

Human Rhinovirus/Enterovirus in Pediatric Acute Respiratory Distress Syndrome

Michele E. Smith¹ Patrick T. Wilson¹ 

¹Department of Pediatrics, Columbia University Medical Center, New York-Presbyterian Children's Hospital, New York, United States

Address for correspondence Michele E. Smith, MD, Department of Pediatrics, Columbia University Medical Center, New York-Presbyterian Children's Hospital, 3959 Broadway CHN 10-25, New York, NY 10032, United States (e-mail: mes9138@nyp.org).

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Abstract

Keywords

- ▶ rhinovirus
- ▶ enterovirus
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- ▶ pediatric acute respiratory distress syndrome

The role of human rhinovirus/enterovirus (HRV/HEV) in severe lower respiratory tract infections remains unclear. We characterized the respiratory status of children admitted to a large academic pediatric intensive care unit (PICU) who tested positive for only HRV/HEV. One hundred and fifty-five children met inclusion criteria with 62% requiring positive pressure respiratory support of 5 cm of water pressure or more within the first 24 hours of admission. Among them, 34% had SaO₂ to FiO₂ ratios of 264 or less with 22 patients (14%) meeting criteria for pediatric acute respiratory distress syndrome. HRV/HEV is associated with significant respiratory disease in children admitted to the PICU.

Introduction

In the 1950s, human rhinovirus (HRV), a member of the *Enterovirus* genus (HEV) and Picornaviridae family, was first identified as the most important cause of the “common cold.” Initial research suggested that HRV is a benign virus restricted to grow within the upper airways of humans.^{1–3} However, current scientific evidence contradicts these early notions and instead suggests that HRV may not be as benign as originally postulated. Recent studies have shown that HRV is not only able to effectively reach, penetrate, and replicate within the lower airway epithelium of individuals *in vivo*, but that infection with HRV is also associated with histologic changes of the lung interstitium and alveoli.^{4–6} Furthermore, HRV has now been shown to be an important cause of bacterial superinfection, with proposed mechanisms established for infection with *Streptococcus pneumoniae* and *Staphylococcus aureus*.^{7,8}

Recent clinical studies in pediatrics have also concluded that rhinovirus is associated with lower respiratory tract disease processes. Several studies have demonstrated associations between positivity for HRV and hospital admissions for asthma, bronchiolitis, and pneumonia.^{9–13} Despite the mounting scientific and clinical evidence, it remains controversial as to whether HRV can cause significant respiratory disease as a sole pathogen. This controversy stems from both the long-standing

belief that HRV is a benign upper airway pathogen and from studies showing asymptomatic individuals test positive for HRV 12 to 40% of the time.^{14–16} Additionally, it has also been shown that both HRV and HEV shed in the nasopharynx of children following acute infection for up to 6 weeks and 3 weeks, respectively.¹⁷ Therefore, it is difficult to show a causal relationship between a positive nasopharyngeal swab for HRV and significant clinical illness.

We aim to characterize children admitted to the pediatric intensive care unit (PICU) at a tertiary children's hospital over a 1-year period who tested positive for HRV/HEV (the hospital clinical assay does not differentiate between the two picornaviruses) with negative blood, urine, respiratory, and cerebrospinal fluid (CSF) bacterial cultures. The goal is to determine if HRV/HEV as a sole pathogen is associated with significant lower respiratory tract disease in critically-ill children.

Methods

Study Design and Patients

A retrospective study was conducted at a tertiary children's hospital with a 41-bed PICU consisting of a medical-surgical unit, cardiac unit, and neurology unit with approximately 1,800 admissions per year. Children admitted to the PICU between January 1, 2017 and December 31, 2017 with a

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respiratory pathogen panel (RPP) positive for HRV/HEV were identified. Inclusion criteria included a positive RPP within 1 calendar day of PICU admission, RPP negative for all other viruses and bacteria, and negative blood, urine, respiratory, and cerebrospinal fluid bacterial cultures, if performed. Bacterial cultures were collected within 24 hours before or after PICU admission and the final result was determined after 5 days of incubation. Patients were excluded if admitted postoperatively or did not have a positive RPP within 24 hours of PICU admission.

Approval for the study was obtained by the Institutional Review Board of Columbia University Medical Center.

Detection of HRV/HEV

Detection of HRV/HEV was performed in the hospital's clinical laboratory using the Biofire FilmArray (Salt Lake City, Utah, United States) nested PCR analysis of submitted nasopharyngeal swabs. The assay detects the following viruses and bacteria at a sensitivity and specificity of 95 and 99%, respectively: adenovirus, coronavirus OC43, coronavirus NL63, metapneumovirus, HRV/HEV, influenza A, influenza A/H1, influenza A/H1-2009, influenza A/H3, influenza B, parainfluenza 1, parainfluenza 2, parainfluenza 3, parainfluenza 4, respiratory syncytial virus, *Bordetella pertussis*, *Chlamydia pneumonia*, and *Mycoplasma pneumonia*.¹⁸

Data Collection

Admission vital signs were collected from the electronic medical record (EMR) along with white blood cell count (WBC), C-reactive protein (CRP), admission diagnosis, comorbidities, and outcome data. Fraction of inspired oxygen (FiO₂) and level of respiratory support at time of admission were recorded and the ratio of oxygen saturation to FiO₂ (S:F ratio) was calculated in patients receiving a positive end expiratory pressure (PEEP) of 5 cm of water pressure or greater. S:F ratios were calculated in patients receiving invasive and noninvasive ventilation as arterial lines were not placed on a majority of patients, thus preventing us from reporting PaO₂ to FiO₂ ratios in most patients. Chest radiograph (CXR) results as reported by attending radiologists were grouped into the following categories: (1) focal opacity/consolidation/infiltrate, (2) bilateral airspace opacities, (3) other infiltrate (definitive edema and/or atelectasis), and (4) normal. CXRs in categories 1 and 2 were considered to be consistent with pulmonary parenchymal disease. As per the 2015 guidelines from the Pediatric Acute Lung Injury Consensus Conference Group,¹⁹ children in the study were said to meet criteria for pediatric acute respiratory distress syndrome (pARDS) at the time of PICU admission if (1) they received invasive or noninvasive positive pressure respiratory support of at least 5 cm of water pressure or greater with S:F ratios less than or equal to 264, (2) had a CXR consistent with pulmonary parenchymal disease, and (3) had respiratory failure not fully explained by cardiac failure or fluid overload.

Statistical Analysis

Data were entered into an electronic database and analysis performed in GraphPad Prism version 6 (GraphPad Software,

La Jolla, California, United States). Median and interquartile range (IQR) or number with corresponding percentage are reported.

Results

Patients

A total of 734 patients admitted to the PICU in 2017 were tested positive for HRV/HEV. Among them, 538 were excluded secondary to their RPPs not being collected within one day of PICU admission or the patient being postoperative. Another 17 patients were excluded because the RPP was positive for other viruses and 24 more children were excluded because of a positive bacterial culture. Ultimately, 155 children met the defined inclusion criteria with HRV/HEV isolated as a sole pathogen within one calendar day of PICU admission (►Fig. 1).

Patient characteristics, admission vital signs, laboratory data, and outcomes are shown in ►Table 1. The median age of the study population was 4 years (IQR = 1–8) with a median admission WBC count of 12,000/μL (IQR = 9–17) and CRP of 22 mg/L (reference range 0–10 mg/L; IQR 3–83). The most common comorbidities of the population were pulmonary (33%) and cardiac disease (17%), while 25 (15%) of patients had none (►Table 2). In terms of seasonality, the majority of patients with HRV/HEV were admitted in March, May, September, and October (►Fig. 2). The most common PICU admission diagnoses were status asthmaticus (55%), acute respiratory failure (54%), bronchiolitis (5%), and shock (5%). One hundred twenty-five children (81%) were transferred to the floor after their PICU admission, 28 (18%) were sent

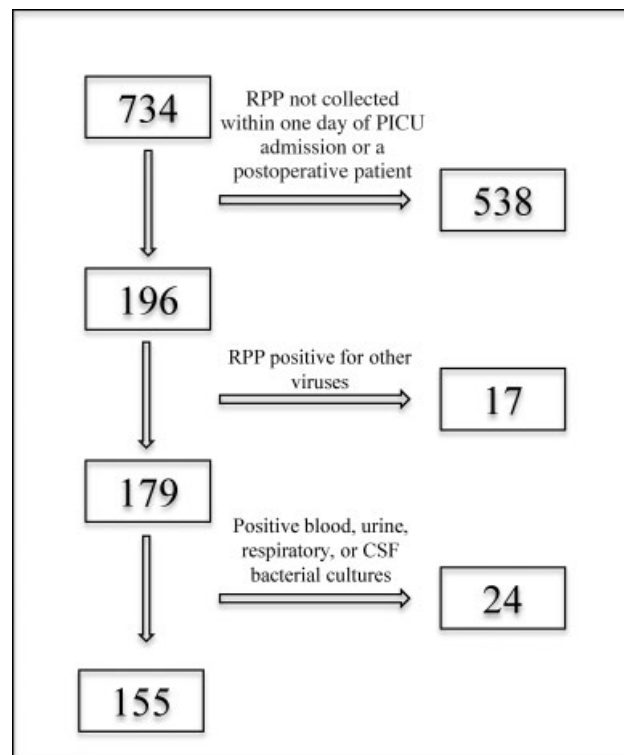


Fig. 1 Enrolment flow chart. CSF, cerebrospinal fluid; PICU, pediatric intensive care unit; RPP, respiratory pathogen panel.

Table 1 Baseline characteristics and disposition from the PICU

Patient characteristics	Median (IQR) or n (%)
Age (y)	4 (1–8)
Weight (kg)	17 (11–27)
Sex (female)	65 (42)
Systolic blood pressure (mm Hg)	105 (97–118)
Heart rate (beats per min)	147 (127–160)
Respiratory rate (breaths per min)	29 (24–36)
Oxygen saturation (%)	97 (95–99)
Temperature (°C)	37 (36–37)
White blood cell count (number/ μ L; <i>n</i> = 102)	12 (9–17)
C-reactive protein (reference range 0–10 mg/L; <i>n</i> = 44)	22 (3–83)
Transferred to floor	125 (81)
Discharged home	28 (18)
Death	2 (1)

Abbreviations: IQR, interquartile range; PICU, pediatric intensive care unit. Note: number (*n*), percentage (%). *n* = 155 unless otherwise specified.

Table 2 Comorbidities of the study population

Comorbidity <i>n</i> = 168 comorbidities	Number (%)
Pulmonary	56 (33)
Cardiac	28 (17)
None	25 (15)
Genetic	17 (10)
Neurologic	14 (8)
Prematurity	9 (5)
Oncologic	7 (4)
Endocrine	5 (3)
Gastrointestinal	2 (1)
Hematologic	2 (1)
Renal	1 (0.6)
ENT	1 (0.6)
Musculoskeletal	1 (0.6)

Abbreviation: ENT, ear–nose–tongue.

Note: thirteen of the 155 children had more than one comorbidity making a total of 168 comorbidities.

directly home from the PICU, and 2 children (1%) died during their PICU stay (► **Table 1**).

Respiratory Support, S:F Ratio, and CXR Data

Ninety-six children (62%) admitted to the PICU with HRV/HEV required respiratory pressure support with a PEEP of at least 5 cm of water pressure. At the time of PICU admission, 53 patients (34%) required bi-level positive airway pressure (BPAP), 29 (19%) required continuous positive airway pressure

(CPAP), 12 (8%) required invasive mechanical ventilation via endotracheal tube, and 2 (1%) were mechanically ventilated via tracheostomy. Of the 97 patients on positive pressure ventilation (including ventilation by endotracheal tube, tracheostomy, BPAP, and CPAP), 34 patients (35%) had admission S:F ratios \leq 264. One hundred and twenty-seven patients had an admission CXR. Fifty-nine CXRs (46%) demonstrated a focal opacity/infiltrate/consolidation or bilateral airspace opacities consistent with pulmonary parenchymal disease (► **Table 3**). Ultimately, 22 (14%) patients were on positive pressure respiratory support with S:F ratios \leq 264, CXR data consistent with pulmonary parenchymal disease and respiratory disease not consistent with cardiac failure or fluid overload, thus meeting the criteria for pARDS criteria.

Individuals Meeting pARDS Criteria

Characteristics of the 22 patients meeting pARDS criteria are shown in ► **Table 4**. Fifteen of the 22 patients were diagnosed with acute respiratory failure, 4 with status asthmaticus, and 1 with ARDS, intracranial hemorrhage, and status epilepticus each. A majority of the patients had comorbidities while 14% of children were previously healthy.

Discussion

Growing evidence supports the hypothesis that HRV is a pathogen of the lower respiratory tract and can contribute to significant respiratory disease in pediatric patients. To our knowledge, only one previous study has focused specifically on the pediatric critical care population admitted with HRV/HEV. Spaeder et al performed a retrospective cohort study to describe pediatric mortality in the PICU population who tested positive for HRV/HEV.²⁰ Our study is unique in that it focuses on the PICU population with HRV/HEV isolated as a sole pathogen. Their study used the 1994 American–European Consensus Criteria for Acute Respiratory Distress Syndrome for an ARDS diagnosis, whereas the current study uses the 2015 guidelines from the Pediatric Acute Lung Injury Consensus Conference Group.^{19,21} Other studies have described children admitted to the hospital with HRV/HEV, with a subset of children ultimately requiring admission to the ICU, and/or requiring mechanical ventilation.^{9,10,22–24} Some studies concluded that children admitted with HRV/HEV were as likely to require ICU admission or need mechanical ventilation, as children admitted with other respiratory viruses historically considered to be more severe, such as influenza.^{22,23} Our results in combination with other studies suggest that HRV/HEV is not an innocent by-stander and is associated with significant respiratory disease in pediatric patients.

It is important to note that the majority of children in our cohort had one or more comorbidities, with the most common being underlying cardiopulmonary disease. Previous studies also reported that a majority of children requiring hospitalization for HRV/HEV had underlying chronic medical conditions involving the cardiorespiratory, immune, or neurologic system, as well as prematurity.^{11–13,25} However, Messacar et al found that half of the children in their study

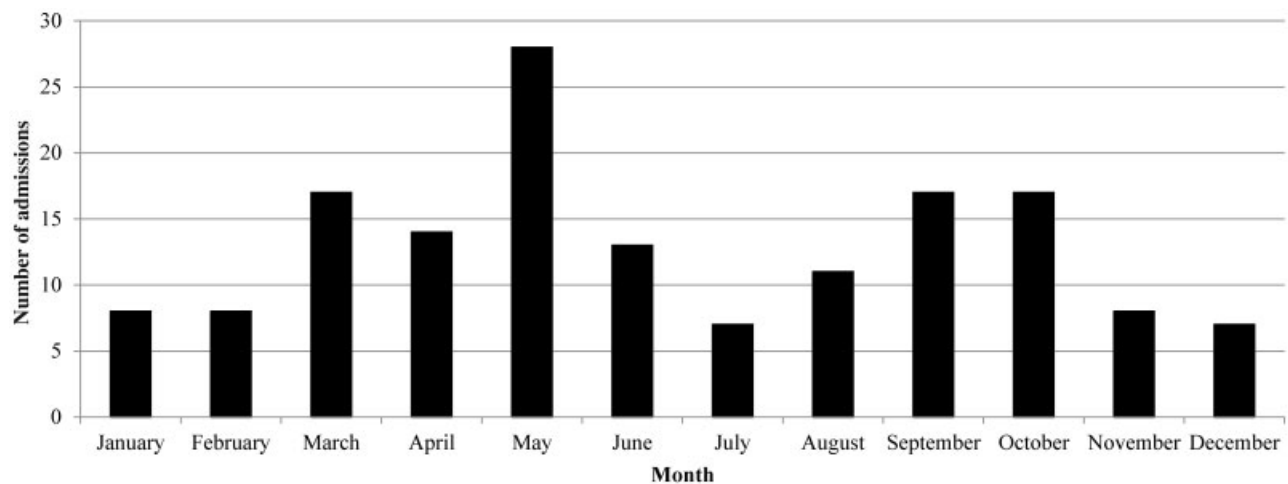


Fig. 2 Number of admissions for children positive for only HRV/HEV by calendar month. HEV, enterovirus; HRV, rhinovirus.

Table 3 Respiratory support, S:F ratios, chest radiograph categories, and pARDS criteria at time of PICU admission

Highest level of respiratory support in first 24 h	Number (%)
BPAP	53 (34)
Room air	40 (26)
CPAP	29 (19)
Intubated	12 (8)
Facemask	11 (7)
Nasal cannula	4 (3)
Nonrebreather	3 (2)
High-flow nasal cannula	1 (0.6)
Tracheostomy to ventilator	2 (1)
Admission S:F \leq 264 (n = 97)	34 (35)
Chest radiograph category (n = 127):	
1. Focal opacity/consolidation/infiltrate	25 (20)
2. Bilateral airspace opacities	34 (27)
3. Other infiltrate (edema/atelectasis)	35 (28)
4. Normal	33 (26)
Pediatric acute respiratory distress syndrome	
Patients meeting criteria	22 (14)
Patients not meeting criteria	133 (86)

Abbreviations: BPAP, bi-level positive airway pressure; CPAP, continuous positive airway pressure; pARDS, pediatric acute respiratory distress syndrome; PICU, pediatric intensive care unit; S:F, ratio of oxygen saturation to FiO_2 .

Note: Oxygen saturation to fraction of inspired oxygen ratio (S:F) was calculated for patients receiving invasive or noninvasive positive pressure ventilation of at least 5 cm H_2O .

requiring hospitalization with HRV/HEV were previously healthy.²² In our study, 25 children had no comorbidities and still required admission to the PICU. Furthermore, 3 out of 22 children who met criteria for pARDS in our study had no previous medical history, demonstrating that previously healthy children can have significant clinical illness in the

setting of HRV/HEV positivity and require admission to the PICU.

PICU admissions for HRV/HEV occurred throughout the year with peak activity in March, May, September, and October. This finding is consistent with previous studies reporting biannual peaks of HRV/HEV infection in Spring and Fall.^{10,24,26} The majority of children in our cohort had an admission diagnosis of status asthmaticus. Johnston et al showed that HRV infection accounted for two-thirds of all virally induced severe asthma exacerbations in the cohort of children studied.²⁷ Additionally, Miller et al showed that children with a history of wheezing or asthma had the highest rate of HRV-associated hospital admissions, drawing further associations between HRV and airway reactivity.¹⁰

Sixty-two percent of patients in the study required positive pressure respiratory support during their ICU admission with 14% meeting criteria for pARDS. Spaeder et al also examined children admitted to the PICU with HRV/HEV and retrospectively examined how many patients met multiple organ dysfunction syndrome (MODS) and ARDS criteria.^{21,28} The rate of MODS and ARDS in their study was 3 and 2%, respectively.²⁰ Three case reports are reporting associations between HRV/HEV and ARDS in individuals under the age of 22 years have also been published.²⁹⁻³¹ Our study, in combination with previous data, highlights the importance of physicians being aware that children admitted with HRV/HEV, as the sole pathogen are at risk of developing pARDS.

Limitations

There are several limitations to this single-center, retrospective study including the lack of a control group including patients with negative RPPs, missing documentation of patient symptomatology, and inability of the RPP to differentiate between the two picornaviruses, HRV and HEV. Additionally, our study was limited to the first day of PICU admission preventing us from following the progression of respiratory disease throughout the hospital stay and potentially missing patients testing positive for HRV/HEV later in their admission.

Table 4 Characteristics of the 22 patients meeting pediatric acute respiratory distress syndrome criteria

Age (y)	Sex	S:F ratio	Admission respiratory support	Chest radiograph category	Admission diagnosis	Comorbidities
0	F	194	Intubated	2	Shock	Endocrine
1	M	240	BPAP	2	Status asthmaticus	None
13	F	198	BPAP	2	Status asthmaticus	Asthma
7	M	200	Intubated	2	Acute respiratory failure	Prematurity, neurologic
1	M	242	BPAP	2	Status asthmaticus	None
11	F	242	Tracheostomy to ventilator	1	Acute respiratory failure	Musculoskeletal, genetic
1	M	232	BPAP	2	Acute respiratory failure	Neurologic
7	M	188	BPAP	2	Acute respiratory failure	Neurologic
8	M	217	CPAP	1	Acute respiratory failure	Asthma
1	M	198	BPAP	1	Acute respiratory failure	Prematurity
3	M	98	Intubated	1	Intracranial hemorrhage	Oncologic
0	M	245	BPAP	2	Acute respiratory failure	Hematologic
1	F	222	Intubated	2	Status epilepticus	Neurologic
2	M	245	CPAP	2	Acute respiratory failure	Prematurity
15	M	69	BPAP	2	Acute respiratory failure	Genetic, cardiac
0	M	154	Intubated	2	Acute respiratory failure	None
20	M	222	BPAP	2	Acute respiratory failure	Oncologic
1	M	125	Intubated	2	ARDS	Cardiac
2	M	138	BPAP	2	Acute respiratory failure	Genetic
13	F	208	BPAP	2	Acute respiratory failure	Neurologic, cardiac
7	M	132	CPAP	1	Status asthmaticus	Asthma
0	M	94	Intubated	2	Acute respiratory failure	Prematurity

Abbreviations: BPAP, bi-level positive airway pressure; CPAP, continuous positive airway pressure; F, female; M, male; S:F, ratio of oxygen saturation to FiO_2 .

Conclusion

In conclusion, a majority of children admitted to the PICU with HRV/HEV, as a sole pathogen required positive pressure ventilation with 14% meeting criteria for pARDS. Future prospective, controlled studies differentiating HRV from HEV are needed to definitively prove HRV/HEV alone can lead to pARDS and to provide a better understanding of the natural disease course throughout hospital admissions.

Funding

None.

Conflict of Interest

None declared.

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