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Original Scientific Paper

DISTRIBUTION OF RESPIRATORY VIRUSES IN CHILDREN ADMITTED TO PEDIATRIC INTENSIVE CARE UNIT

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SUMMARY – Acute lower respiratory tract infection (LRTI) is common in children and associated with high morbidity and mortality. The aim of this study was to determine the distribution of respiratory viruses leading to admission of a child with the diagnosis of LRTI to pediatric intensive care unit (PICU). The distribution of viral pathogens was determined using viral multiplex polymerase chain reaction (PCR) in children with LRTI admitted to PICU at a tertiary-level reference pediatric hospital. The LRTI patients without a positive viral multiplex PCR finding were excluded from the study. Most patients were under 2 years of age (78.3%), and the most common viral pathogen resulting in PICU admission due to viral LRTI was RSV A/B (32.8%). Thirty three patients had an underlying disease. Ten (16.6%) patients required invasive mechanical ventilation (IMV), 37 (61.6%) required high-flow oxygen therapy (HFOT), and two patients (3.3%) progressed to pediatric acute respiratory distress syndrome (PARDS). Underlying chronic disease presence was the highest in the IMV group with 90%, which decreased to 54% and 30.7% in the HFOT and standard oxygen treatment groups, respectively (p=0.018). The patients with IMV requirements had significantly longer hospital stay (median 8 days, range 6-13 days) compared to HFOT group (median 6 days, range 4-7.5 days] and regular oxygen treatment group (median 3 days, range 2-3.5 days) (p<0.001). The use of multiplex PCR for respiratory viruses may help in discriminating etiologic viral agents in patients admitted to PICU and estimating possible complications associated with viral-specific disease. The presence of an underlying disease in a patient with viral LRTI affects the treatment level, and treatment level affects the duration of PICU stay.

Keywords: *Viral infection; Pediatric intensive care unit; Multiplex PCR; Mechanical ventilation; High-flow oxygen therapy*

Introduction

Acute lower respiratory tract infection (LRTI) is common in children and associated with high morbidity and mortality rates (1). It is a frequent reason for hospital admissions, with 15% of hospitalized cases

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requiring transfer to a pediatric intensive care unit (PICU). LRTI is one of the most frequent reasons for mechanical ventilation support in PICU (1).

In children under the age of one, viral bronchiolitis is the predominant cause of LRTI, whereas after the age of one, pneumonia becomes more common (2). Bronchiolitis is characterized by acute inflammation, edema, and necrosis of epithelial cells lining small airways, increased mucus production, and bronchospasm (3). Severe bronchiolitis is characterized by persistently increased respiratory effort (tachypnea; nasal flaring; intercostal, subcostal, or suprasternal retractions; use of accessory muscles; (grunting), hypoxemia, apnea, or acute respiratory failure) (3). Viral bronchiolitis is the predominant reason for hospital admission due to LRTI in the first year of the life. Hospitalization rates for viral bronchiolitis are approximately 2%3% in children younger than one year in the USA and Europe (4, 5). Up to 10% of these patients may need PICU admission for supportive treatment and monitoring (5, 6).

The Center for Disease Control (CDC) defines pneumonia as an infection of the lungs that can cause mild to severe illness in people of all ages. According to the World Health Organization (WHO) data, pneumonia is the leading infectious cause of death in children worldwide, accounting for 15% of all deaths of children under five years of age (6). Viruses were found to be the most common etiologic agent of community-acquired pneumonia (CAP) in older infants and children younger than five years of age (7). Viruses are a major cause of CAP, either alone or as part of mixed infections. Children and infants who have signs of respiratory distress caused by moderate to severe CAP should be hospitalized (8). In up to two-thirds of children aged six months to 15 years, viruses including respiratory syncytial virus (RSV), parainfluenza viruses, rhinoviruses, and newly emerging viruses, such as human metapneumovirus, human bocavirus, and coronaviruses, are the leading causes of LRTI.

This study aimed to determine the distribution of the respiratory viruses leading to PICU admission of children diagnosed with LRTI, in the period from November 2013 to April 2014, at a tertiary-level reference pediatric hospital in Turkey.

Patients and Methods

This retrospective study evaluated the distribution of viral pathogens in children who were hospitalized at Dr. Behçet Uz Children Research and Training Hospital and admitted to PICU between November 2013 and April 2014. Dr. Behcet Uz Children's Hospital is a tertiary care pediatric research and training hospital. PICU at the hospital has 24 beds with approximately 750 inpatients every year.

The Institutional Research Board and Ethics Committee approved the study. The demographic characteristics of the patients were collected from medical and computerized microbiology laboratory records.

Table 1. The distribution of viral pathogens by patient age groups

Age group (years)	Virus (No. of cases, %)								
	Human metapneumo virus	Influenzavirus	RSV	Boca virus	Parainfluenza virus	Adenovirus	Coronavirus	Enterovirus	Total
<2	4 (44.4)	12 (80.0)	19 (90.5)	3 (75.0)	10 (90.9)	-	2 (100)	1 (100)	51 (79.7)
2-5	1 (11.1)	-	1 (4.8)	1 (25.0)	-	1 (100)	-	-	4 (6.3)
>5	4 (44.4)	3 (20.0)	1 (4.8)	-	1 (9.1)	-	-	-	9 (14.1)
Total	9 (100)	15 (100)	21 (100)	4 (100)	11 (100)	1 (100)	2 (100)	1 (100)	64 (100)

Inclusion and exclusion criteria

Children in respiratory distress admitted to PICU at our hospital according to the criteria based upon international guidelines (7, 8) were included in our study. The PICU admission criteria were the need for ventilatory support that can be only provided within the intensive care unit (e.g., invasive mechanical ventilation, noninvasive positive pressure ventilation or heated humidified high flow therapy with close monitoring, failure to maintain oxygen saturation [SpO_2] >92% in FiO_2 >0.6), signs of impending respiratory failure (lethargy, increasing work of breathing, and/or exhaustion with or without hypercarbia), slow irregular respirations or recurrent apnea, and cardiovascular compromise with progressive tachycardia and/or hypotension that requires fluid treatment assessment.

The neonates under 28 days of age were excluded from the study because they were hospitalized in neonatal intensive care (NICU). Patients who had a positive blood culture obtained at the time of PICU admission or positive tracheal aspirate at the time of intubation were excluded. Patients in whom the aforementioned samples were taken after 72 hours of hospitalization were also excluded from the study.

Molecular testing

A routine multiplex polymerase chain reaction (PCR) assay (Fast Track Diagnostics, FTD, Belgium) using nasopharyngeal aspirate sample was performed in each patient upon PICU admission. The assay included 20 respiratory viruses (influenza [A, H1N1, and B]; coronavirus [NL63, 229E, OC43, and HKU1]; parainfluenza [PIV1, 2, 3, and 4]; rhinovirus [HRV], respiratory syncytial virus [RSV A/B]; human metapneumovirus [hMPV A/B]; adenovirus [ADV]; enterovirus; parechovirus, and bocavirus [hBoV]). Additional multiplex PCR tests were carried out during the course of PICU stay when infection with one of these viruses was clinically suspected.

Blood cultures included routine blood culture obtained at the time of PICU admission for associated bacterial infections. Standard aerobic and anaerobic blood culture media were used in automated blood culture systems (BacT/Alert, *BioMerieux*, France). Additional blood cultures were taken during the course of PICU admission when it was clinically indicated.

Tracheal aspirate was obtained if the patient was intubated.

Statistical analysis

Statistical analysis was performed using SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). Data were presented as numbers (percentages), mean±standard deviation (SD), or median (range) as appropriate. Numerical variables were compared using one-way ANOVA and categorical variables were compared using chi-square test or Fisher's exact test. $P<0.05$ was interpreted as statistically significant.

Results

Demographic characteristics and PCR multiplex results

A total of 60 patients with positive nasopharyngeal multiplex PCR test results were included in the study. The median age of patients was 12.5 months (range 1 month to 17 years). Twenty-two of 60 patients were female. Most patients were under two years of age (47 of 60 patients), 5 patients were aged between 2 and 5 years and 8 patients were aged >5 years.

Among 60 patients, 33 had an underlying disease including 11 patients with neurometabolic diseases, 9 with congenital heart disease, 5 with genetic syndromes, 4 with underlying respiratory diseases, 3 with hematologic malignancies, and one patient with renal transplant. However, the distribution of patients with an underlying disease did not differ significantly among RSV, human metapneumovirus, parainfluenza, and bocavirus groups ($p>0.05$).

LRTIs due to RSV infections were most commonly observed in children under two years of age. Most patients who were hospitalized due to influenza and parainfluenza infections were also under two years of age. The distribution of the viral pathogens is presented in Table 2. The most common viral pathogens resulting in PICU admission were RSV A/B and influenza virus. There were four different combinations of co-detected viruses including enterovirus – parainfluenza, RSV – coronavirus 6, RSV – coronavirus 229, and human bocavirus – ınfluenza type A.

Table-2 : The distribution of the viral pathogens in children admitted to pediatric intensive care unit (PICU)

Virus	No. of cases (%)
Adenovirus	**1 (1.6)**
Coronavirus Coronavirus 229 Coronavirus 6	**2 (3.2)** 1 (1.6) 1 (1.6)
Enterovirus	**1** (1.6)
Human Bocavirus	**4 (6.3)**
Human Metapneumovirus A/B	**9 (14.1)**
Influenzavirus Influenzavirus A Influenzavirus B	**15 (23.5)** 14 (21.9) 1 (1.6)
Parainfluenzavirus Parainfluenzavirus 1 Parainfluenzavirus 2 Parainfluenzavirus 3	**11 (17.2)** 3 (4.7) 2 (3.1) 6 (9.4)
Respiratory sinsitial virus (**RSV) A/B**	**21 (32.8)**
Total	**64* (100)**

* A total of 4 patients had co-detection with more than one virus species.

The distribution of viral infections from winter 2013 to spring 2014 was reviewed (Fig. 1). Patients with influenza virus were admitted to our hospital mostly from December to February, while RSV infections were observed from December to April, peaking in February and March. Parainfluenza viruses were circulating from November onwards.

Treatment and outcomes

Among 60 patients, 10 required invasive mechanical ventilation (IMV), including three children with parainfluenza infections, two with human metapneumovirus infections, two with influenza, two with coronavirus infections, and one with enterovirus infection. Thirty-seven patients received only high-flow oxygen therapy (HFOT), and the remaining 13 patients required neither IMV nor HFOT.

The clinical condition progressed to pediatric acute respiratory syndrome (PARDS) in 2 of 10 patients who required IMV. One of these two patients was an 8-year-old boy with acute lymphoblastic leukaemia (ALL). He had a positive viral multiplex PCR finding for parainfluenza and developed severe PARDS. He required mechanical ventilation for 15 days and was discharged without any sequelae. The other patient was a 16-year-old boy with a positive viral multiplex PCR finding for influenza who was diagnosed with cerebral palsy sequelae and died after 33 days of mechanical ventilation due to severe PARDS and sepsis.

Among the patients admitted to PICU, 55% had an underlying disease. An underlying disease was

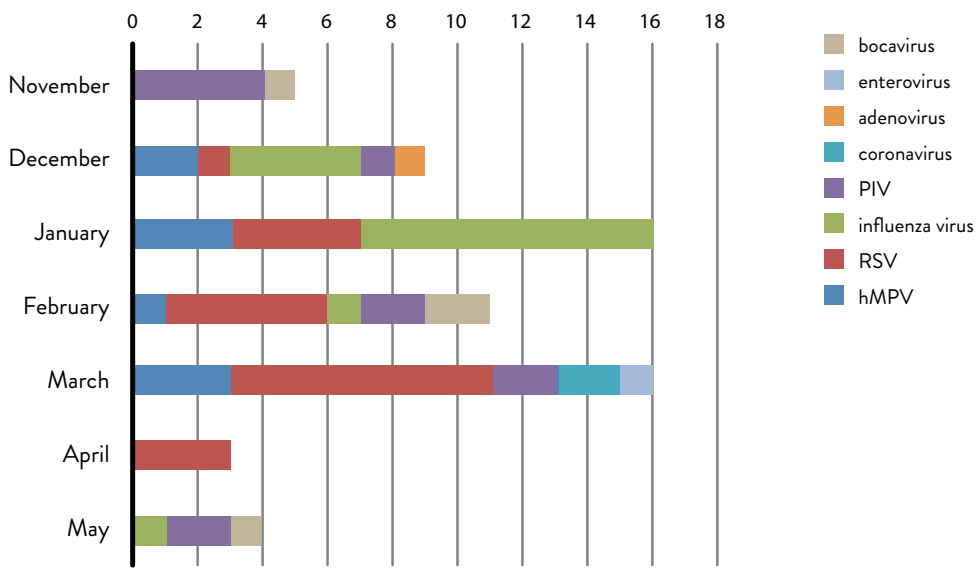

Fig. 1. The distribution of viral pathogens in children hospitalized at pediatric intenstive care unit (PICU) between November 2013 and May 2014.

present in 90% patients requiring IMV, 54% of those who needed only HFOT, and 30.7% of those who needed neither HFOT nor IMV. The difference in the presence of underlying disease among these three groups was statistically significant (p=0.016).

The median duration of overall PICU stay was 5 days (range 3-8). The median hospital stay duration was 8 days (range 6-13) in the IMV group, 6 days (range 4-7.5) in only HFOT group, and 3 days (range 2-3.5) in patients who needed neither HFOT nor IMV, showing a statistically significant difference among the three groups (one-way ANOVA, p<0.001).

Discussion

We found that RSV A/B was the predominant virus leading to PICU admission in the study period, and acute bronchiolitis was the predominant clinical picture. A French study that focused on admission to PICU during three winter months of the 2012/2013 season also found RSV as the predominant viral pathogen (9). Nearly 80% of the patients in our study had RSV infection, which is mainly a disease of children under two years of age (10). An Italian study on the seasonal virus-related frequency in infants and children hospitalized for LRTI during the winter-spring 2006/2007 reported a sharp peak of RSV-related LRTIs in winter, specifically December (11). In our study, RSV-related hospitalizations had a broad peak lasting from December to April and reaching its maximum in March. In a recent systematic review focusing on geographic variations in seasonality of laboratory-confirmed influenza and RSV epidemics in 137 global locations, RSV was reported to have a broader distribution of peak timings relative to that of influenza, even locations with peak activity outside of typical winter months (12). Our results are in line with these findings.

In our study, the second most common respiratory virus responsible for PICU admission was influenza virus, found in nearly 80% of our patients with influenza virus aged under two years. Influenza virus-related LRTIs peaked sharply in winter (December-January) and remained in circulation for two months. In a recent review, influenza peak was reported in winter months, from December to March with a mode in February (12). A similar study from China found human rhinovirus (117 cases) as the dominant viral pathogen, followed by RSV (60 cases), influenza virus A (20 cases), adenovirus (10cases), parainfluenza virus type 3 (6 cases), human Boca virus (6 cases), influenza virus C (5 cases), parainfluenza virus type 4 (4 cases), human coronavirus-HKU1/OC43 (4 cases), 3 for influenza virus B (3 cases), parainfluenza virus type 1 (2 cases), human metapneumovirus (2 cases), and human coronavirus-NL63/229E (1 case) (13). In our study, human rhinovirus was not among the most frequent viruses, and parainfluenza virus was the third most prevalent virus. This difference could be due to the geographical and latitudinal variations as reported for other viruses (12).

hMPV shows a seasonal variation from late winter to early spring in the United States, the Netherlands, the United Kingdom, Norway, and Finland, and in late spring and summer in Hong Kong [14-17]. In our study, hMPV circulated from December to March. Regarding the recent pandemic and its consequences, it seems that seasonal shifts may occur for every virus type, as it happened in Australia (18). Therefore, we should have a continuous seasonal mapping of the circulating viruses. If one of the viruses did not peak when expected, we should be alert for an off-season surge of the virus for that year.

hMPV causes upper and lower respiratory tract infections in patients of all age groups, but the symptomatic disease is reported mostly in young children or older adults. A Canadian experience was that 35% of the cases were children under the age of five (19). In another large-scale study, the mean age was 11.6 years of age (16). In our study, not only children under two years of age; but also children aged 7 to 17 years were infected with hMPV. While all patients older than five years with hMPV had underlying diseases including congenital heart diseases, allergic asthma, and hematologic malignancies, only one child under the age of five years had associated underlying condition. Our findings were consistent with a previous study reporting that most inpatients and outpatients less than five years of age with hMPV infection had no underlying conditions (20).

The severity of viral respiratory tract infections depends on the type of virus and associated co-morbidities, but there are conflicting studies (21). In our study, nearly half of the PICU patients had no underlying chronic disease, suggesting that the viral respiratory

pathogens could cause severe clinical picture in previously healthy children. Also, the proportion of chronic diseases did not differ by specific viral etiology. The clinicians should be alert to the signs of disease progression in patients with common pathogens such as RSV, influenza, hMPV, parainfluenza, and coronavirus, and with other viruses such as bocavirus and adenovirus. Underlying diseases were more common in IMV or HFOT group than in the standard oxygen therapy group. Also, the IMV patients had the longest PICU stay compared to HFOT oxygen treatment group.

In conclusion, the distribution of the respiratory viruses in different geographical regions generally shows nearly the same pattern, whereas a detailed analysis may reveal slight differences. The use of multiplex PCR for respiratory viruses may help discriminate etiologic viral agents in patients administered to PICU and estimate possible complications associated with viral-specific disease. Also, the underlying disease may affect the treatment modality and treatment modality determines the PICU admission duration.

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Sažetak

DISTRIBUCIJA RESPIRATORNIH VIRUSA U DJECE HOSPITALIZIRANE U DJEČJOJ JEDINICI INTENZIVNE NJEGE

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Akutna infekcija donjih dišnih puteva (LRTI) uobičajena je kod djece i povezana je s velikim pobolom i smrtnošću. Cilj ovog ispitivanja bio je utvrditi distribuciju respiratornih virusa koji dovode do hospitalizacije djece s dijagnozom LRTI u jedinici intenzivnog liječenja djece (PICU). Procijenjena je raspodjela virusnih patogena dijagnosticiranih virusnom multipleks PCR metodom u djece koja su bila hospitalizirana u PICU referentne dječje bolnice tercijarne razine skrbi. Većina djece bila je mlađa od 2 godine (78,3 %), a najčešći virusni patogen koji je rezultirao prijemom u PICU bio je RSV A/B (32,8 %). Trideset troje bolesnika imalo je neku drugu bolest u podlozi. U 10 (16,6 %) bolesnika bila je potrebna invazivna mehanička ventilacija (IMV), 37 (61,6 %) bolesnika zahtijevalo je terapiju visokim protokom kisika (HFOT), a dva bolesnika (3,3 %) razvila su kliničku sliku akutnog respiratornog distres sindroma djece (PARDS). Prisutnost neke druge bolesti u podlozi bila je 90 % i najviša u skupini IMV koja se smanjila na 54 % i 30,7 % u skupinama HFOT odnosno standardne terapije kisikom (p = 0,018). Također bolesnici s potrebom za IMV-om imali su značajno najduže trajanje hospitalizacije (medijan 8 dana, raspon 6-13 dana) u usporedbi s HFOT skupinom (medijan 6 dana, raspon 4-7.5 dana) i skupinom liječenom standardnom terapijom kisikom (medijan 3 dana, raspon 2-3.5 dana) (p < 0,001). Upotreba multiplex PCR metode za respiratorne viruse može biti korisna i za diskriminaciju etioloških virusnih uzročnika u bolesnika koji se primaju u PICU i za procjenu mogućih komplikacija povezanih s virusnom bolešću. Prisutnost neke druge bolesti u podlozi virusnog LRTI-ja utječe na razinu liječenja, a razina liječenja utječe na trajanje boravka u PICU.

Ključne riječi: *Virusna infekcija; Intenzivno liječenje djece; Multipleks PCR; Mehanička ventilacija; Terapija visokim protokom kisika*