

The investigation of community-acquired and nosocomial respiratory syncytial virus and other viral respiratory tract infections in children

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SUMMARY

Although respiratory viruses are known as the major causes of community-acquired respiratory tract infections all over the world, they can also cause serious nosocomial respiratory infections and hospital outbreaks. The aim of this study is to investigate the incidence of community-acquired and nosocomial RSV and other viral respiratory tract infections in children hospitalized at the Pediatric Intensive Care Unit of Cukurova University Faculty of Medicine. Nasopharyngeal swab samples were taken from 100 children aged 0-16 years with suspected community-acquired (60) and nosocomial (40) respiratory tract infections from September 2018 to June 2021. The Multiplex real-time PCR test was used for the diagnosis of respiratory viruses. Of children with community-acquired respiratory tract infections, 65% (39/60) were positive for at least one virus and the rate of coinfection in this group was 35.9% (14/39). In children with nosocomial respiratory tract infection, positivity was detected to be 62.5% (25/40) and the coinfection rate was 40% (10/25). The most predominant virus in community-acquired respiratory tract infections was influenza A virus (25%), followed by ADV (18.3%), hBoV (15%), RSV (11.7%), and RhV (10%). In nosocomial viral respiratory tract infections, the most common virus was RSV (20%), followed by influenza A virus (12.5%), RhV (12.5%), ADV (12.5%), hMpV (10%), and hBoV (10%). Early diagnosis of respiratory viral infections with real-time PCR test is important in terms of reducing morbidity and mortality, applying control methods to prevent the spread of nosocomial viruses, shortening the hospitalization period, preventing the use of unnecessary antibiotics, and giving appropriate antiviral treatment.

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INTRODUCTION

Respiratory tract infections cause a serious disease burden, especially in preschool children, as well as severe lower respiratory tract infections (LRTIs) when upper respiratory tract infections cannot be treated. Viral respiratory tract infections are the leading cause of infant and child deaths and serious illness worldwide. Approximately 53% of infants have a viral lower respiratory tract infection in the first year of life. It is difficult to distinguish clinically whether the causative agent of respiratory tract infection is bacterial or viral. However, with the increased failure rate in antibacterial therapy and the widespread

use of molecular diagnostic techniques, the role of viruses is increasingly understood. Influenza virus, parainfluenza virus (PIV), respiratory syncytial virus (RSV), human metapneumovirus (hMPV), rhinovirus (RV), human coronavirus (hCOV), adenovirus (ADV), and human bocavirus (hBOV) are important viral agents of respiratory tract infections. Accurate identification of respiratory tract infection in children both reduces general antibiotic use and increases the potential for recovery with the right treatment. In addition, rapid diagnosis of viral infections can help keep nosocomial transmission under control (Troy NM., Bosco A., 2016).

Nosocomial infections are caused by microorganisms such as bacteria, viruses, and fungi acquired by the patient during hospitalization, occurring 48-72 hours after hospitalization or acquired in the hospital or health care unit and occurring within 10 days after discharge. Nosocomial infections can significantly increase morbidity and mortality rates in hospitalized patients and are very important because of their economic consequences. Nosocomial

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viral respiratory tract infections prolong the hospital stay, increase the cost of health care, lead to the emergence of multi-antibiotic-resistant microorganisms, and thus reduce the chance of treatment. Especially in developing countries, the lack of effective infection control programs, inadequate adherence to hygiene practices, and the lack of trained personnel in infection control measures play an important role in increased morbidity and mortality due to hospital-acquired infections. Viruses are also very important in nosocomial infections, but there is not enough literature data to study the incidence trends, except in certain situations such as the investigation of epidemics (Pichler *et al.*, 2018; Leung *et al.*, 2018; Khan *et al.*, 2015).

While most viral respiratory infections are confined to the upper airways, causing relatively mild symptoms such as sneezing and runny nose, they can affect the lower airways in newborns, resulting in wheezing, shortness of breath, bronchiolitis, or pneumonia. Transmission can be by contact and droplet, airborne, collaborative use, and vector origin. Viral particles that can spread rapidly can be transmitted from contaminated items to mucous membrane inoculation and from contaminated respiratory support devices in hospitals. The incidence of nosocomial viral respiratory tract infections is parallel to those seen in the community. Generally, viral respiratory tract infections are seen in winter and spring (Ramasethu, 2017; Sikora, Zahra 2020).

Premature birth is the most important risk factor in nosocomial and community-acquired viral respiratory tract infections. In addition, delayed enteral nutrition and long-term parenteral nutrition, intravascular catheterization, long-term respiratory support with ventilators, gastrointestinal surgery and broad-spectrum antibiotic use are known risk factors for neonatal nosocomial infections. The probability of infection is determined by two factors: age and exposure to infection. Once it occurs, the severity of the infection is determined by both environmental and genetic risk factors (Poole, 2019).

MATERIALS AND METHODS

In this study, nasopharyngeal samples were taken from 100 children hospitalized in Çukurova University Faculty of Medicine Balcalı Hospital Pediatric Intensive Care Service and respiratory tract viruses were investigated in community-acquired and nosocomial viral infections using real time RT-PCR method.

The presence of human respiratory syncytial virus (hRSV); human metapneumovirus (hMPV); human parainfluenza virus-1-4 (hPIV); human coronavirus (hCoV) (OC43, E229, NL63 and HKUI); human rhinovirus (hRv); adenovirus (ADV) and human bocavirus (hBoV) was investigated with the ARVI Screen Real-TM kit (Sacace Biotechnologies, Italy), which is

a multiplex real-time PCR test. In addition, influenza A/B r-gene real-time PCR kit (Argene, BioMérieux, France) was used for detection of influenza A and B viruses.

RNA/DNA extraction and reverse transcription steps from nasopharyngeal swab samples were performed using the Ribo-Sorb RNA/DNA purification kit and Reverta kits included in the ARVI Screen Real-TM kit. Real-time PCR tests were performed on the Bio-Rad iQ5 PCR (USA) device.

RESULTS

The study included children aged 0-16 years old who were admitted to the Pediatric Intensive Care Unit (PICU) of Cukurova University Faculty of Medicine to detect RSV and other respiratory tract viruses. The PCR test was performed on nasopharyngeal swab samples taken from a total of 100 children (51 female, 49 male); 60 (60%) had community-acquired (CA) respiratory tract and 40 (40%) had nosocomial (NC) respiratory tract infections. 51 (51%) patients were female and 49 (49%) were male. The patients included in the study were mostly (61%) between 0-48 months of age (*Table 1*).

Patients with suspected community-acquired infection had clinical signs of respiratory tract infection at the time of admission to the hospital. On the other hand, patients with suspected nosocomial infection had no clinical signs of respiratory tract infection during hospitalization and showed clinical symptoms at least 3 days after hospitalization. After using real-time RT-PCR test for respiratory tract viruses, 64 (64%) of 100 cases were positive. At least one viral agent was detected in 39 (65%) of 60 community-acquired respiratory tract infections and in 25 (62.5%) of 40 nosocomial respiratory tract infections.

During admission to the intensive care unit, clinical symptoms such as fever, cough, dyspnea, runny nose, tachycardia, tachypnea, wheezing, vomiting, confusion, nausea, sore throat, apnea, and cyanosis were observed in patients with community-acquired infections. Similar symptoms have been observed in patients with nosocomial respiratory viral infections. Patients with community-acquired and nosocomial respiratory tract viral infections were followed up with the diagnoses of Upper Respiratory Tract (URI) disease, Pneumonia, Bronchopneumonia, ARDS (Acute Respiratory Distress Syndrome), Bronchiolitis, and Bronchitis. The rate of diagnoses in the patients is given in *Table 1*.

In 60 patients with community-acquired viral respiratory tract infection, the positivity rate was 65% (39/60) and the most common virus in the form of single or multiple infections was influenza A virus with 25% (15/60), followed by ADV 18.3% (11/60), hBoV 15% (9/60), RSV 11.7% (7/60), RhV 10% (6/60), influenza B virus 5% (3/60), PIV-3 5% (3/6), hMPV

Table 1 - Patient Characteristics.

	Patients	CA Infections	NC Infections	Total
Ages	0-12 mo.	8	13	21
	13-24 mo.	13	6	19
	25-48 mo.	10	11	21
	49-72 mo.	9	2	11
	7-10 age	10	1	11
	11-16 age	10	7	17
Gender	Girl	32	19	51
	Boy	28	21	49
Diagnoses	URI Disease	23 (38.3%)	14 (35%)	37
	Pneumonia	13 (21.7%)	14 (35%)	27
	Bronchopneumonia	10 (16.7%)	4 (10%)	14
	ARDS	9 (15%)	6 (15%)	15
	Bronchiolitis	4 (6,6%)	1 (2,5%)	5
	Bronchitis	1 (1,7%)	1 (2,5%)	2
Symptoms	Fever	37 (%22,4)	14 (%31,2)	51
	Cough	27 (%16,3)	4 (%8,9)	31
	Dyspnea	20 (%12,1)	9 (%20)	29
	Runny nose	18 (%10,9)	1 (%2,2)	19
	Tachycardia	18 (%18,9)	5 (%11,1)	23
	Tachypnea	18 (%18,9)	7 (%15,6)	23
	Wheezing	9 (%5,4)	-	9
	Vomiting	5 (%3)	2 (%2,2)	7
	Confusion	3 (%1,8)	1 (%2,2)	4
	Nausea	-	1 (%2,2)	1
	Sore throat	2 (%1,2)	-	2
	Apnea	2 (%1,2)	-	2
	Cyanosis	1 (%0,6)	1 (%2,2)	2
	Total		60	40

URI: Upper Respiratory infection. ARDS: Acute Respiratory Distress Sendrome.

3.3% (2/60), COV (HKU1/OC43) 3.3% (2/60), PIV-2 1.7% (1/60), and PIV-4 with 1.7% (1/60) (Figure 1).

The positivity rate in 40 patients with nosocomial viral respiratory tract infection was 62.5% (25/40) and

the most common virus in the form of single or multiple infections was RSV with 20% (8/40), followed by influenza A virus 12.5% (5/40), RhV 12.5% (5/40), ADV 12.5% (5/40), hMpV 10% (4/40),

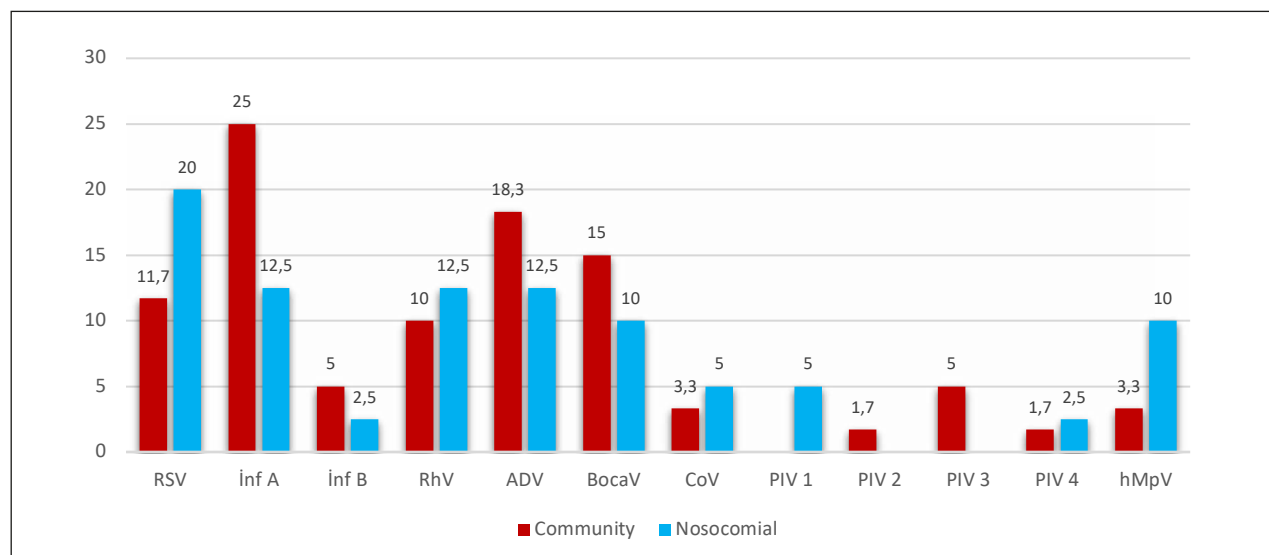


Figure 1 - Prevalence of viruses in community-acquired and nosocomial respiratory tract infection-positive patients.

*RSV: Respiratory Syncytial virus, Inf: Influeanza virus, RhV: Rhinovirus, BocaV: Bocavirus, CoV: Coronavirus PIV: Parainfluenza virus, hMpV: Human Metapneumovirus.

(4/40), PIV- 1 5% (2/40), CoV 5% (2/40), influenza B virus 2.5% (1/40), and PIV-4 2.5% (1/40) (Figure 1).

When we examined the hospitalization period of children with community-acquired respiratory viral infections, it was found that they stayed in the hospital for an average of 10.7 days (2-27 days). However, the hospitalization time of children with nosocomial respiratory tract viral infections averaged 22.6 days (5-128 days).

Community-acquired viral respiratory tract infections were seen mostly between 13-24 months, and ADV was found to be the most dominant with 6.7%. RSV infections had a 5% rate between 0-12 months, hBoV infection 5% between 25-48 months, influenza A virus 5% between 49-72 months, influenza A and

ADV both 5% between 7-10 years, and influenza A virus was dominant with a rate of 5% between the ages of 11-16 years.

Nosocomial viral respiratory tract infections were seen mostly between 0-12 months, and RSV was detected as the most dominant virus with 10%. Influenza A virus (7.5%) between 13-24 months, all viruses at the same rate between 25-48 months, RhV (5%) between 49-72 months, all viruses at the same rate between 7-10 years of age, while at 11-16 years of age RSV, ADV, and hBoV were found to be predominant all at the same rate (5%).

Out of 39 children with community-acquired viral respiratory tract infections, 25 (64.1%) had a single infection and 14 (35.9%) had multiple infections.

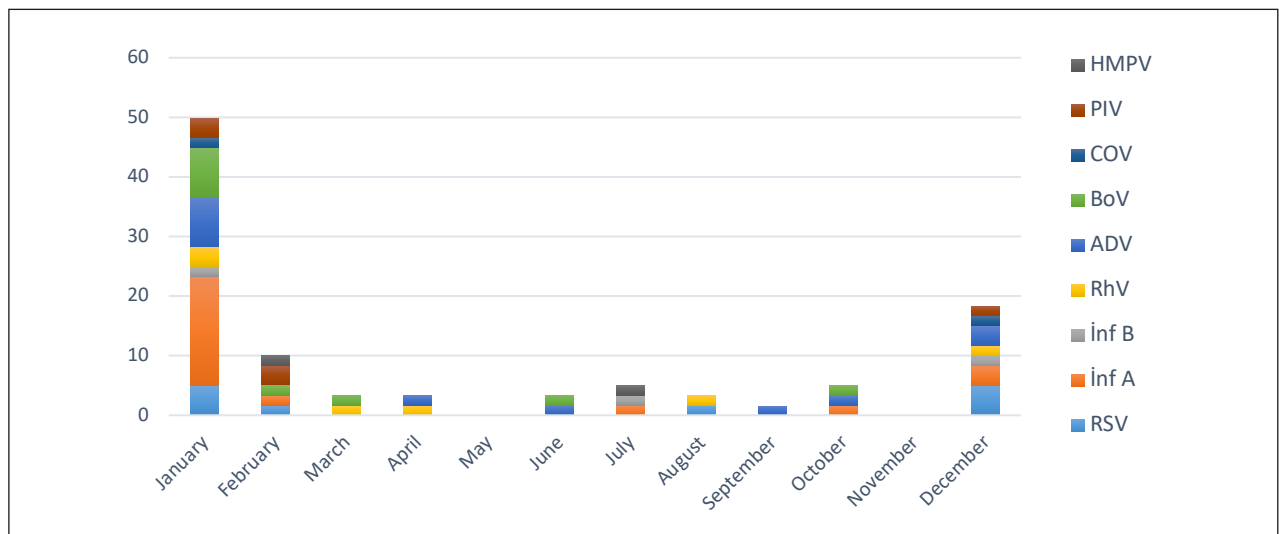


Figure 2 - Seasonal distribution of viruses in community-acquired viral respiratory tract infections.

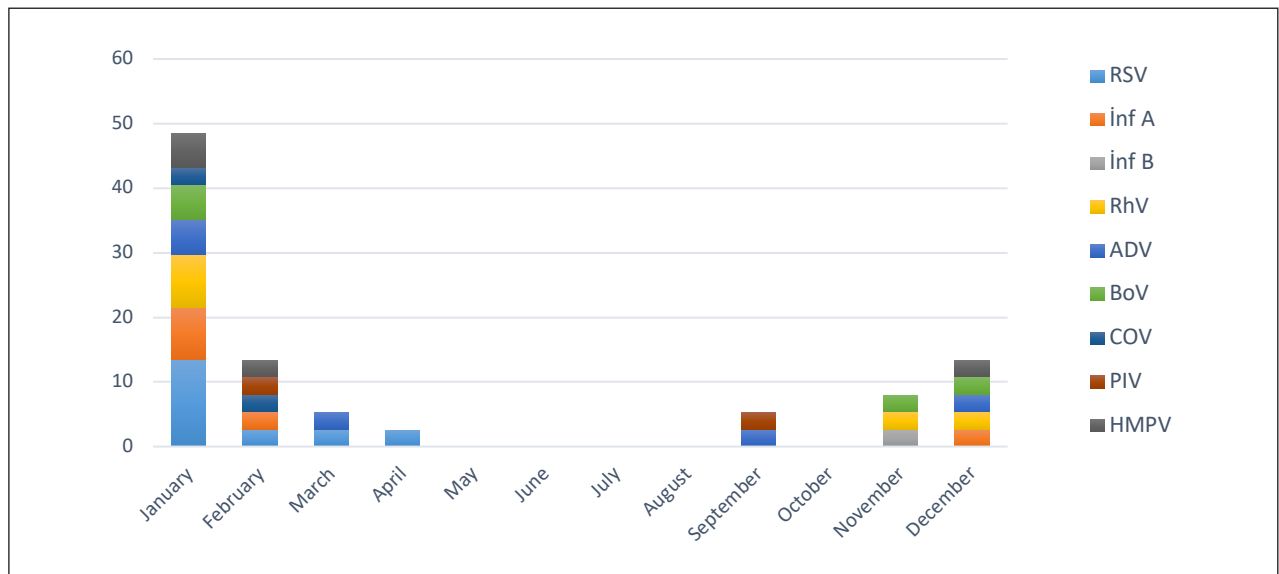


Figure 3 - Seasonal distribution of viruses in nosocomial viral respiratory tract infections.

The most common single infection virus was influenza A virus with 20.5% (8), followed by RSV 12.8% (5), influenza B virus 7.7% (3), ADV 7.7% (3), RhV 5.1%, hMpV 5.1% (2), hBoV 2.6% (1), and PIV 3 2.6%.

Of the community-acquired multiple infections, 10 (25.6%) were identified as double, 2 (5.1%) as triple infection, 1 (2.6%) as quadruple infection, and 1 (2.6%) was with 5 viruses. In addition, influenza A virus and ADV 7.6% (4), ADV and hBoV 5% (2) were determined as the most frequently detected viruses. The most frequently detected virus in multiple infections was hBoV with 15.4%.

Out of 25 children with nosocomial viral respiratory tract infections, 15 (60%) had a single infection and 10 (40%) had multiple infections. The virus most frequently detected as a single infection was RSV with 12% (5), followed by influenza A virus 12% (3), ADV 12% (3), hMpV 12% (3), RhV 4% (1), hBoV 4% (1), and PIV 1 4% (1).

Eight of the nosocomial multiple infections (32%) were found to be double and 2 (8%) triple. In addition, RSV and hBoV were determined as the viruses most frequently detected together with 12% (3). The most frequently detected viruses in multiple infections were RSV and ADV with 16%.

When we examined the seasonal distribution of viruses in community-acquired infections, viruses were detected most frequently in the winter: December (18.4%), January (49.9%), and February (6.8%). In January, when viruses were detected most frequently, influenza A virus was the most dominant virus with 18.3% (Figure 2). When we examined the seasonal distribution of viruses in nosocomial infections, viruses were detected most frequently in the winter: 13.5% in December, 48.6% in January, and 13.5% in February. In January, when viruses were detected most frequently, RSV was determined as the most dominant virus with 13.5%. In addition, hBoV and PIV 1 were detected mostly in the autumn (Figure 3).

DISCUSSION

Respiratory tract infections are an important public health problem due to their high incidence and ease of spread in the community. Viral infections are the leading cause of death and serious illness in infants and especially in children under 5 years of age worldwide. Viruses are the leading cause of LRTIs, with epidemiological variability depending on climate, season and regions. Lower respiratory tract infections (LRTIs) are associated with significant morbidity and are the most common cause of outpatient visits and hospitalizations among young children. Limited data are available on viral RTI in pediatric ICUs in the developing world. Specifically, few studies have investigated severe viral respiratory illness. All these studies were done before the invention of highly sensitive polymerase chain reaction (PCR) techniques.

Until recently, viral isolation and identification techniques were suboptimal for cell culture or antigen detection, both of which are time-consuming and poorly sensitive. Nosocomial viral respiratory tract infections are often unrecognized in neonatal and pediatric intensive care units, or 52% of admissions are clinically underdiagnosed. However, very limited published data are available on the general epidemiological features of nosocomial infection by respiratory viruses, particularly viruses other than influenza virus (Poole *et al.*, 2019).

When we compared our positivity rate (65%) in community-acquired viral respiratory tract infections in our study group with similar studies from other countries, we saw reported positivity rates between 49.2% and 86.5% (Liu *et al.*, 2019; Li *et al.*, 2019; Lin *et al.*, 2020; Finianos *et al.*, 2016; Prasad *et al.*, 2018; Alfaraidi *et al.*, 2020; Aramburo *et al.*, 2011; Calvo *et al.*, 2010; Frobert *et al.*, 2011). In addition, the positivity rate in our country was found to be between 42.1% and 83.9% (Avcu *et al.*, 2017; Sancakli *et al.*, 2012; Aktürk *et al.*, 2015; Akyüz Özkan *et al.*, 2021; Kanberoğlu *et al.*, 2021; Uyar *et al.*, 2014; Okulu *et al.*, 2018).

RSV, RhV and Influenza virus, respectively, are the most important viruses causing respiratory illnesses in community-acquired respiratory tract infections among children worldwide. In our study, Influenza, ADV and BocaV were the most frequently detected respiratory viruses; RSV and RhV, fourth (11.7%) and fifth (10%) were the most frequently detected pathogens. When we compared our study with studies conducted in other countries, unlike us, 5 studies found RSV (Liu *et al.*, 2019; Lin *et al.*, 2020; Prasad *et al.*, 2018; Calvo *et al.*, 2010; Frobert *et al.*, 2011), 3 studies RhinoV (Finianos *et al.*, 2016; Alfaraidi *et al.*, 2020; Aramburo *et al.*, 2011), and 1 study found Influenza (Li *et al.*, 2019) as the most dominant strain. When we compared our study with the studies conducted in our country, 3 studies (Avcu *et al.*, 2017; Uyar *et al.*, 2014; Okulu *et al.*, 2018) found RSV, 3 studies (Sancakli *et al.*, 2012; Özkan *et al.*, 2021; Kanberoğlu *et al.*, 2021) RhinoV, and 1 study (Aktürk *et al.*, 2015) found Influenza as the most dominant strain.

We analyzed our positivity rate (62.5%) in nosocomial viral respiratory tract infections in our study group with studies conducted abroad and found that rates in other studies ranged from 0.8% to 34.5% (Zinna *et al.*, 2016; Dan *et al.*, 2019; Choi *et al.*, 2017; Sidler *et al.*, 2012; Moynihan *et al.*, 2020; Chow *et al.*, 2017; de-Paris *et al.*, 2014). We could not find any similar studies conducted recently in our country. In our study, RSV (32%), influenza (24%), RhV (20%), and ADV (20%) were the most frequently detected viruses. When we compared our study with studies conducted in other countries, as in our findings, 1 study (de-Paris *et al.*, 2014) found RSV, and 6 studies (Zinna *et al.*, 2016; Dan *et al.*, 2019; Choi *et al.*, 2017;

Sidler *et al.*, 2012; Moynihan *et al.*, 2020; Chow *et al.*, 2017) found RhinoV as the second most dominant species in our study.

The positivity rate found in other countries is at least half as low as in our study. The rate we found in our study reveals that nosocomial infections are at a substantial level, especially in children.

RSV, Influenza A, and RhinoV infections are frequently seen in both community-acquired and nosocomial infections since they are viruses that circulate in the community throughout the year. These viruses are detected frequently, especially when children suffering from nosocomial infections are constantly exposed to this scatter both by their weak immunity and by health personnel and visitors. Other viruses are detected at lower rates because they cause more limited infections compared to these viruses.

CONCLUSION

In our country, this is one of few studies investigating nosocomial and community-acquired respiratory tract viral infections in children, using the multiplex Real time RT-PCR test. As a result, in our study group, community-acquired infections were detected at a high rate of 65% and nosocomial viral infections at 62.5%. In addition, it was determined that the hospital stay (22.6 days) for patients with nosocomial respiratory viral infections was twice as long as the stay for patients with community-acquired respiratory viral infections (10.7 days).

Our study had strengths and weaknesses. Strengths: study of respiratory tract samples with the fastest method, including all respiratory tract viruses and both community-acquired and hospital-acquired infections in the study, and systematic and detailed interpretation of patients' medical records. The weakness is that we can include a single service in the study. We also showed that hospital-acquired viral respiratory tract infections, especially RSV, are common in children of all ages. The role of viruses as well as bacteria in hospital-acquired respiratory tract infections should be further investigated in prospective studies. In respiratory tract infections, multiplex real-time PCR testing is recommended in the early diagnosis of viral respiratory tract infections to reduce unnecessary antibiotic usage, to give early antiviral treatments, to shorten the hospitalization period, and to prevent virus transmission.

Ethics Committee Approval

This study was approved by Çukurova University Institutional Review Board (project number 82/48 - 2 November 2018).

Informed Consent

Written informed consent was obtained from each patient.

Data Sharing Statement

Data available on request from the authors. The data that support the findings of this study are available from the corresponding author.

Author Contributions

Concept- S.O., F.Y.; Design- S.O.; Data Collection or Processing- S.O., O.O.H., G.O.; Analysis or Interpretation- S.O., F.Y.; Literature Search- S.O.; Writing- S.O.

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