (67%) of the respiratory virus panel were obtained at the time of admissions of the FN episode, and 15 (33%) during the follow-up of the FN episode. We found positivity in 45 (97.8%) of

46 patients in Group A. While oropharynx hyperemia was detected in 19 episodes (41.3%) in Group A, it was detected in 34 episodes (25.4%) in Group B. The difference was statistically significant ($X^2(1)=4.184, p=0.041$). While pneumonia findings were detected in 4 episodes in Group A, they were detected in 8 episodes (6%) in Group B. The difference with the Fischer Exact test was not statistically significant ($p=0,506$). There was no statistical difference between the groups in terms of duration of fever and duration of neutropenia (p values were 0.707 and 0.324, respectively).

Table 1. The patients' demographic and clinic features

Features	n, (%)
Median age, (minimum-maximum values)	7 year, (1 month – 17 years)
Gender	
Male	52, (56%)
Female	41, (44%)
Diagnosis	
Central nervous system tumor	19, (20.4%)
Malignant bone tumors	19, (20.4%)
Ewing sarcoma	15, (16.1%)
Osteosarcoma	4, (4.3%)
Neuroblastoma	15, (16.1%)
Rhabdomyosarcoma and other soft-tissue sarcomas	15, (16.1%)
Lymphomas	12, (13%)
Non-Hodgkin lymphoma	11, (11.9%)
Hodgkin lymphoma	1, (1.1%)
Renal tumors	4, (4.3%)
Germ cell tumor	4, (4.3%)
Retinoblastoma	4, (4.3%)
Langerhans cell histiocytosis	1, (1.1%)

Table 2: The demographic and clinical features and cost characteristic of the groups A and B

	Group A	Group B	P values
Mdn age year, (minimum-maximum values)	7 (0.1-16)	7 (0.3-17)	0.411
Duration of fever, days	2 (1-12)	2 (1-26)	0.707
Duration of neutropenia, days	4 (1-12)	5 (1-17)	0,324
Modification			0.570
No	32 (69.6%)	99 (73.9%)	
Yes	14 (30.4%)	35 (26.1%)	
Mdn total cost (\$), IQR	663.18 (850.1)	596.24 (728.81)	0.141

Mdn: median, IQR: interquartile range

While modification of treatment was required in 14 FN episodes (30.4%) in Group A, modification was required in 35 FN episodes (26.1%) in group B. The difference was not statistically significant ($X^2(1)=0.322, p=0.570$). Of the 46 FN episodes in Group A, only 5 (10.8%) were modified according to the respiratory virus panel. In these modifications, clarithromycin (n=2), azithromycin (n=1), sulfamethoxazole trimethoprim (n=1) or oseltamivir (n=1) were added to the antibiotics of the patients.

The microorganisms detected in the respiratory virus panel taken at the time of admission and during the episode are in **Table 3.**

Table 3: Detected microorganisms on the respiratory virus panel

Respiratory Pathogens	At admission	At follow-up period	Total
Virus	24	15	39
Influenza virus	4	3	7
Influenza A	1	2	3
Influenza B	3	1	4
Parainfluenza virus	1	2	3
PIV 1	1	1	2
PIV 2	0	1	1
Respiratory syncytial virus	4	6	10
RSV A	2	3	5
RSV B	2	3	5
Rhinovirus	10	3	13
Coronavirus	3	2	5
CoV 229E	1	1	2
CoV NL63	1	0	1
CoV HKU	1	0	1
Adenovirus	2	0	2
Bacteria	23	7	30
<i>Staphylococcus aureus</i>	8	2	10
<i>Streptococcus pneumoniae</i>	4	2	6
<i>Haemophilus influenzae</i> spp.	5	1	6
<i>Moraxella catarrhalis</i>	6	0	6
<i>Mycoplasma pneumoniae</i>	0	1	1
<i>Chlamydia pneumoniae</i>	0	1	1

Cost features

The respiratory virus panel prices in episodes were \$72.43 (interquartile range, \$38.8). The ratio of the respiratory virus panel cost to the total cost was 9.67% (interquartile range 11.6). The median total cost of group A was \$663.18 (interquartile range, 850.1), while that of group B was \$596.24 (interquartile range, 723.81). Mann Whitney U test showed that the difference was not statistically significant ($p=0.141$).

DISCUSSION

Today, the success of treatment in childhood malignant diseases has increased significantly. Developments in other treatment approaches, especially chemotherapy, and developments in supportive treatments have an important place in this increase in survival. Especially with more intensive chemotherapy applications, there is an increase in the frequency of infection. In children with malignant disease, infection is an important cause of morbidity and mortality. In these patients, FN is one of the most common oncological emergencies. Bacterial infections in children with FN episode have been successfully treated with the use of empirical antibiotic therapy. However, other microorganisms, especially fungal infections, started to come to the forefront as a cause of morbidity and mortality in these patients.^[1-3]

Clinically defined infections are seen in 20-30% of FN episodes and only 10-30% of FN cases can be documented microbiologically.^[3] Studies showing the role of viruses in the FN episode are few.^[17-19] Different rates of virus have been

detected in children with FN. However, the problem here is that it is not known whether these microorganisms are the real cause of infection. Viral study in FN attack, although not a routine study, should be considered in some circumstance: (i) seasonal viruses including especially respiratory syncytial virus, influenza and enterovirus; and (ii) Herpes simplex virus seen in children with mucocutaneous lesions. Since late 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing was routinely administered to these children.^[3,20]

Respiratory infections have an important place in FN studies investigating viruses. Since the respiratory viral panel is usually performed with real-time PCR-based tests, an expensive test, the issue to be considered is cost-effectiveness. In the study of Aydın-Koker et al.^[17] 108 pediatric cancer patients receiving chemotherapy, nasopharyngeal aspirate was analyzed in 219 episodes. They found the acute viral respiratory positivity rate to be 39.1%. The most frequently detected viruses are human rhinovirus, parainfluenza 3 and respiratory syncytial virus. The authors commented that viral upper respiratory tract infections do not increase mortality in cancer patients, but cause significant delays in chemotherapy, which may have an indirect effect on patient survival rates. In the study, the prevalence and clinical outcomes of respiratory viral infection in patients with cancer and FN episodes by Meena et al.^[19] were investigated. The authors found a high prevalence of respiratory viral infection in this patient group. They also determined that the number of days with fever and the duration of antibiotic use were prolonged. In the study of Shinn et al.^[21] respiratory viral panel positivity and the outcomes of this positivity such as length of hospital stay or intensive care unit and death were examined. The authors emphasized that respiratory viral panel positivity during febrile neutropenia does not impact length of hospital stay or intensive care unit. They also commented that the question of whether respiratory viral panel testing contributes to clinical treatment in this population remains unanswered. In the study of Büyükkapu-Bay et al.^[22] they examined 72 episodes in 48 children with cancer. The most common microorganisms were rhinovirus, respiratory syncytial virus, and coronavirus. They used oseltamivir in their patients with whom they had influenza. In their comments, they mentioned that respiratory viral panel test may not be cost-effective for children with cancer and FN, because it would not alter the duration of hospitalization.

In our study, we detected positivity in 45 of 46 episodes in which respiratory viral panel testing was performed. The high rate of this rate can be explained by performing respiratory viral panel only in selected patients in this period. However, the interesting thing was that although the rates of antibiotic modification were slightly higher in Group A, the difference was not statistically significant. Another important finding of ours is modification according to respiratory viral panel in only 6 episodes in Group A. In these modifications, clarithromycin,

azithromycin, trimethoprim-sulfamethoxazole or oseltamivir were added to the antibiotics of the patients. Although the difference was not statistically significant, the cost of patients who underwent SVP testing was higher and the ratio of respiratory viral panel to total bill was 9.67%.

CONCLUSION

The respiratory virus panel may contribute to the preference of antibiotics by giving rapid results in FN attacks. However, no effect on modification rates was observed, and only a small percentage of patients underwent antibiotic modification according to respiratory virus panel.

ETHICAL DECLARATIONS

Ethics Committee Approval: Permission for this study was obtained from Selçuk University Faculty of Medicine, Local Ethics Committee with the number 2021/02 dated 27.01.2021.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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