

# Respiratory Viruses in Febrile Neutropenic Patients with Respiratory Symptoms

## Abstract

**Background:** Respiratory infections are a frequent cause of fever in neutropenic patients, whereas respiratory viral infections are not frequently considered as a diagnosis, which causes high morbidity and mortality in these patients. **Materials and Methods:** This prospective study was performed on 36 patients with neutropenia who admitted to hospital were eligible for inclusion with fever (single temperature of  $>38.3^{\circ}\text{C}$  or a sustained temperature of  $>38^{\circ}\text{C}$  for more than 1 h), upper and lower respiratory symptoms. Sampling was performed from the throat of the patient by the sterile swab. All materials were analyzed by quantitative real-time multiplex polymerase chain reaction covering the following viruses; influenza, parainfluenza virus (PIV), rhinovirus (RV), human metapneumovirus, and respiratory syncytial virus (RSV). **Results:** RV was the most frequently detected virus and then RSV was the most. PIV was not present in any of the tested samples. Furthermore, no substantial differences in the distribution of specific viral species were observed based on age, sex, neutropenia duration, hematological disorder, and respiratory tract symptoms and signs ( $P > 0.05$ ). **Conclusion:** Our prospective study supports the hypothesis that respiratory viruses play an important role in the development of neutropenic fever, and thus has the potential to individualize infection treatment and to reduce the extensive use of antibiotics in immunocompromised patients with neutropenia.

**Keywords:** Fever, neutropenic patients, respiratory viruses

## Introduction

Fever is a common problem in neutropenic patients and associated with nonmalignant morbidity and mortality in these patients.<sup>[1]</sup> Respiratory infections are a frequent cause of fever in neutropenic patients with high morbidity and mortality rate. In these patients, bacterial and fungal agents are common lower respiratory tract infections, whereas respiratory viral infections are not frequently considered as a diagnosis.<sup>[2,3]</sup> However, influenza infection may occur among neutropenic patients, especially during influenza season, with high rates of fatality, such as general population, and the clinical presentation of a viral infection is often not specific in neutropenic patients.<sup>[4,5]</sup> Moreover, in stem cell transplantation patients, viruses are recognized to frequently cause posttransplant fever such as cytomegalovirus and herpesvirus.<sup>[6-9]</sup>

Since polymerase chain reaction (PCR) has been introduced, a revolution in the diagnosis

of viral infections has been occurred. PCR has highly sensitivity in detection of respiratory viruses, including those that cannot, or are difficult, to culture.<sup>[10-12]</sup> In patients with neutropenia, PCR has shown to have more sensitivity than viral culture,<sup>[9,13]</sup> but these studies did not mention viral prevalence during neutropenic fever. This study was designed to evaluate the prevalence of respiratory viruses including influenza, parainfluenza virus (PIV), rhinovirus (RV), metapneumovirus, and respiratory syncytial virus (RSV) in throat samples of febrile neutropenic patients with respiratory symptoms.

## Materials and Methods

### Procedure

This prospective study was performed to evaluate the prevalence of respiratory viruses in patients with neutropenia who admitted to hospital were eligible for inclusion with fever (single temperature of  $>38.3^{\circ}\text{C}$  or a sustained temperature of  $>38^{\circ}\text{C}$  for more than 1 h), upper and lower respiratory symptoms including

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frequent cough, nasal congestion, rhinitis, itchy throat, sore throat, rapid breathing, or dyspnea, and neutrophil count below  $1500/\text{mm}^3$  at presentation. Patients with existence obvious focus of infection in the investigation were excluded from the study. Participants were recruited between August 2014 and December 2014 from Omid Hospital in Isfahan in Iran. All patients who were hospitalized for upper respiratory symptoms and fever with neutropenia diagnosed by resident of infectious disease specialists during this time were eligible for participation. Thirty-eight cases selected based on inclusion and exclusion criteria, two of them not participate in the study. The study received ethics approval from the relevant institutional review committees, and all participants gave written informed consent.

Sampling was performed from the throat of the patient by the sterile swab. All materials were analyzed by quantitative real-time multiplex PCR covering the following viruses; influenza, PIV, RV, human metapneumovirus (hMPV), and RSV. Physicians were not aware of the study results during patient treatment.

### Data analysis

Analysis was done using descriptive statistics such as mean and standard deviation and analytical statistics such as Chi-square and *t*-test by SPSS 20 software (SPSS version 20, Chicago, IL, USA).

### Results

The mean age of the patients was (22 males, 14 females)  $54.8 \pm 7.6$  years. Table 1 shows demographic findings of patients. Most of the patients had acute myeloid leukemia (AML) (33.3%), and then non-Hodgkin lymphoma had the most frequency in patients (19.4%). Moreover, respiratory tract signs or symptoms were defined as coughing, sneezing, sore throat, dyspnea, and crackles or wheezes at auscultation. Sore throat and coughing had more frequency from upper and lower respiratory tract symptoms, respectively (69.4% and 63.8%). The distribution of viral species found in throat samples of patients is described in Table 1. RV was the most frequently detected virus then RSV was the most. PIV was not present in any of the tested samples [Table 1]. Furthermore, no substantial differences in the distribution of specific viral species were observed based on age, sex, neutropenia duration, hematological disorder, and respiratory tract symptoms and signs ( $P > 0.05$ ) [Table 2].

### Discussion

In the treatment of fever in neutropenic patients due to hematological malignancies remain unknown that symptoms are often nonspecific and cannot help physicians to found the etiologic of fever. In this study, we performed a prospective study to evaluate the respiratory viruses in causing fever in neutropenic patients and it's correlation with the symptoms to assess diagnostic screening for respiratory viruses.

**Table 1: Demographic variables in febrile neutropenic patients**

Variables	Values
Age	
Mean±SD	54.8 (7.6)
Sex, <i>n</i> (%)	
Male	22 (61.2)
Female	14 (38.8)
Hematological disorder, <i>n</i> (%)	
AML	12 (33.3)
CML	1 (2.7)
ALL	4 (11.1)
CLL	1 (2.7)
MM	5 (13.8)
HL	4 (11.1)
NHL	7 (19.4)
Other	2 (5.5)
Duration of neutropenia: Mean±SD	8.2 (2.8)
Smoking, <i>n</i> (%)	5 (13.8)
Respiratory tract symptoms and signs: <i>n</i> (%)	
Upper	
Rhinitis	21 (58.3)
Ear/nose congestions	15 (41.6)
Sneezing	7 (19.4)
Itchy throat	6 (16.6)
Sore throat	25 (69.4)
Lower	
Dyspnea	14 (38.8)
Cough	23 (63.8)
Tachypnea	13 (36.1)
Abnormal auscultation	7 (19.4)
Abnormal image	4 (11.1)
Viral species, <i>n</i> (%)	
Inf	3 (8.3)
PIV	0
RV	5 (13.8)
hMPV	3 (8.3)
RSV	4 (11.1)
Total	15 (41.6)

AML: Acute myeloid leukemia, CML: Chronic myeloid leukemia, ALL: Acute lymphoblastic leukemia, CLL: Chronic lymphoblastic leukemia, HL: Hodgkin lymphoma, NHL: Non-Hodgkin lymphoma, Inf: Influenza, PIV: Parainfluenza virus, RV: Rhinovirus, hMPV: Human metapneumovirus virus, RSV: Respiratory syncytial virus, SD: Standard deviation

This study emphasizes on the role of respiratory viruses in the development of respiratory signs and symptoms in febrile neutropenic patients. Based on the collected data, 41.6% of febrile neutropenic patients had virus as etiology, which is considerable prevalence. Moreover, respiratory viruses that were present in specimens obtained throat samples of neutropenic patients did not have significant relation with the neutropenia duration and the hematological disorder. These observations suggest that the prevalence of virus in causing fever and

**Table 2: Comparison of studied variables based on viral species**

Variables Mean ( $\pm$ SD, n)	Viral species				P	
	Inf	RV	hMPV	RSV		
Age						
Mean $\pm$ SD	52.1 ( $\pm$ 6.7)	51.8 ( $\pm$ 10.2)	53.2 ( $\pm$ 9.4)	54.1 ( $\pm$ 9.1)	0.451	
Duration of neutropenia						
Mean $\pm$ SD	8 ( $\pm$ 2.3)	8.2 ( $\pm$ 3.3)	8.3 ( $\pm$ 1.9)	8.4 ( $\pm$ 3.4)	0.144	
Sex: n (%)						
Male	1 (2.7)	3 (8.3)	2 (5.5)	2 (5.5)	0.096	
Female	2 (5.5)	2 (5.5)	1 (2.7)	2 (5.5)		
Hematological disorder: n (%)						
AML	1 (2.7)	2 (5.5)	1 (2.7)	1 (2.7)	0.367	
CML	0	0	0	1 (2.7)		
ALL	1 (2.7)	0	0	0		
CLL	0	0	0	0		
MM	0	1 (2.7)	1 (2.7)	2 (5.5)		
HL	0	0	0	0		
NHL	1 (2.7)	2 (5.5)	1 (2.7)	0		
Other	0	0	0	0		
Respiratory tract symptoms and signs: n (%)						
Upper						0.088
Rhinitis	1 (2.7)	3 (8.3)	1 (2.7)	2 (5.5)		
Ear/nose congestions	2 (5.5)	0	0	0		
Sneezing	0	0	0	0		
Itchy throat	0	0	0	0		
Sore throat	2 (5.5)	1 (2.7)	2 (5.5)	2 (5.5)		
Lower						
Dyspnea	0	2 (5.5)	1 (2.7)	0		
Cough	1 (2.7)	3 (8.3)	2 (5.5)	2 (5.5)		
Tachypnea	1 (2.7)	0	1 (2.7)	0		
Abnormal auscultation	0	0	0	0		
Abnormal image	0	0	0	0		

AML: Acute myeloid leukemia, CML: Chronic myeloid leukemia, ALL: Acute lymphoblastic leukemia, CLL: Chronic lymphoblastic leukemia, HL: Hodgkin lymphoma, NHL: Non-Hodgkin lymphoma, Inf: Influenza, PIV: Parainfluenza virus, RV: Rhinovirus, hMPV: Human metapneumovirus virus, RSV: Respiratory syncytial virus, SD: Standard deviation

respiratory signs and symptoms in neutropenic patients was not as more as general population, but near half of the patients had virus as etiology. However, it should be noted that the virus species detected in our samples were mostly species that are considered to be less pathogenic (e.g., RV, hMPV, and RSV). Influenza was found in 8.3% of samples due to the season of sampling (which was in the epidemic of influenza). In the study of Jansen *et al.* found that respiratory viruses were recovered in 14% of the patients before neutropenia. In 13% of neutropenic patients without fever and in 19% of those with fever, a respiratory virus was detected.<sup>[14]</sup> While our results show higher prevalence of virus as etiology of fever, which may be due to the season of study and the epidemic of influenza.

Moreover, Täger *et al.* found that respiratory viruses were detected in 25% of 44 febrile neutropenia episodes occurring in 25 children with AML. Viruses detected were influenza (3/11), PIV (3/11), RSV (2/11), adenovirus (1/11), PIV + RSV (1/11), and PIV + adenovirus (1/11).

Four (36%) cases were nosocomial.<sup>[5]</sup> Suryadevara *et al.* demonstrated that respiratory viruses were detected in 26 (52%) febrile episodes. A single virus was detected in 22 febrile episodes; multiple viruses were detected in the remaining 4. RV/enterovirus was most frequently detected.<sup>[15]</sup> Although routine screening for respiratory is not warranted, in subject with respiratory symptoms viral testing is useful to determine the etiology for the complaints, the start of barrier precautions, and the start of adequate treatment in the case of influenza. In these patients, testing of lower respiratory tract samples is favorable to upper respiratory samples.<sup>[16,17]</sup>

## Conclusion

Our prospective study supports the hypothesis that respiratory viruses play an important role in the development of neutropenic fever, and thus has the potential to individualize infection treatment and to reduce the extensive use of antibiotics in immunocompromised patients with neutropenia.

## Limitation

First, patients were selected from one hospital in Isfahan city, so the results of the study may have limited generalizability. Second, further research should extend the follow-up period to assess the longer-term outcomes of febrile neutropenic patients. Third, our study was performed in a small study group and represents only limited time span. The circulation and the pathogenicity of viruses can differ from the year, and therefore, the findings of our study cannot be directly extrapolated to future viral respiratory seasons in other clinical settings.

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## Conflicts of interest

There are no conflicts of interest.

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