Research Article

Pathogens in acute respiratory failure in the pediatric intensive care unit in Tokyo, Japan, 2015-2017

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Received on: 08-Dec-2021 Accepted for Publication: 02-Feb-2022

ABSTRACT

Background: Acute respiratory failure, frequently accompanied by acute respiratory infection, is the main reason for pediatric intensive care unit (PICU) admissions. In general, viruses are the chief pathogen in acute respiratory infections in children; however, few studies have focused on the viral etiology of acute respiratory failure in PICU. The present study therefore analyzed cases of acute respiratory failure in patients at a PICU using real-time PCR to identify the causative pathogens.

Methods: Patients admitted to the PICU at Tokyo Metropolitan Children's Medical Center in Japan between April 2015 and March 2017 for acute respiratory failure were prospectively enrolled. Respiratory samples were obtained on the day of PICU admission. Real-time PCR for 11 viruses was used for viral detection, and data on the demographic and clinical characteristics of the subjects were analyzed. Bacterial cultures were performed only when sputum was collected from airway-secured patients.

Results: This present study enrolled 256 patients with the median age of 19 months. An underlying disease was present in 69% of the patients. Viral pathogens were detected in 119 patients (46%). The most common pathogen was the respiratory syncytial virus A (n=38, 32%), followed by respiratory syncytial virus B (n=21, 18%), enterovirus/rhinovirus (n=25, 21%), and human metapneumovirus (n=14, 12%). Bacterial pathogens were detected in 120 patients (47%). The mortality rate at 30 days was 4%.

Conclusions: Respiratory viruses were detected in 46% of children with acute respiratory failure at a PICU.

Keywords: respiratory virus, acute respiratory failure, pediatric intensive care unit, real-time PCR, Japan

INTRODUCTION

Acute respiratory failure is the main reason for intensive care admission in children (1). Acute respiratory infection (ARI), the main cause of acute respiratory failure, is chiefly due to a viral pathogen (2). Real-time polymerase chain reaction (PCR) is currently the preferred method of diagnosing ARI caused by viruses. Real-time PCR findings revealed that 36-49% of adult patients with severe ARI in the intensive care unit had a viral infection (3). However, only a few studies have reported the frequency of viral etiologies in ARI among critically ill children in pediatric intensive care units (PICUs) (4, 5). We therefore investigated the cause of respiratory

failure in the PICU with the aim of identifying the causative pathogen and analyzing the impact of viruses on acute respiratory failure in children.

Methods

Children admitted to the PICU (20 beds) at Tokyo Metropolitan Children's Medical Center for acute respiratory failure between April 2015 and March 2017 were prospectively enrolled. We defined acute respiratory failure if the patient had respiratory symptoms and needed respiratory support. Respiratory samples were obtained upon PICU admission. Suctioned sputum was obtained from patients with intubation or a tracheostomy. Otherwise, nasopharyngeal swabs were used to obtain specimens. Patients from whom a specimen was unable to be collected and those with insufficient data were excluded. All the specimens were either tested immediately or stored at -80 degrees Celsius until testing. Data on the patients' age, sex, gestational age, underlying diseases, prior antibiotic use within 24 hours, and use of 13-valent pneumococcal conjugate vaccine were collected from the electronic medical records. Clinical data were also reviewed to determine the duration of mechanical ventilation such as non-invasive positive pressure ventilation (NPPV) and mechanical ventilation with endotracheal intubation, laboratory and radiographic findings, length of PICU admission, total hospital stay, mortality at 30 days, and the pediatric index of mortality 2 score (PIM2 score), which is an estimate of the mortality risk in the pediatric intensive care unit (6). Radiographic findings were evaluated by two pediatricians. Informed consent for testing was obtained from the parents or legal guardians. We used the seasonal definitions of the Japan Meterological Agency (7). The present study was approved by an ethical committee at Tokyo Metropolitan Children's Medical Center (H27b-5).

Viral nucleic acids were extracted using QIAamp MinElute Virus Spin Kit (QIAGEN, Hilden, Germany). Real-time PCR was performed using the QuantStudio5 Real-Time PCR System (Applied Biosystems, Foster city, the USA) and primers and probes (ScyMed, Tokyo, Japan). We tested for adenovirus (AdV), human bocavirus (hBoV), human metapneumovirus (hMPV), influenza virus (Flu) A H1N1pdm2009/A H3N2/B, respiratory syncytial virus (RSV) A/B, human coronavirus OC43 (hCoV-OC43), parainfluenza type 3 virus (PIV 3), and enterovirus (EV)/rhinovirus (RV). Bordetella pertussis was also tested when clinically suspected. More detailed identification of EV and RV was performed using specific primers (ScyMed, Tokyo, Japan) (Note: The manufacturer removed PIV3 of the Multiplex PCR assay in July 2016).

Bacterial cultures were performed only when sputum was collected from airway-secured patients. WalkAway 96 Plus (Beckman Coulter, Brea, the USA) was used to identify bacterial pathogens in the specimens (8).

RESULTS

In total, 329 children admitted to the PICU for acute respiratory failure. Seventy-three patients were excluded, 52 had no samples and 21 had insufficient clinical data, so 256 patients (78%) were enrolled. The median age and proportion of males was 19 months and 63%, respectively, and 69% had an underlying disease (Table 1). Viral pathogens were detected in 119 patients (46%). The most frequently detected pathogen was RSV A (n=38,

32%), followed by RSV B (n=21, 18%), EV/RV (n=25, 21%), hMPV (n=14, 12%), AdV (n=9, 8%), hCoV-OC43 (n=5, 4%), B. pertussis (n=5, 4%), FluA H3N2 (n=3, 3%), Flu A H1N1 pdm2009 (n=3, 3%), Flu B (n=3, 3%), and hBoV (n=2, 2%). Nine patients had two viruses, but no patient had three or more viruses.

In RSV A, RSV B, EV/RV and hMPV, median age was 15 months (interquartile range: 3-28), 9 months (IQR: 1-29), 33 months (IQR: 10-61) and 18 months (IQR: 5-48), respectively. Underlying diseases were 24 (63%), 9 (43%), 16 (67%), and 9 (64%), respectively. Mechanical ventilation with intubation was performed in 26 (68%), 14 (67%), 16 (67%) and 8 (57%), respectively.

Patients with acute respiratory failure were admitted to the PICU most frequently in winter. However, RSV infection was observed even during summer despite the general perception that it is a winter virus. Peaks in RSV infection were observed in autumn and winter. hMPV was observed in spring, summer, and autumn but not in winter. (Figure 1).

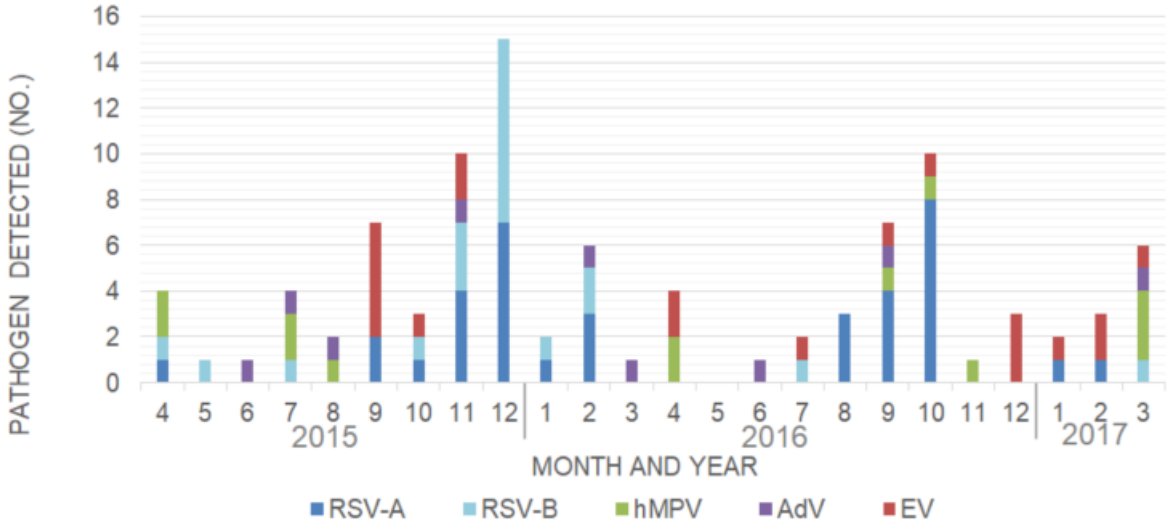

Figure 1. Numbers of respiratory viruses detected in children with acute respiratory failure in a pediatric intensive care unit

Figure legends: Children with acute respiratory failure were admitted most frequently in winter 2015, but admission for this reason continued steadily in 2016 as well. RSV was most frequently detected in autumn and winter. In September 2015, there was an epidemic of EV infections in Japan.

Abbreviations: RSV, respiratory syncytial virus; hMPV, human metapneumovirus; AdV, adenovirus; EV, enterovirus

In 183 airway-secured patients, sputum samples were collected (71%), and bacterial pathogens were detected in 120 patients (47%). The most common bacterial pathogens were Staphylococcus aureus (n=21, 18%), followed by Moraxella catarrhalis (n=14, 12%) and Haemophilus influenzae (n=13, 11%). Viruses and bacteria were co-detected in 53 patients (21%). Forty-nine percent of the RSV positive patients were co-infected with a bacterial pathogen. Ten patients were dead at 30 days (4%). Bacterial pathogens isolated with viruses were shown in Table 2.

Background		
Age, month (median, IQR)	19	(8-51)
<2yr., no.(%)	142	(55)
2-4yr., no.(%)	58	(23)
5-9yr., no.(%)	31	(12)
10yr.<, no.(%)	25	(10)
Male, no.(%)	161	(63)
Gestational age, week (median, IQR)	38	(37-40)
Underlying diseases †, no.(%)	176	(69)
Congenital heart disease	92	(36)
Neuromuscular disease	90	(35)
Congenital malformation	83	(32)
Chronic respiratory disease	70	(27)
Gastrointestinal disease	35	(14)
Hemato-oncologic disease	13	(5)
Others ‡	11	(4)
Prior antibiotic use, no. (%)	60	(23)
ampicillin	17	(7)
ampicillin/sulbactam	8	(3)
cefotaxime	4	(2)
Others §	10	(4)
PCV13 vaccination, no. (%)	150	(59)
Laboratory data		
WBC (/mcl) (median, IQR)	10,520	(6,878-14,315)
CRP (mg/dl) (median, IQR)	1.1	(0.3-4.1)
AST (IU/L) (median, IQR)	35	(27-49)
ALT (IU/L) (median, IQR)	19	(14-28)
Radiographic finding		
Consolidation, no.(%)	171	(67)
Hyperlucency, no.(%)	8	(3)
CPA dull, no.(%)	3	(1)
None, no.(%)	74	(29)
Pathogens		
Single viral detection, no.(%)	57	(22)
Two viral detections, no.(%)	9	(4)
Co-detection of virus and bacteria, no.(%)	53	(21)
Single bacterial pathogen, no.(%)	67	(26)
No pathogen, no.(%)	70	(27)
Treatments		
Antibiotics, no.(%)	245	(96)
Steroids, no.(%)	86	(34)
Outcomes		
Duration of PICU stay (days, median, IQR)	8	(4-12)
NPPV, no.(%)	85	(33)
Mechanical ventilation with intubation, no (%)	176	(69)
Duration of mechanical ventilation (days, median, IQR)	5	(2-9)
PIM2 score (median, IQR)	3.2	(1.1-6.1)
Mortality at 30 days, no.(%)	10	(4)

Table 1. Patient's demographic data and clinical characteristics of children with acute respiratory failure (n=256)

† Underlying diseases included duplications.

‡ Others: kidney disease (n=3), hypothyroid (n=3), musculoskeletal disorders (n=3), primary immunodeficiency (n=1), ovarian disease (n=1)

Abbreviations IQR: Interquartile range; PCV13: 13-valent pneumococcal conjugate vaccine; WBC: White blood cell; CRP: C-reactive protein; AST: Aspartate aminotransferase; ALT: Alanine transaminase; CPA: Costophrenic angle; PCR: Polymerase chain reaction; NPPV: Non-invasive positive pressure ventilation; PIM2: Pediatric index of mortality [2]

Respiratory syncytial virus A (n=38)	n	%
Staphylococcus aureus	5	(13)
Moraxella catarrhalis	5	(13)
Haemophilus influenzae	4	(11)
Stenotrophomonas maltophilia	3	(8)
Pseudomonas aeruginosa	3	(8)
Serratia marcescens	1	(3)
Respiratory syncytial virus B (n=21)		
Staphylococcus aureus	4	(19)
Moraxella catarrhalis,	4	(19)
Haemophilus influenzae	3	(14)
Pseudomonas aeruginosa	3	(14)
Enterovirus/Rhinovirus (n=25)		
Staphylococcus aureus	6	(24)
Haemophilus influenzae	4	(16)
Moraxella catarrhalis	2	(8)
Serratia marcescens	1	(4)
Human metapneumovirus (n=14)		
Staphylococcus aureus	1	(7)
Haemophilus influenzae	1	(7)
Moraxella catarrhalis	1	(7)
Adenovirus (n=9)		
Moraxella catarrhalis	1	(11)
Influenza virus A H3N2 (n=3)		
Streptococcus pyogenes	1	(33)
Influenza virus A H1N1 pdm2009 (n=3)		
Haemophilus influenzae	2	(67)
Streptococcus pyogenes	2	(67)
Influenza virus B (n=3)		
Staphylococcus aureus	1	(33)
Human bocavirus (n=2)		
Staphylococcus aureus	1	(50)
Pseudomonas aeruginosa	1	(50)
Human coronavirus OC43 (n=5)		
Staphylococcus aureus	1	(20)
Haemophilus influenzae	1	(20)
Pseudomonas aeruginosa	1	(20)
Klebsiella pneumoniae	1	(20)
Streptococcus pyogenes	1	(20)

Table 2. Viruses isolated with bacterial pathogens (n=53)

DISCUSSION

The present descriptive study, the largest of its kind ever to be conducted in a Japanese PICU, focused on the etiology of infections in acute respiratory failure. Our study was able to identify infectious pathogens in 46% of the patients tested. Viruses were the chief infectious agent in ARI in critically ill children. Previous studies of the etiology of infections in ARI conducted in pediatric general wards targeted non-severe cases (6, 9). In Germany, and one or more viral pathogens were detected in 65% of 254 children admitted to the general ward with ARI (9). A study in Japan analysed 903 hospitalized children with community-acquired pneumonia who were enrolled within five days of disease onset and found that 34.4%, 21.8%, and 17.5% had a viral infection, bacterial infection, and viral/bacterial co-infection, respectively (6). Viruses were also the leading cause of non-serious ARI among pediatric patients. The current era of pneumococcal vaccines has seen a significant reduction in the disease burden caused by pneumococcal pneumonia in children (10). Therefore, developing treatment and

prevention strategies against viruses, such as RSV and hMPV, has become the priority in stemming the ARI rate among children.

The finding of the present study that RSV was the most common pathogen in ARI among pediatric patients mirrors that of previous reports. Previous European studies also found that children admitted to a PICU for respiratory failure were infected with RSV at 44-70% (8, 9). The prevalence of hMPV was somewhat higher in our study than in previous studies (3-4%). However, the latter studies were conducted for only six to ten months and may therefore have failed to consider the effect of seasonality on the viral infection rates (8, 9). The present study revealed that EV was the second most common pathogen, followed by RSV A /B. A pandemic of EV-D68 infection resulting in respiratory failure and possibly acute flaccid paralysis in children occurred in fall 2014 (11). Interestingly, Japan did not experience a large outbreak in 2014, but did so in the following fall during the present study. EV cases in fall 2015 comprised 40% of the total EV cases for that year. The EV strain detected in this period was subsequently typed as EV-D68.

Our study found S. aureus to be the most common bacterial pathogen. S. aureus is part of the normal skin flora, and community-acquired, methicillin-resistant S. aureus was reported in the US as the causative pathogen in necrotizing pneumonia in children (12). In general, S. aureus rarely causes community-acquired pneumonia in children in Japan. Determining whether this organism is a pathogen or colonizer may be difficult, given that most critically ill children receive antibiotic therapy in the PICU. Further study may be needed.

H. influenzae and M. catarrhalis are among the other possible pathogens in ARI in children. Surprisingly, Streptococcus pneumoniae was not isolated in our cohort possibly due to the administration of pneumococcal conjugate vaccinations as part of the national immunization program. Another possible explanation for the absence of S. pneumoniae is the common practice of antibiotic administration prior to PICU admission. Further, collecting sputum samples in children without airway securement was often not feasible.

The present study had several limitations. First, the detection of viruses did not prove their pathogenicity despite the use of the highly sensitive PCR. While 35.4% of asymptomatic subjects younger than 5 years in Sweden were found to have a viral infection (13), the pathogenicity of RV in lower ARI is still controversial. However, our study detected well-known pathogenic viruses, in line with the findings of previous studies. Second, the present study was performed at a single center and might therefore have a location bias. Further multicenter PICU studies are therefore warranted. Third, data on the acute respiratory patients were not fully inclusive, as some of patients had no PCR testing performed. This might have caused some bias in selection. Forth, the present study also assessed the impact of viral and bacterial co-infections, but some of sampling bias could not be excluded. Many patients had been treated with antibiotics prior to PICU admission, rendering it difficult to identify causative bacteria in children with ARI. Moreover, some of airway secured patients had no sputum bacterial culture with difficulty of suctioning specimen. We did not perform bronchial alveolar lavage for pathogen identification at routine basis.

CONCLUSION

Viruses were identified in 46% of critically ill pediatric patients with acute respiratory failure. Viruses are the main cause of ARI in the PICU.

ACKNOWLEDGEMENTS

We thank James R. Valera for his assistance in editing this manuscript.

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