# Evaluation of Viral Acute Lower Respiratory Tract Infections Detected with Real-Time Polymerase Chain Reaction

## Real-Time Polymerase Chain Reaction ile Tespit Edilen Viral Akut Alt Solunum Yolu Enfeksiyonlarının Değerlendirilmesi

Emine POLAT, Husniye YUCEL

SBU Ankara Dr. Sami Ulus Obstetrics, Children Health and Diseases Training and Research Hospital, Department of Child Health and Diseases, Ankara, Turkey

## ABSTRACT

**Objective:** Acute lower respiratory tract infection (ALRTI) is the most frequent cause of hospitalization in infantsyounger than 5 years. In the main, alveolar and bronchial infections are responsible for 90% of deaths from respiratory disease. The aim of this study was to investigate the epidemiology, clinical findings, and treatment modalities of respiratory viruses detected with real-time polymerase chain reaction (PCR).

**Material and Methods:** A total of 235 children between the age of 1 and 24 months who were hospitalized due to ALRTI between January 2014 and December 2018 and who had positive PCR results for respiratory viruses were included in the study. Demographics, clinical findings, laboratory tests, treatment modalities, need for the high-frequency nasal cannula (HFNC) or mechanical ventilation, length of hospital stay, and the requirement for treatment within a pediatric intensive care unit (PICU) were recorded.

**Results:** In total, 55.5% of the children were male with a mean age of 6.1±6 months. Respiratory syncytial virus (RSV) was present in 106, rhinovirus in 35, influenza in 23, and other viruses in the remaining 71. There was a significant seasonal difference among the various etiologies. Fever was present in patients with influenza, multiple viral infections, adenovirus, and human metapneumovirus (HMPV). There was no significant difference in the physical examination among patients presenting with a pertussis-like cough, feeding difficulty, or lethargy. The white blood cell (WBC) count increased due to adenovirus and HMPV infection; however, differences in C-reaktif protein(CRP), mean platelet volume (MPV), and eosinophilia were not significant. There was no significant difference between the chest X-ray findings and medical treatment based on the viral etiology. Fifty-four patients were followed up in the PICU. Although influenza was only the third most common etiology, it was the most common cause of PICU admission.

**Conclusion:** RSV continues to be an important viral etiology for hospitalization in children below 2 years old. Influenza was the most frequent virus requiring admission to the PICU. Widespread immunization against influenza has been related to the decline of the LRTI in children.

**Key Words:** Acute lower respiratory tract infection, Children, Viruses

## ÖZ

**Amaç:** Akut alt solunum yolu enfeksiyonu (ALRTI), 5 yaşından küçük bebeklerde en sık hastaneye yatış nedenidir. Çoğunlukla, alveolar ve bronşiyal enfeksiyonlar, solunum hastalıklarından kaynaklanan ölümlerin %90'ından sorumludur. Bu çalışmanın amacı, real-time PCR ile saptanan solunum yolu virüslerinin epidemiyolojisini, klinik bulgularını ve tedavi yöntemlerini incelemektir.

POLAT E : 0000-0003-3034-5037
YUCEL H : 0000-0002-7477-0302

**Conflict of Interest / *Çıkar Çatışması*:** On behalf of all authors, the corresponding author states that there is no conflict of interest.

**Ethics Committee Approval / *Etik Kurul Onayı*:** The study was approved by the local ethics and research committee ( Health Sciences University Ankara Child Health and Diseases Hematology Oncology SUAM, Protocol: 2019/223).

***Contribution of the Authors / Yazarların katkısı*: *POLAT E:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Reviewing the article before submission scientifically besides spelling and grammar. ***YUCEL H:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in the writing of the whole or important parts of the study.

**How to cite / *Atıf yazım şekli* :** Polat E, Yücel H. Evaluation of Viral Acute Lower Respiratory Tract Infections Detected with Real-Time Polymerase Chain Reaction . Turkish J Pediatr Dis 2021;15:129-136.

**Additional information / *Ek bilgi*:** We would like to express our appreciation to Associate Professor Dr. Sanliay SAHIN for her valuable and constructive suggestions during the planning and development of this research work.

Correspondence Address / Yazışma Adresi:

**Emine POLAT**
SBU Ankara Dr. Sami Ulus Obstetrics,
Children Health and Diseases Training and Research Hospital,
Department of Child Health and Diseases, Ankara, Turkey
E-posta: emine227@yahoo.com

Received / Geliş tarihi : 18.11.2020
Accepted / Kabul tarihi : 22.12.2020
Online published : 25.02.2021
Elektronik yayın tarihi
DOI: 10.12956/tchd.827700

**Gereç ve Yöntemler:** Ocak 2014-Aralık 2018 tarihleri arasında ALRTI nedeniyle hastaneye yatırılan ve solunum yolu virüsleri için pozitif PCR sonuçları olan 1-24 aylık toplam 235 çocuk çalışmaya dahil edildi. Demografik veriler, klinik bulgular, laboratuvar testleri, tedavi modaliteleri, yüksek frekanslı nazal kanül (HFNC) veya mekanik ventilasyon ihtiyacı, hastanede kalış süresi ve çocuk yoğun bakım ünitesinde (ÇYBB) tedavi gereksinimi kaydedildi.

**Bulgular:** Toplamda çocukların %55.5'i erkekti ve yaş ortalaması 6.1±6 aydı. Respiratuvar sinsityal virüs (RSV) 106'da, rinovirüs 35'te, influenza 23'te ve diğer virüsler kalan 71'de mevcuttu. Çeşitli etiyolojiler arasında önemli bir mevsimsel farklılık vardı. Ateş influenza, çoklu viral enfeksiyonlar, adenovirüs ve human metapnömovirüs (HMPV) hastalarında vardı. Boğmaca benzeri öksürük, beslenme güçlüğü veya letarji ile başvuran hastalar arasında fizik muayenede anlamlı fark yoktu. Adenovirüs ve HMPV enfeksiyonu nedeniyle WBC sayısı arttı; ancak CRP, MPV ve eozinofilideki farklılıklar anlamlı değildi. Viral etiyolojiye göre akciğer grafisi bulguları ile medikal tedavi arasında anlamlı bir fark yoktu. ÇYBB'de elli dört hasta izlendi. İnfluenza sadece üçüncü en yaygın etiyoloji olmasına rağmen, ÇYBB'ye kabulün en yaygın nedeniydi.

**Sonuç:** RSV iki yaşın altındaki çocuklarda hastaneye yatış için önemli bir viral etiyoloji olmaya devam etmektedir. İnfluenza, ÇYBB'de izlenmeyi gerektiren en sık görülen virüstür. İnfluenzaya karşı yaygın aşılama, çocuklarda ASYE'nin azalmasıyla ilişkilidir.

**Anahtar Sözcükler:** Alt solunum yolu enfeksiyonu, Çocuk, Virüsler

## INTRODUCTION

Acute lower respiratory tract infection (ALRTI) presenting as pneumonia or acute bronchiolitis is the most frequent cause of hospitalization in infants below 2 years old worldwide (1-3). The etiology of ALRTI in infants may be either bacterial (Streptococcus pneumoniae, Haemophilus influenzae type b, Mycoplasma pneumonia) or viral (respiratory syncytial virus (RSV), influenza, parainfluenza, adenovirus, rhinovirus, human metapneumovirus (HMPV), coronavirus or bocavirus) (4,5). Viruses cause the majority of these childhood respiratory infections and are associated with significant morbidity and mortality, especially in developing countries (5-7). Prevention and treatment of these infections is a major health problem, not only for the people but also for pediatricians, because ALRTI accounts for many emergency room visits and hospitalizations.

We investigated the epidemiology, clinical presentation, and treatment of respiratory viruses detected with real-time PCR in infants hospitalized due to ALRTI.

## MATERIAL and METHODS

A total of 235 children between the age of 1 and 24 months who were hospitalized due to ALRTI between January 2014 and December 2018 and who had positive PCR results for respiratory viruses were included in the study. A total of 606 patients with ALRTI were tested during the study period, and 38.7% had positive PCR results. The results of all patients' medical history, vital signs, physical examination, routine laboratory tests, and chest X-ray were collected. A viral etiology was investigated using nasopharyngeal swab samples with a real-time Respiratory PCR Kit (Fast-track diagnostics Multiplex Real-Time PCR). Data, including age, gender, presence of fever, cough, pertussis-like coughing, vomiting, runny/congested nose, nutritional status, lethargy, contact with anyone having an upper respiratory tract infection (URTI), smoking status of the family, vaccination status of the infant, being born prematurely or at term, presence of heart disease, PCR results, laboratory test results, blood culture, chest X-ray interpretation, and treatment modalities were recorded. Also, the need for the high-frequency nasal cannula (HFNC) or mechanical ventilation, length of hospital stay, and admission to the pediatric intensive care unit (PICU) were recorded. Nosocomial infections and clinical complications, such as pneumothorax, effusion, and cardiac failure, were also recorded. The results of the viral PCR testing were compared. Patients who were <1 month of age; who had an underlying chronic disease or malignancy, malnutrition, immunodeficiency, or incomplete medical records; or were born preterm and diagnosed with chronic lung disease or bronchopulmonary dysplasia were excluded. Infants born late preterm without any known pulmonary problems were included. Some of the patients were diagnosed with mild congenital heart disease following admission due to ALRTI. Any patient followed up at our hospital, who was diagnosed with congenital heart disease not requiring medical or surgical treatment (insignificant structural heart defects, mild congenital valve malformations, patent foramen ovale, small patent ductus arteriosus, etc.), were included.

The study was approved by the local ethics and research committee ( Health Sciences University Ankara Child Health and Diseases Hematology Oncology SUAM, Protocol: 2019/223).

### Statistical analysis

SPSS for Windows 20 (Statistical Package for the Social Sciences Inc., Chicago, IL) was used for data analysis. The distributionof continuous variableswas examined byShapiro–Wilk and Kolmogorov–Smirnov normality tests, and the data were analyzed by Student's t-test, chi-squared test, and Mann–Whitney U test. For the significance amongmore than two independent groups, the Kruskal–Wallis test was used. Multivariate analysis of independent variables was conducted using logistic regression analysis. P values < 0.05 were considered significant.

## RESULTS

Of the patients, 128 (55.5%) were male and 107 (45.5%) were female, and the mean age was 6.1 ± 6 months. The viral etiology by PCR was RSV 106 (45.1%); rhinovirus 35(14.9%); influenza 23 (9.8%); multiple respiratory viruses 20 (8.5%); adenovirus 14(6%); bocavirus 13 (5.5%); parainfluenza 9 (3.8%); HMPV 9 (3.8%) and coronavirus 6 (2.6%). The viral etiologies are listed in Table I. RSV infection 80 (75.5%), influenza 17 (73.9%), multiple viral infections 13 (65%), adenovirus 7 (50%) and bocavirus 6 (46.2%) were primarily observed in winter; parainfluenza evenly spaced with 33.3% in spring and 33.3% in winter; and rhinovirus 16(45.7%), HMPV 6(66.7%) and coronavirus 5(83.3%) in spring. The frequency of viral agents by seasons is shown in Figure 1. Seasonal differences were statistically significant ($p < 0.001$).

Patients' demographics and clinical features are summarized in Table 2. Patients admitted due to ALRTI caused by influenza, adenovirus, HMPV, and multiple viral infections presented with fever, whereas those infected with RSV, rhinovirus, bocavirus, parainfluenza, and coronavirus did not, indicating a significant difference in terms of presentation with fever ($p = 0.005$, Table II).

The presenting symptoms of ALRTI caused by adenovirus and parainfluenza were primarily vomiting ($p = 0.006$), whereas rhinorrhea was the primary presenting symptom of ALRTI caused by RSV, multiple viral infections, adenovirus, parainfluenza, and coronavirus ($p < 0.05$). The presenting complaints including cough, pertussis-like coughing, feeding difficulty, and lethargy had no relationship with the type of virus associated with ALRTI ($p> 0.05$). When we encountered pertussis-like coughing, we performed both bacterial cultures and PCR to distinguish a viral etiology from pertussis. As a result, pertussis-positive cases were not observed in our study group. Physical examination findings (tachypnoea, retractions, rhonchi, and wheezing) were not significantly different among the various aetiologies ($p > 0.05$). Only crackles were significant ($p = 0.003$), which were primarily present with RSV, influenza, multiple infections, and adenovirus.

White blood cell (WBC) count significantly increased due to adenovirus and HMPV infections ($p = 0.001$). However, the CRP and MPV levels and eosinophilia were not significant predictors of the type of virus associated with ALRTI ($p > 0.05$).

Chest X-ray was performed on 225 patients, of whom 34 (14.5%) had normal findings and 160 (68%) had mild pericardiac infiltration. Hyperinflation was present in 25 (10.6%), 22 (9.3%) had lobar infiltration, 17 (7.2%) had atelectasis, 6 (2.5%) had pneumothorax and 4 (1.7%) had pleural effusion. There was no statistically significant relationship between the chest X-ray findings and viral etiology ($p > 0.05$). The patients' medical care is summarized in Table III. There was no statistically significant relationship between medical treatment and viral etiology ($p > 0.05$).

A high percentage of the patients, i.e. 54 (23%), were admitted to the PICU, and this was significantly related to the viral etiology ($p = 0.002$). More than one-third of patients with ALRTI caused by influenza (39.1%) required PICU admission. This was followed by multiple viral infections (30%), rhinovirus (25.7%), parainfluenza (22.2%), adenovirus (21.4%), and RSV (20.8%). Fifteen patients (6.4%) required intubation and mechanical ventilation. The average duration of PICU stay was 8±13.3 days, and the duration of total hospital stay was 9.4±8.6 days. Also, we compared single viral infections with cases with co-infections regarding hospital stay and observed a longer hospital stay in patients with co-infections ($p = 0.006$).

Complications occurred as follows: pneumothorax 7 (2.9%), pleural effusion 4 (1.7%), congestive heart failure 2 (0.8%), bronchiolitis obliterans 1 (0.4%), subcutaneous emphysema/pneumopericardium 1 (0.4%) and necrotizing pneumonia 1 (0.4%). A total of 11 (4.7%) patients developed nosocomial infections, and 49 (20.9%) had recurrent ALRTI at follow-up. Recurrence was primarily observed with HMPV infections (66.7%) followed by influenza (43.5%), rhinovirus (37.1%)

**Table I:** Viral agents identified in the infant's nasopharyngeal swab samples.

| Patogen virus | Frequency | Percentage |
|---|---|---|
| **RSV** | 106 | 45.1 |
| **Rhinovirus** | 35 | 14.9 |
| **Influenza** | 23 | 9.8 |
| **Multıble respiratory viruses** | 20 | 8.5 |
| **Adenovirus** | 14 | 6 |
| **Bocavirus** | 13 | 5.5 |
| **Parainfluenza** | 9 | 3.8 |
| **HMPV** | 9 | 3.8 |
| **Coronavirus** | 6 | 2.6 |

***RSV:*** *Respiratory syncytial virus,* ***HMPV:*** *Human metapneumovirus*

**Table II:** Demographics and clinical features.

| Variables | ALRTI (n = 235) | p |
|---|---|---|
| **Age, Mean ± SD (median)** | 6.1 ± 6.0 (4) | p > 0.05 |
| **Gender** | | |
| Male, n (%) | 128 (55.4) | |
| Female, n (%) | 107 (45.5) | p > 0.05 |
| **Season, *** | | |
| Spring | 67 (28.5) | |
| Summer | 20 (8.5) | p < 0.001 |
| Autumn | 12 (5.1) | |
| Winter | 136 (57.9) | |
| **Primary symptom on admission, *** | | |
| Cough | 226 (96.2) | p > 0.05 |
| Rhinorrhea | 138 (58.7) | p < 0.05 |
| Fever | 100 (42.6) | p = 0.005 |
| Vomiting | 71 (30.2) | p = 0.006 |
| Pertussis-like coughing | 68 (28.9) | p > 0.05 |
| Feeding difficulty | 59 (25.1) | p > 0.05 |
| Lethargy | 19 (8.1) | p > 0.05 |
| **Contact with a person who had a URTI, *** | 179 (67.7) | p > 0.05 |
| **Parental smoking, *** | 125 (53.2) | p > 0.05 |
| **Incomplete vaccination, *** | 26 (11.1) | p > 0.05 |
| **Any diagnosed disease, *** | 31 (13.2) | p > 0.05 |
| **Congenital heart disease, *** | 42 (17.9) | p > 0.05 |
| **Prematurity, *** | 38 (16.2) | p > 0.05 |
| **Physical examination, *** | | |
| Tachypnea | 173 (73.6) | p > 0.05 |
| Crackles | 146 (62.1) | p = 0.003 |
| Retractions | 131 (55.7) | p > 0.05 |
| Rhonchi | 100 (42.6) | p > 0.05 |
| Wheezing | 26 (11.1) | p > 0.05 |
| **Anaemia, *** | 129 (54.9) | p > 0.05 |
| **White blood cell count, *** | | p = 0.001 |
| Low | 46 (19.6) | |
| Normal range | 129 (54.9) | |
| High | 60 (25.5) | |
| **Mean platelet volume count, *** | | p > 0.05 |
| Low | 20 (8.5) | |
| Normal range | 191 (81.3) | |
| High | 24 (10.2) | |
| **C-Reaktif protein, *** | | p > 0.05 |
| Normal range | 103 (43.8) | |
| High | 132 (56.2) | |
| **Eosinophilia, *** | 24 (10.2) | p > 0.05 |
| **Elevated liver enzymes, *** | 20 (8.5) | p > 0.05 |
| **Elevated renal enzymes, *** | 1 (0.4) | p > 0.05 |
| **Need for HFNC, *** | 77 (32.8) | p > 0.05 |
| **Duration of HFNC (days)** | 3.4 ± 2.3 (3)<br>min=1; max=14 | p > 0.05 |
| **Need For PICU admission, *** | 54 (23) | p = 0.002 |
| **Need for mechanical ventilation,*** | 15 (6.4) | p > 0.05 |
| **Duration of mechanical ventilation (days)** | 10.8 ± 10.4 (5) | min=1; max=31 |
| **Duration of PICU stay (days)** | 8 ± 13.3 (3) | p > 0.05 |
| **Total length of stay (days)** | 9.4 ± 8.6 (7)<br>min:2,max:78 | p > 0.05 |

***:** *n(%),* ***HFNC:** High-frequency nasal cannula;* ***PICU:** Pediatric intensive care unit*

**Table III:** Medical treatment received.

| Medications | n (%) | p |
|---|---|---|
| **Inhaled medications** | | |
| Oxygen | 230 (97.9) | p > 0.05 |
| Salbutamol | 181 (77) | p > 0.05 |
| Adrenaline | 44 (18.7) | p > 0.05 |
| Inhaled steroids | 41 (17.5) | p > 0.05 |
| Inhaled NaCl | 8 (3.4) | p > 0.05 |
| **Intravenous medications** | | p > 0.05 |
| Steroids | 126 (53.6) | p > 0.05 |
| MgSO4 | 77 (32.8) | |
| **Antibiotics** | | p > 0.05 |
| No antibiotics | 8 (3.4) | |
| SAM | 56 (23.8) | |
| AMC + Clarithromycin | 39 (16.5) | |
| AMC | 25 (10.6) | |
| SAM + Clarithromycin | 21 (8.9) | |
| Ceftriaxone | 20 (8.5) | |
| Cefotaxime–Ampicillin | 12 (5.1) | |
| Ceftriaxone-Clarithromycin | 10 (4.2) | |
| Cefotaxime | 6 (2.6) | |
| Clindamycin | 3 (1.2) | |
| Meropenem–Vancomycin | 2 (0.8) | |
| Piperacillin–Tazobactam | 2 (0.8) | |
| Other combinations | 29 (12.3) | |
| **Antivirals** | 76 (32.3) | p > 0.05 |
| Oseltamivir | 1 (0.4) | |
| Acyclovir | | |

***SAM:*** *Ampicillin–Sulbactam,* ***AMC:*** *Amoxicillin–Clavulanate*

**Table IV:** Characteristics of patients who died.

| Case | Gender/Age (month) | Duration of PICU stay (days) | Viral etiologies |
|---|---|---|---|
| **1** | M/6 | 4 | Multiple respiratory viruses |
| **2** | F/2 | 6 | Corona virus |
| **3** | F/8 | 35 | Influenza |
| **4** | M/5.5 | 4 | Rhinovirus |

and multiple viral infections (35%). These findings were highly significant ($p < 0.001$). No difference was observed among the groups regarding complications and nosocomial infections ($p > 0.05$).

A total of four patients died. The patients who died are summarized in Table IV. No significant difference was observed between viral aetiologies and mortality ($p > 0.05$).

## DISCUSSION

Over time, we had observed clinically that alrti caused by influenza is more severe than expected and often required intensive care; however, we did not know if this would be statistically significant. Therefore, we investigated the epidemiology and clinical presentation of viral alrti detected with real-time pcr in infants < 24 months of age.As noted in a previous study, male patients predominated in our study (8). The mean age for patients in our study was 6.1 Months, as opposed to 9.5 Months for rsv infection in a recent study and 4 months in a large, prospective, multicentre study (8,9). The difference can be attributed to different inclusion criteria. Although testing for viral etiology in current clinical care is limited due to false negatives when rapid antigen testing is used and is not strongly recommended in guidelines, it is strongly recommended in clinical trials and epidemiological studies to identify crucial outcome differences based on the viral etiology (10-14). We found rsv to be the most frequently identified virus in patients with alrti as have others (8,13,15,16). Rsv was followed by rhinovirus (14.9%), Influenza (9.8%), And multiple viral infections (8.5%). It has previously been reported that alrti caused by rsv, rhinovirus, bocavirus, and hmpv frequently requires hospitalization,as opposed to that caused by influenza (1.2%) In a prospective multicentre study (16,17). In our study, influenza was the third most common cause of hospitalization. That differs from the low frequency of hospitalization caused by influenza in the global literature, possibly due to differing vaccination strategies (8,16,17). We observed that approximately 40% of the patients with alrti caused by influenza required picu admission, thus making influenza the most frequent cause of picu admission in our study. This is likely because influenza vaccination is not routinely administered in our country.

We found RSV, influenza, multiple viral infections, adenovirus, and bocavirus to occur primarily in winter. Rhinovirus, HMPV, and coronavirus occurred primarily in spring, and parainfluenza was distributed evenly between winter and spring. A previous study from our country reported that RSV and rhinovirus primarily presented in January through March, coronavirus in February, and HMPV in February and March (13).

Some infants with ALRTI may present with fever. Therefore, laboratory tests are often conducted to evaluate for possible serious bacterial infection even though the possibility of bacteremia or bacterial meningitis in infants with ALRTI is low (18,19). In our study, fever was present on admission to a significant degree primarily with influenza, multiple viral infections, adenovirus, and HMPV. This finding differs from that of the literature where no relationship between etiology and fever was found (20). Vomiting was the presenting symptom of ALRTI caused by adenovirus and parainfluenza, whereas rhinorrhea was most often the presenting symptom of ALRTI caused by RSV and multiple viral infections. The cough was noted in 96.2% of the patients followed by nasal congestion and fever, as noted previously (11,13). We found that cough, pertussis-like coughing, feeding difficulty, lethargy, and physical examination findings did not differ significantly depending on the viral etiology. Only crackles were significantly greater in RSV, influenza, multiple viral infections, and adenovirus. Wheezing was present in 11.1% of the patients in our study, as opposed

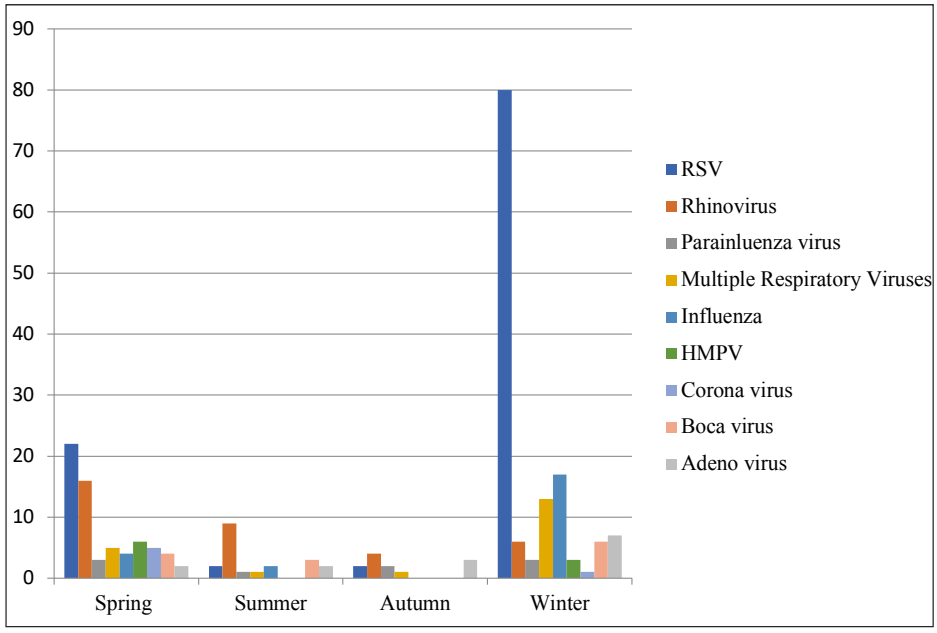


**Figure 1:** Distribution of respiratory viruses by seasons (RSV: Respiratory syncytial virus, HMPV: Human metapneumovirus)

to the study by Akcali et al. (13), in which 43.3% of the patients were wheezing. This is likely since their study included children up to the age of 10 years and may have included children with established asthma.

In a study by Calvo et al.(9), WBC counts were found to be increased when the patient was infected with the rhinovirus. In our study, WBC counts were significantly higher with adenovirus and HMPV infections. In a study in which RSV, bocavirus, and rhinovirus were compared, eosinophilia was significantly greater in the rhinovirus group (21). However, CRP and MPV levels and eosinophilia were not significant predictors for the type of virus associated with ALRTI ($p > 0.05$) in our study.

The 2014 American Academy of Pediatrics (AAP) subcommittee clinical practice guideline-recommended no routine laboratory or radiologic testing for the diagnosis and management of bronchiolitis, but there is evidence that a large amount of testing is still being conducted (11). One analysis found a statistically significant decrease in testing from 65% before the AAP guideline to 49% after the guideline (22). In our study, there was no statistically significant relationship between chest X-ray findings and viral etiology, which supports the guideline. Chest X-ray is still performed, but only on half of the children with bronchiolitis to avoid high cost, radiation exposure, and antibiotic administration (3, 23). In our study, 68% of the patients had an infiltrate on chest X-ray, which is similar to the rate found in the literature (13).

Even though the hospitalization of children has decreased from 2000 to 2009, an increase in the number of children with high-risk medical conditions and disease severity was demonstrated by the increased use of mechanical ventilation (24). Similar to the results in the literature, we found that clinical factors might be more predictive of the severity of ALRTI presenting as bronchiolitis rather than a specific viral etiology (25). Although randomized trials of HFNC are necessary to assess the efficacy, safety, and optimal timing of initiation, following the introduction of HFNC oxygen delivery, intubation rates for infants were significantly reduced (26,27). Almost one-quarter of our patients were admitted to the PICU. As opposed to literature reports of RSV and rhinovirus being the primary etiology of PICU admissions, more than one-third of our patients with ALRTI caused by influenza (39.1%) required admission to the PICU, followed by multiple viral infections, rhinovirus, parainfluenza, adenovirus, and RSV (17). This can be attributed to the absence of influenza vaccine in the routine vaccination schedule in our country. Altogether, 32.8% of our patients received HFNC support with a median of 3 days, and 15 patients (6.4%) of those admitted to the PICU required intubation and mechanical ventilation. No significant differences were observed between the groups, which was similar to previous reports (17,28). Some studies have reported no difference in disease severity and outcomes between patients with single respiratory infections and those with co-infections (28,29). The average duration of PICU stay was 8 days. A large, prospective, multicentre study reported an increased length of stay for those with RSV infections (8). There are studies reporting that the duration of hospital stay in patients with co-infection is longer than in patients with a single agent (17,28,29). We also found longer hospital stays in patients with co-infections.

When the medication was evaluated, general supportive methods included superficial suctioning, hydration, and supplemental oxygen (12,30). The need for oxygen did not differ depending on the viral etiology, and this was consistent with the meta-analysis of Asner et. al (28). Similar to our routine approach, beta-agonists were continuously used commonly in ALRTI presenting as bronchiolitis, despite the evidence that

they do not decrease hospital admissions or length of hospital stay (3,22). We believe, as suggested in the AAP guideline, that a carefully monitored trial of beta-agonists is an option, and clinical improvement can be interpreted as a response to salbutamol (11,12). A meta-analysis involving 2256 patients revealed a significant reduction in hospitalization rates with epinephrine compared with placebo (31). Nevertheless, treatment options that were initially considered promising have been proven to be ineffective subsequently in studies on corticosteroids, nebulized racemic epinephrine, and hypertonic saline (3,32-34). Our clinical practice has been consistent with the literature in this regard. Since we cannot rule out bacterial causes in some infants below 2 years old, we start empirical antibiotic therapy until the results of the PCR are available. Often, the infant's symptoms make it difficult to distinguish viral causes from bacterial causes. Once a positive PCR result is obtained, antibiotic treatment is discontinued.

ALRTI is still a significant cause of mortality in children below 5 years old and is responsible for 11% of deaths from all causes in this age group (4). In our study, mortality occurred in 1.7% of patients admitted to the hospital due to ALRTI.

We found no difference between the various viral aetiologies regarding complications and nosocomial infection. Kotaniemi-Syrjänen et al. (35) found that rhinovirus was an important inducer of wheezing in infancy and was associated with atopy and asthma development. However, in our study, recurrence was mostly seen with HMPV infections (66.7%) followed by influenza, rhinovirus, and multiple viral infections. We believe that further studies are required to confirm the detected rate of recurrence with HMPV infection.

The limitations of this study include its single-center, retrospective design, and thelack ofopportunities in a developingcountry. The strengths of this study include the sample size and the 5-year time frame in which patients were recruited.

## CONCLUSION

RSV still constitutes an important etiology in patients below 2 years old who are hospitalized due to ALRTI. As opposed to prior reports, influenza was one of the most common etiologic agents causing severe ALRTI in our country. We also found that influenza was the most frequent virus associated with PICU admission. Influenza vaccination needs to be recommended routinely in developing countries.

## REFERENCES


1. Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. The Lancet 2010;375:1545-55.
2. Baraldi E, Lanari M, Manzoni P, Rossi GA, Vandini S, Rimini A, et al. Inter-society consensus document on treatment and prevention of bronchiolitis in newborns and infants. Ital J pediatr 2014;40:65.
3. Schroeder AR, Mansbach JM. Recent evidence on the management of bronchiolitis. Curr Opin Pediatr 2014;26:328-33.
4. Derrar F, Izri K, Kaddache C, Boukari R, Hannoun D. Virologic study of acute lower respiratory tract infections in children admitted to the paediatric department of Blida University Hospital, Algeria. New Microbes New Infections 2019;30:100536.
5. Tregoning JS, Schwarze J. Respiratory viral infections in infants: causes, clinical symptoms, virology, and immunology. Clin Microbiol Rev 2010;23:74-98.
6. Liu W, Chen D, Tan W, Xu D, Qiu S, Zeng Z, et al. Epidemiology and clinical presentations of respiratory syncytial virus subgroups A and B detected with multiplex real-time PCR. PloS one 2016;11:e0165108.
7. Picone S, Fabiano A, Roma D, Paolillo P. Comparing of two different epidemic seasons of bronchiolitis. Ital J pediatr 2018;44:11.
8. Mansbach JM, Piedra PA, Teach SJ, Sullivan AF, Forgey T, Clark S, et al. Prospective multicenter study of viral etiology and hospital length of stay in children with severe bronchiolitis. Arch Pediatr Adolesc Med 2012;166:700-6.
9. Calvo C, García-García ML, Pozo F, Paula G, Molinero M, Calderón A, et al. Respiratory syncytial virus coinfections with rhinovirus and human bocavirus in hospitalized children. Medicine 2015;94:e1788.
10. Aslanzadeh J, Zheng X, Li H, Tetreault J, Ratkiewicz I, Meng S, et al. Prospective evaluation of rapid antigen tests for diagnosis of respiratory syncytial virus and human metapneumovirus infections. J Clin Microbiol 2008;46:1682-5.
11. Ralston S, Lieberthal A, Meissner H. American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. Pediatrics 2014;134:e1474-e502.
12. Lieberthal AS, Bauchner H, Hall CB, Johnson DW, Kotagal U, Light MJ, et al. Diagnosis and management of bronchiolitis. Pediatrics 2006;118:1774-93.
13. Akçalı S, Yılmaz N, Güler Ö, Şanlidağ T, Anıl M. (Frequency of respiratory viral agents in children with lower respiratory tract infection. Turk Arch Ped 2013;48:215-20.
14. Mahony JB. Detection of respiratory viruses by molecular methods. Clin Microbiol Rev 2008;21:716-47.
15. Mansbach JM, McAdam AJ, Clark S, Hain PD, Flood RG, Acholonu U, et al. Prospective multicenter study of the viral etiology of bronchiolitis in the emergency department. Acad Emerg Med 2008;15:111-8.
16. García-García ML, Calvo C, Pozo F, Villadangos PA, Pérez-Breña P, Casas I. Spectrum of respiratory viruses in children with community-acquired pneumonia. Pediatr Infect Dis J 2012;31:808-13.
17. Richard N, Komurian-Pradel F, Javouhey E, Perret M, Rajoharison A, Bagnaud A, et al. The impact of dual viral infection in infants admitted to a pediatric intensive care unit associated with severe bronchiolitis. Pediatr Infec Dis J 2008;27:213-7.
18. Ralston S, Hill V, Waters A. Occult serious bacterial infection in infants younger than 60 to 90 days with bronchiolitis: a systematic review. Arch Pediatr Adolesc Med 2011;165:951-6.
19. Levine DA, Platt SL, Dayan PS, Macias CG, Zorc JJ, Krief W, et al. Risk of serious bacterial infection in young febrile infants with respiratory syncytial virus infections. Pediatrics 2004;113:1728-34.
20. García-García ML, Calvo C, Rey C, Díaz B, del Mar Molinero M, Pozo F, et al. Human metapnuemovirus infections in hospitalized

children and comparison with other respiratory viruses. 2005-2014 prospective study. PloS one 2017;12:e0173504.

21. Midulla F, Scagnolari C, Bonci E, Pierangeli A, Antonelli G, De Angelis D, et al. Respiratory syncytial virus, human bocavirus and rhinovirus bronchiolitis in infants. Arch Dis Child 2010;95:35-41.
22. Johnson LW, Robles J, Hudgins A, Osburn S, Martin D, Thompson A. Management of bronchiolitis in the emergency department: impact of evidence-based guidelines. Pediatrics 2013;131:S103-S9.
23. Schuh S, Lalani A, Allen U, Manson D, Babyn P, Stephens D, et al. Evaluation of the utility of radiography in acute bronchiolitis. Pediatr 2007;150:429-33.
24. Hasegawa K, Tsugawa Y, Brown DF, Mansbach JM, Camargo Jr CA. Trends in bronchiolitis hospitalizations in the United States, 2000–2009. Pediatrics 2013;132:28-36.
25. Ricart S, Marcos MA, Sarda M, Anton A, Muñoz-Almagro C, Pumarola T, et al. Clinical risk factors are more relevant than respiratory viruses in predicting bronchiolitis severity. Pediatr Pulmonol 2013;48:456-63.
26. Schibler A, Pham T, Dunster K, Foster K, Barlow A, Gibbons K, et al. Reduced intubation rates for infants after introduction of high-flow nasal prong oxygen delivery. Intensive Care Med 2011;37:847-52.
27. Hegde S, Prodhan P. Serious air leak syndrome complicating high-flow nasal cannula therapy: a report of 3 cases. Pediatrics 2013;131:e939-44.
28. Asner SA, Tran D, Smieja M, Merglen A, Mertz D. Clinical disease severity of respiratory viral co-infection versus single viral infection: a systematic review and meta-analysis. PLoS One 2014;9:e99392.
29. Scotta MC, Chakr VCBG, de Moura A, Becker RG, de Souza APD, Jones MH, et al. Respiratory viral coinfection and disease severity in children: a systematic review and meta-analysis. J Clin Virol 2016;80:45-56.
30. Mussman GM, Parker MW, Statile A, Sucharew H, Brady PW. Suctioning and length of stay in infants hospitalized with bronchiolitis. JAMA Pediatr 2013;167:414-21.
31. Hartling L, Bialy LM, Vandermeer B, Tjosvold L, Johnson DW, Plint AC, et al. Epinephrine for bronchiolitis. Cochrane Database Syst Rev 2011.6:CD003123.
32. Ralston S, Garber M, Narang S, Shen M, Pate B, Pope J, et al. Decreasing unnecessary utilization in acute bronchiolitis care: results from the value in inpatient pediatrics network. J Hosp Med 2013;8:25-30.
33. Jacobs JD, Foster M, Wan J, Pershad J. 7% Hypertonic saline in acute bronchiolitis: a randomized controlled trial. Pediatr 2014;133:e8-e13.
34. Fernandes RM, Bialy LM, Vandermeer B, Tjosvold L, Plint AC, Patel H, et al. Glucocorticoids for acute viral bronchiolitis in infants and young children. Cochrane Database Syst Rev 2010;10:CD004878.
35. Kotaniemi-Syrjänen A, Vainionpää R, Reijonen TM, Waris M, Korhonen K, Korppi M. Rhinovirus-induced wheezing in infancy—the first sign of childhood asthma? J Allergy Clin Immunol 2003;111:66-71.