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. 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. 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.

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. 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. 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. 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 admitted to the PICU.

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 positive nasopharyngeal swab for HRV/HEV were included in the study. The goal was to determine if HRV/HEV as a sole pathogen is associated with significant lower respiratory tract disease in critically-ill children.

Abstract

Keywords

► rhinovirus
► enterovirus
► pediatric intensive care units
► 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.

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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, para-influenza 1, para-influenza 2, para-influenza 3, para-influenza 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](Image 317x75 to 551x358)
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           | 12 (9–17)             |
| Creactive protein (reference range 0–10 mg/L; n = 44) | 22 (3–83) |
| Transferred to floor             | 125 (81)              |
| Discharged home                  | 28 (18)               |
| Death                            | 2 (1)                 |

Table 2 Comorbidities of the study population

| Comorbidity n = 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)    |

Table 3 Characteristics of the 22 patients meeting pARDS criteria

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. 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. 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. 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. 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. However, Messacar et al found that half of the children in their study...
requiring hospitalization with HRV/HEV were previously healthy. 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. 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. 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.

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. The rate of MODS and ARDS in their study was 3 and 2%, respectively. Three case reports are reporting associations between HRV/HEV and ARDS in individuals under the age of 22 years have also been published. 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 3

| 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 ≤ 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)    |

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 H₂O.
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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### 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 FiO2.
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