

Evaluation of Etiologic Agents of Lower Respiratory Tract Infections in Children Hospitalized Just Before Normalization of COVID-19

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Abstract

Lower respiratory tract infections (LRTIs) are one of the most common causes of hospitalization among children in the early childhood period. Knowing the pathogens that cause pneumonia, its management will be more exact and effective. In this study, we aimed to investigate the frequency of pathogens causing LRTIs in children at the end of the COVID-19 pandemic by performing a real-time multiplex polymerase chain reaction (RT-MPCR) test within our hospital. We included two hundred forty-seven children, aged between 1 month and 18 years, diagnosed with LRTIs, and hospitalized between May 2021 and April 2022. Demographic characteristics and clinical and laboratory findings were retrospectively collected from patients' hospital records. Of the 247 children diagnosed with LRTIs, 153 (61.9%) were female. At least one pathogen was identified in the nasopharyngeal swap specimens of 218 (88.3%) patients, and 74.9% (n=185) of them were viruses. The most common identified pathogens were respiratory syncytial virus (24.7%), human bocavirus (21.1%), and severe acute respiratory syndrome coronavirus 2 (15.4%). 7.7% of identified pathogens were bacteria. *Haemophilus influenzae* was the most commonly detected bacteria. Despite a lengthy period of isolating the community causative agents of pneumonia, their frequency remains unchanged from before the isolation time. RT-MPCR is beneficial for the early detection of pathogens and in the prevention of unnecessary antibiotic usage.

Keywords: Children, etiologic agents, lower respiratory tract infections, real-time multiplex polymerase chain reaction test, viruses



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Introduction

Lower respiratory tract infections (LRTIs) are one of the most common causes of hospitalization in children during the early childhood period. According to the World Health Organization, pneumonia is responsible for 14% of deaths of children under five years of age, and approximately annually 740.180 child deaths occur worldwide.¹ The causative pathogens vary depending on the region and age of the children. Viruses are responsible for the majority of diseases, especially among children aged 5 years, and the incidence decreases with age increase.²⁻⁴ The respiratory syncytial virus (RSV) is the most common virus causing LRTIs in young children; parainfluenza viruses 1, 2, and 3 (PIV 1,2,3), influenza A and B viruses (IFV A/B), adenovirus (AdV), rhinovirus (RV), human metapneumovirus (hMPV), human bocavirus (HboV), parechovirus, coronaviruses (CoV), and enterovirus are the others.⁵⁻⁸ *Streptococcus pneumoniae* (*S. pneumoniae*) is the most common bacterial cause in all age groups of children; others are non-typeable *Haemophilus influenzae* (*H. influenzae*) and *H. influenzae* type b, *Streptococcus pyogenes* (*S. pyogenes*), *Staphylococcus aureus* (*S. aureus*), *Moraxella catarrhalis* (*M. catarrhalis*), *Mycoplasma pneumoniae* (*M. pneumoniae*) and *Chlamydia pneumoniae* (*C. pneumoniae*).^{2,7,9} Although most LRTIs are caused by viruses, there is no specific clinical finding to distinguish viral infections from bacterial infections. Therefore, early and accurate detection of etiological pathogens and the initiation of appropriate treatment will significantly reduce unnecessary antibiotic usage and enable appropriate treatment to reduce morbidity and mortality. Studies have shown that blood cultures have a low rate of pathogen detection (1-3%), and routine serologic tests have limited usage. On the other hand, recent studies have shown that real-time multiplex polymerase chain reaction (RT-MPCR) is helpful in rapidly diagnosing etiologic bacterial and viral pathogens of LRTIs.^{2,10-14} Our study aims to identify pathogens of LRTIs and their frequency in children after long isolation periods in the community to prevent unnecessary antibiotic usage.

Material and Method

This was a retrospective cross-sectional study. The study population comprised children aged between 1 month and 18 years hospitalized due to LRTIs in the Pediatric Department between May 1, 2021 and April 30, 2022. Patients' demographic data, clinical and laboratory findings, treatment, and outcomes were recorded from their medical files. LRTI was defined as the presence of clinical findings of fever, cough, chest pain, tachypnea, and dyspnea with abnormal auscultatory findings and/or radiographic findings in chest X-rays. Radiographic findings were classified as bronchiolitis, bronchopneumonia, and lobar pneumonia. Bronchiolitis was defined as the presence of poorly defined small, multifocal nodules or air-trapping areas characterized by hyperlucency. Bronchopneumonia was defined as the presence of focal nodular opacities and patchy areas of

consolidation involving one or more segments of a single or multiple lobes. Lobar pneumonia was defined as the presence of focal dense opacification of most the entire lobe. Children with chronic lung disease, congenital heart diseases, immune deficiency, muscular disease, neurometabolic disease, hospital-acquired pneumonia, and children who had undergone tracheostomy and/or home ventilation devices were excluded from the study.

RT-MPCR tests were conducted on 23 pathogens including AdV, HboV, RSV, PIV 1, 2, 3, 4, IFV A, B, RV, enterovirus, hMPV, CoV-OC43, CoV-229E, CoVNL63, human parechovirus, HcoV, SARS-CoV-2, *M. pneumoniae*, *L. pneumoniae*, *S. pneumoniae*, *C. pneumoniae*, and *Bordetella pertussis*.

Statistical Analysis

All analyses were performed using the SPSS 23.0 statistical software package (IBM SPSS Statistics). Categorical variables were expressed as numbers (n) and percentages, whereas continuous variables were summarized as mean with standard deviation or as median with minimum-maximum where appropriate. Chi-square tests were used to compare categorical variables between groups. The normality of distribution for continuous variables was tested using the Kolmogorov-Smirnov test. For continuous variables that had normal distribution, >2-group comparisons were performed using One-Way ANOVA. For the pairwise corrections of the ANOVA, we used the Bonferroni correction. The statistical level of significance for all tests was defined as a p-value of <0.050.

The study was approved by the Ethics Committee of Medeniyet University Göztepe Training and Research Hospital (approval date: 16.03.22; approval number: 2022/0150) before the experiment was started and was conducted in accordance with the principles set forth in the Helsinki Declaration.

Results

Of the 247 children diagnosed with LRTIs, 153 (61.9%) were male. The mean age of the patients was 2.93±4.09 (0.1-17.7) years, and 148 (59.9%) of them were under 2 years old. The most common symptoms at admission were cough (74.5%), fever (46.6%), and wheezing (29.1%). High-flow nasal cannula (HFNC) oxygen therapy was administered to 66 patients (26.7%) with respiratory distress (**Table 1**).

At least one pathogen was detected in 218 (88.3%) of the nasopharyngeal swap specimens. Of the detected pathogens, 74.9% (n=185) were viruses, 7.7% (n=19) were bacteria, and 5.7% (n=14) were both bacteria and viruses. The leading pathogens were RSV (27.1%), HBoV (21.1%), RV (15.8%), and SARS-CoV-2 (15.4%). In addition, RSV (37.9%) and HBoV (25.8%) were the most commonly identified pathogens in patients requiring HFNC (**Table 2**).

When the pathogens were evaluated in terms of their distribution according to age, RSV (80.6%), HBoV (57.7%), RV (51.3%), PIV-3 (68.6%), and *H. influenzae* (85.7%) were most commonly detected in children

under 2 years of age, whereas SARS-CoV-2 was predominantly found in children over 10 (47.4%) and under 2 years of age (44.7%). The comparison of the incidence of viruses according to age showed that the incidence of RSV and *H. influenza* was significantly higher in children under 2 years old based on statistical comparisons ($p < 0.001$ and 0.026 , respectively). While the incidence of SARS-CoV-2 was significantly higher in children over 10 years of age, the incidence of HBoV was significantly lower in children over 10 years of age based on statistical comparison ($p < 0.001$ and $p = 0.022$, respectively). In addition, the incidence of RV was significantly higher in children between the ages of 2 and 5 than in children under the age of 2 and over the age of 10 ($p = 0.047$) (Table 3).

Comparing clinical and laboratory results indicated by pathogens detected as virus, bacteria, or virus and bacteria, there was no significant difference in terms of clinical results, radiographic results, neutrophil count, neutrophil/lymphocyte ratio, and C-reactive protein levels among the pathogens. The white blood cell count was significantly higher in children who tested positive for both virus and bacteria in their respiratory tract specimens than in children who tested positive for only virus, and the lymphocyte count was significantly higher in children who detected virus in their respiratory tract specimens ($p = 0.013$ and $p < 0.01$, respectively) (Table 4).

While empirical antibiotic therapy was started for 80.2% ($n = 198$) of patients at the time of initial diagnosis, only 19.8% ($n = 49$) of patients were not given antibiotics. The

rate of starting empirical antibiotic therapy in patients with a virus identified in their respiratory tract specimens was 80.5% ($n = 145$).

There was no significant difference in the duration of hospitalization according to pathogens and the patients' gender ($p = 0.341$, $p = 0.774$), however there was longer hospitalization with children over the age of 10 years ($p = 0.011$).

Highlights

- Lower respiratory tract infections (LRTIs) are one of the most common causes of hospitalization in the early childhood period
- Using real-time multiplex polymerase chain reaction, at least one pathogen was identified in 88.3 % of patients with LRTIs
- Viruses were responsible for 74.9% of LRTIs
- Respiratory syncytial virus (24.7%) and human bocavirus (21.1%) were the most common viruses causing LRTIs
- Bacteria were detected in 7.7% of patients, and *Haemophilus influenzae* was the most common etiological agent.

Discussion

LRTIs are an important cause of morbidity and mortality in children aged under five years, especially in developing countries. In European and North American countries, the incidence of pneumonia has been reported to be 34-40% in children aged under five years and 7% in adolescence.¹⁵ In Türkiye, Saka Umit et al.¹⁶ reported that 81% of children hospitalized with pneumonia were aged 5 years. Similarly, in our study, the rate of children hospitalized with LRTI aged 5 years was high (82.6%).

In many studies, it has been reported that LRTIs are more common in males. Michelow et al.⁶ reported that 62% of patients with LRTIs were male, and Aksoy et al.¹⁷ reported that 65.5% were male. In contrast, Saka Umit et al.¹⁶ reported that 46.7% of patients with LRTIs were male. In our study, males comprised 61.9% of the study group.

Etiologic pathogens of LRTIs vary according to patient age. RSV is the most common viral pathogen, especially in infants; it is responsible for 30-67% of hospitalizations of children with pneumonia.^{2,10} *S. pneumoniae* is the

Table 1. Demographic and clinical characteristics of 247 children with lower respiratory infections

	n (%)		n (%)
Age (year)		Symptoms during the hospital admission	
1ay-<2	148 (59.9)	Cough	184 (74.5)
		Fever	115 (46.6)
		Wheezing	72 (29.1)
		Nasal congestion	52 (21.1)
2-<5	56 (22.7)	Dyspnea	46 (18.6)
5-10	21 (8.5)	Tachypnea	32 (13)
>10	22 (8.9)	Auscultation findings	
Sex (Male/Female)	153/94 (61.9-38.1)	Crepitation	141 (57.1)
		Prolonged expiration/sibilant rhonchi	96 (38.9)
Gestational age		Using accessory respiratory muscles	151 (61.1)
37 weeks	189 (76.5)	Decrease in breath sounds	18 (7.3)
<37 weeks	58 (23.5)	None	11 (4.5)
Route of delivery		HFNCO	66 (26.7)
Vaginal delivery	94 (38.1)	Admission time (day)	6.13±2.93 (2-20)
Cesarean section	153 (61.9)		

HFNCO; High-flow nasal cannula oxygen

Table 2. Results of respiratory samples analyzed by real-time multiplex polymerase chain reaction

Pathogens	All patients (n=247) n (%)	Patients treated with HFNCO (n=66) n (%)
Virus	185 (74.9)	50 (75.8)
Bacteria	19 (7.7)	4 (6.1)
Virus + bacteria	14 (5.7)	3 (4.5)
RSV	67 (27.1)	25 (37.9)
HBoV	52 (21.1)	17 (25.8)
RV	39 (15.8)	9 (13.6)
SARS-CoV-2	38 (15.4)	5 (7.6)
PIV-3	35 (14.2)	9 (13.6)
<i>H. influenzae</i>	28 (11.3)	7 (1.6)
<i>S. pneumonia</i>	5 (2)	-
CoV OC43	5 (2)	-
IFV A	3 (1.2)	-
hMPV	2 (0.8)	-
AdV	1 (0.4)	-
Negative samples	29 (11.7)	9 (13.6)

RSV; Respiratory syncytial virus, HBoV; Human bocavirus, RV; Rhinovirus, SARS-CoV-2; Severe acute respiratory syndrome coronavirus 2, PIV 3; Parainfluenza viruses 3, CoV; Coronaviruses, IFV A; Influenza viruses A, hMPV; Human metapneumovirus, AdV; Adenovirus, HFNCO; High-flow nasal cannula oxygen

Table 3. Distribution of pathogens analyzed by real-time multiplex polymerase chain reaction according to the age groups

	<2 year	2-<5 year	5-10 year	>10 year	p*
RSV (n=67) n (%)	54 (80.6) ^a	10 (14.9) ^b	1 (1.5) ^b	2 (3) ^b	<0.001
HBoV (n=52) n (%)	30 (57.7) ^a	15 (28.8) ^a	7 (13.5) ^a	0 (0.0) ^b	0.022
RV (n=39) n (%)	20 (51.3) ^a	15 (38.5) ^b	3 (7.7) ^{a,b}	1 (2.6) ^a	0.047
SARS-CoV-2 n (%)	17 (44.7) ^a	2 (5.3) ^a	1 (2.6) ^a	18 (47.4) ^b	<0.001
PIV-3 (n=35) n (%)	24 (68.6) ^a	7 (20) ^{a,b}	4 (11.4) ^a	0 (0.0) ^b	0.172
<i>H. influenzae</i> (n=28) n (%)	24 (85.7) ^a	3 (10.7) ^b	1 (3.6) ^{a,b}	0 (0.0) ^b	0.026
<i>S. pneumonia</i> (n=5) n (%)	3 (60)	1 (20)	0 (0.0)	1 (20)	0.788
CoV OC43 (n=5) n (%)	2 (40)	2 (40)	1 (20)	0 (0.0)	0.497
IFV A (n=3) n (%)	1 (33.3)	1 (33.3)	1 (33.3)	0 (0.0)	0.364
hMPV (n=2) n (%)	1 (50)	1 (50)	0 (0.0)	0 (0.0)	0.790
AdV (n=1) n (%)	1 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0.880

*Chi-square or Fischer's-exact test.
^{a,b}; Indicate the differences between the groups
 RSV; Respiratory syncytial virus, HBoV; Human bocavirus, RV; Rhinovirus, SARS-CoV-2; Severe acute respiratory syndrome coronavirus 2, PIV 3; Parainfluenza viruses 3, CoV; Coronaviruses, IFV A; Influenza viruses A, hMPV; Human metapneumovirus, AdV; Adenovirus

most common cause of bacterial pneumonia in the whole age group.^{3,9,10,18} A systematic review published before the use of conjugated pneumococcal and *H. influenzae* type B vaccines reported that *S. pneumoniae* and *H. influenzae* were the most common bacterial agents. RSV is present in 15-40% of viral pathogens, and IFV A-B, PIV, hMPV, and AdV have been reported as other common viral pathogens.¹⁹ The frequency of viral pathogens in the etiology of pneumonia has begun to increase after the use of conjugated pneumococcal and *H. influenzae* type B vaccines.²⁰ In a recent study conducted in South Africa, at least one virus was found to be the causative agent in 87% of the cases.²¹ In another study conducted in the Netherlands, viruses were identified in 72% of pneumonia.²² At least one viral agent was found in 41.8% and 67.8% of patients in studies conducted in Türkiye.^{23,24} In our study, in 80.6% of the cases, at least one virus was identified. In our country, viral pathogens are increasingly predominant because of the high coverage of pneumococcal and *H. influenzae* type B conjugate vaccination.

The COVID-19 outbreak caused by SARS-CoV-2 started in December 2019 and became a pandemic spreading world.²⁵ The clinical manifestations of the disease range from asymptomatic infection to acute respiratory distress syndrome. Most children show asymptomatic or mild symptomatic disease.²⁶⁻²⁸ According to a recent review conducted in USA, which included of the 82.798 children with laboratory confirmed SARS-CoV-2 infection, 66% of the cases were asymptomatic, 27% were mild, 5% were moderate, and 2% were severe diseases requiring intensive care unit (ICU) admission.²⁶ In our study, SARS-CoV-2 was responsible for 15.4% of the LRTIs, and most of the infected children were under two or older than 10 years. Because of the expectation of severe clinical manifestation, infants with SARS-CoV-2 infection were hospitalized with fever rather than significant respiratory symptoms. In contrast, children older than 10 years were mainly admitted with fever and parenchymal infiltration on radiography. In our study, none of them required ICU admission.

Table 4. Comparison of the clinical and laboratory finding according to the etiological pathogens

	Virus (n=185)	Bacteria (n=19)	Virus+bacteria (n=14)	p
Fever n (%)	88 (47.6)	10 (52.6)	7 (50)	0.547*
Cough n (%)	139 (75.1)	15 (78.9)	9 (64.3)	0.784*
Wheezing n (%)	56 (30.3)	5 (26.3)	5 (35.7)	0.686*
Crepitation n (%)	107 (57.8%)	12 (63.2%)	8 (57.1%)	0.901*
Prolonged expiratory phased/sibilant rhonchi n (%)	75 (40.5%)	3 (15.8%)	5 (35.7%)	0.105*
WBC x10 ³ /mm ³ mean ± SD	12.45±7.15	15.89±5.86	17.22±9.47	0.013**
Neutrophil x10 ³ /mm ³ mean ± SD	7.72±6.04	9.59±8.87	9.15±6.69	0.372**
Lymphocyte x10 ³ /mm ³ mean ± SD	6.37±2.87	3.35±2.44	4.51±2.87	<0.001**
NLR	2.5±4	4.09±4.9	3.72±4.83	0.413**
CRP (mean ± SD)	22.98±38.5	11.06±14.57	15 ±23.16	0.314**
Finding of chest X-ray				
Bronchiolitis	67 (89.3)	7 (9.3)	1 (1.3)	0.208*
Bronchopneumonia	109 (82)	12 (9)	12 (9)	
Lobar pneumonia	9 (90)	0	1 (10)	

*Chi-square or Fischer's-exact test
**One-Way ANOVA
WBC; White blood cell, NLR; Neutrophil/Lymphocyte ratio, CRP; C-reactive protein, SD; Standard deviation

RSV is the most common cause of LRTIs, particularly in infants. Do et al.²² (24%) and Iwane et al.²⁹ (20%) reported that RSV was the most frequently detected viral agent in their studies. In the studies conducted in Türkiye, RSV was reported as a causative agent of LRTIs in 61.2% of pediatric cases by Akçalı et al.²³ and 44.7% by Tanır et al.³⁰ In our study, RSV was again the most common viral agent with a rate of 27.1%. RSV was most frequently observed in children under the age of 5 years as the cause of LRTIs. Appak et al.³¹ reported that the age relation was significant for RSV, which was most frequently identified (89%) in children under 5 years of age. Similarly, 80.6% of RSV infections were detected in patients younger than 2 years of age, and this rate was statistically significant. According to our study, the occurrence of LRTIs caused by RSV was found to be less frequent than that in previous studies conducted with infants or children under 10 years of age. This result may be due to prolonged community isolation due to the COVID-19 pandemic to save infants from droplet infections.

Since its definition in 2005, the prevalence of HBoV has been reported to be 2-21.5%, especially in children aged under three years with upper and LRTIs.³² Its prevalence in children aged under two years with bronchiolitis was reported as 1.8-37.1%, whereas a meta-analysis published in 2020 has been reported as 13%.³³⁻³⁶ Sancaklı et al.²⁴ detected HBoV in 2.3% of children with LRTIs. In our study, HBoV was detected in 21.1% of children with LRTIs.

Sancaklı et al.²⁴ reported that RV was the most common pathogen in children with LRTIs and had a higher prevalence in children aged 3 years. A study from China also reported RV as the most common viral pathogen in LRTIs.²⁵ However, in our study, RV was the third most common pathogen. On the other hand, similar to the literature, it was most frequently observed in children under 2 years of age.

Parainfluenza virus is an important cause of upper and LRTIs at all ages. It can lead to more serious symptoms, especially in infants and during early childhood.³⁷⁻⁴⁰ There are four serotypes of PIV, namely PIV1,2,3,4.

PIV-3 is the most common and is often associated with pneumonia and bronchiolitis.⁴⁰ Zhao et al.⁴¹ found PIV in 31.12% of cases, Iwane et al.²⁹ 7%, and Howard et al.⁴⁰ in 6.6%. In addition, Etemadi et al.⁴² reported the rate of PIV to be 4.8% in hospitalized children under 5 years of age with LRTI, and they reported PIV3 in 50% of these cases. Sancaklı et al.²⁴ reported PIV in 2.3% of children with LRTI. On the other hand, in our study, PIV was the causative agent in 14.2% of the cases, and all were type 3. In addition, its infection was most frequently identified (88.6%, n=31) in children under 5 years of age in our study, which was consistent with the literature.

With the use of the RT-MPCR test for identifying respiratory tract pathogens, researchers have reported that more than one agent was detected in the same patient. Co-infection with more than one pathogen was reported in up to 51.8% of patients.^{23,43,44} Akçalı et al.²³ reported that 10.4% of patients had co-infection with RSV-rhinovirus, RSV-coronavirus, rhinovirus-coronavirus, and RSV-rhinovirus-coronavirus. In our study, 21.5% (n=53) of patients were co-infected with more than one pathogen. PIV and RV were the most common pathogens associated with co-infection. Howard et al.⁴⁰ detected co-infections in 50% of PIV infections, mainly with RV, RSV, and AdV, and 16% of them as bacterial agents. Etemadi et al.⁴² reported that 37.5% of PIV cases had co-infection. In our study, 57.1% (n=20) of PIV patients had co-infection most commonly with HBoV (n=9; 25.7%), RSV (n=7; 20%), and RV (n=6; 17.1%). Co-infection was detected in 48.7% (n=19) of RV infections, and the most common pathogens co-infected with RV were RSV (n=8; 20.5%), PIV (n=6; 15.4%), and HBoV (n=4; 10.3%). Appak et al.³¹ reported that RSV was responsible for 25.2% of the coinfections. In another study, Frobert et al.⁴⁵ reported that RSV (24.3%) was the most commonly detected virus in co-infections. In our study, 38.8% (n=26) of RSV infections were co-infected with other pathogens such as RV (n=8; 11.9%), PIV (n=7; 10.4%), HBoV (n=7; 10.4%), and *H. influenzae* (n=6; 9%). Co-infection of HBoV with other viruses was reported as 51.7% in a study conducted in Rome.⁴⁶ In this study, RSV and RV were the viruses that

most commonly co-infected with HBoV, MPV, PIV, and others.⁴⁶ In our study, 38.5% (n=20) of HBoV was co-infected with the other pathogens. PIV 3 (n=9; 17.3%) was the most co-infected pathogen with HBoV, and the others were RSV (n=7; 13.5), RV (n=4; 7.7%), and *H. influenzae* (n=2; 3.8%).

There are some limitations to our study. First, our study has the limitations of any retrospective study. Second, the study was conducted only with hospitalized patients, and there were no data on outpatients. Third, the RT-MPCR test was able to identify only 23 respiratory tract pathogens.

Conclusion

In our study, we detected a positive pathogen ratio of 88.3% using RT-MPCR in 24 h. Most pathogens responsible for LRTIs were viruses. Although the study was conducted during the last period of the COVID-19 pandemic, after longtime community isolation, RSV was still the leading cause of LRTIs in children. It was remarkable that HBoV was the second leading pathogen. Identifying the causative pathogens of LRTIs in a short time will be important for avoiding unnecessary antibiotic usage.

Ethical Approval: The study was approved by the Ethics Committee of Medeniyet University Göztepe Training and Research Hospital (approval date: 16.03.22; approval number: 2022/0150) before the experiment was started and was conducted in accordance with the principles set forth in the Helsinki Declaration.

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

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

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