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Status asthmaticus requiring extracorporeal membrane oxygenation associated with rhinovirus infection

Lauren Greenawald, DO^a, Abigail Strang, MD^a, Curtis Froehlich, MD^b, and Aaron Chidekel, MD^a

^aDivision of Pulmonology, Nemours/Alfred I. duPont Hospital for Children, Wilmington, DE, USA; ^bPediatric Critical Care Medicine, Nemours/Alfred I. duPont Hospital for Children, Wilmington, DE, USA

ABSTRACT

Objective: Evolving research links human rhinovirus (HRV) with status asthmaticus (SA) as well as severe respiratory illness in patients with atopy and asthma. This case series reviews five episodes of HRV-associated SA that required extracorporeal membrane oxygenation (ECMO). **Methods:** Charts of four patients, five total episodes of ECMO, with SA secondary to HRV were reviewed in this IRB-approved case series. Outcomes included demographic information, past medical history, clinical parameters and spirometry. **Results:** Patients (three male, one female), mean age 9 years (range 7–12 years) at the time of admission, were African American, on Medicaid, carried a diagnosis of persistent asthma, and had documented non-adherence to prescribed, daily controller medications. One patient had passive smoke exposure. All patients had a mean IgE of 734 (range 12–2497) with seasonal allergic rhinitis was diagnosed in three patients. Cases occurred in spring (3/5) and fall (2/5). Venous/venous ECMO (4/5) or venous/arterial ECMO (1/5) was continued for a mean duration of 4.2 days (range 3–7 days). Spirometry after hospitalization had a mean FEV₁ of 1.59 L (81% predicted, range 69%–91%), and an FEF_{25%–75%} 1.13 L (47.5% predicted, range 41%–65%) at an average of 16.7 weeks post ECMO. **Conclusions:** This case series highlights the association between persistent, poorly controlled asthma and severe SA with HRV infection resulting in ECMO. Despite life-threatening illness, these patients did not demonstrate significant large-airway obstruction following infection. However, patients showed persistently abnormal small airway function, which could be a risk factor or early evidence of vulnerability to infection.

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Introduction

Asthma is the most common respiratory disorder of childhood, affecting over 15% of the pediatric population [1]. Approximately 80% of patients are diagnosed by age 5 years, with viral pathogens as the primary trigger for exacerbations [2]. Of these viruses, human rhinovirus (HRV) is a common pathogen that causes respiratory tract infections across all ages. HRV infection occurs in a bimodal distribution in North America with peaks in spring and fall. This virus is known to have an important role in the “September asthma epidemic” when children return to school and increased viral exposure leads to a surge in asthma exacerbations [2].

Over the past several decades, knowledge of HRV has rapidly increased, and recent evidence shows that HRV plays a larger role in lower respiratory tract

infections than previously suspected [3]. A prior study has demonstrated that children with HRV infection and asthma have increased rates of emergency department (ED) visits, hospitalizations and a need for escalated respiratory support [4]. Additionally, children who have acute wheezing episodes from HRV are prone to future episodes of wheezing, which increases the risk for readmission [5].

With the advent and availability of rapid viral polymerase chain reaction (PCR) testing, the ability to understand the impact of various infectious triggers on respiratory pathophysiology is quickly evolving, particularly in children with asthma. There are limited published data regarding the etiology of viral triggers in children with asthma who experience the most severe exacerbations, those requiring extracorporeal membrane oxygenation (ECMO). This retrospective chart review describes pediatric patients with

persistent asthma who required ECMO for treatment of status asthmaticus triggered by HRV. We describe their clinical characteristics, hospital course and post-discharge follow-up lung function.

Methods

This case series is an institutional review board-approved retrospective chart review conducted at Nemours/Alfred I. duPont Hospital for Children, a tertiary pediatric referral hospital in Wilmington, Delaware. Electronic medical records were reviewed for four patients (five total episodes) who were admitted to the pediatric intensive care unit for SA with positive confirmatory testing for HRV and subsequent ECMO cannulation due to severe, refractory respiratory failure. Individual patient data were evaluated for demographic information (age, sex, insurance status) and medical history, with a particular focus on adherence to asthma therapies, visits to the ED and previous hospitalizations. Each patient chart was assessed for time to ECMO initiation, initial blood gas values (arterial or venous) for pH levels and carbon dioxide levels, the duration of ECMO cannulation, medications used for respiratory support and viral testing. Charts were reviewed for asthma medications at discharge and pre-bronchodilator spirometry at the post-hospitalization Pulmonology office visit.

Results

Eight children received ECMO between 2012 and 2016 for a primary diagnosis of respiratory failure; six of whom presented in SA. Four of these patients required ECMO cannulation on five occasions for acute respiratory failure in the setting of SA caused by HRV. Demographic data including sex, age, ethnicity, patient insurance and time of infection are shown in Table 1. All patients had a history of persistent asthma of various severity (mild, moderate and severe) and inconsistent follow up in the Pulmonology office. All patients were African American and had Medicaid as primary insurance. Each patient was prescribed daily inhaled corticosteroids as a component of his or her outpatient asthma action plan, in addition to long-acting beta-agonist therapy, montelukast, or both, as in two cases. Non-adherence was documented in the charts of three patients. All had frequent ED visits (greater than 2 in the past year) for asthma exacerbations. All patients had two or more hospitalizations for an asthma exacerbation, with two patients having a history of

Table 1. Characteristics of patients (Case 1 and 2 are the same patient).

Case	Age	Sex	Ethnicity	Medicaid	Month of illness
1	13	M	AA	Yes	June
2	13	M	AA	Yes	November
3	9	M	AA	Yes	June
4	8	M	AA	Yes	December
5	7	F	AA	Yes	May

AA: African American.

Table 2. IgE levels (normal <60).

Case	IgE (kU/L)
1	363
2	363
3	70.5
4	2497
5	12

Table 3. Initial blood gas measurement and days on ECMO.

Case	pH	pCO ₂	Days on ECMO
1	7.07	103	7
2	7.11	96	4
3	6.89	92	3
4	6.90	128	3
5	6.97	100	4

ECMO: extracorporeal membrane oxygenation.

previous intensive care unit admission for asthma; one of whom required multiple intubations for SA.

Medical history included allergic rhinitis in three patients, with eczema documented in one patient. All patients had serum IgE levels tested during admission (Table 2); three of four patients had abnormal IgE levels. Two patients received radioallergosorbent testing; both of whom had positive results for *alternaria* (class 2 and class 5, respectively). One child was medically complex with a history of microcephaly, chromosomal abnormalities and developmental delay. One patient had documented passive smoke exposure. All patients presented with symptoms ranging from cough and congestion to wheezing and chest pain. Average length of symptoms prior to admission was 6 days (range 1–14 days). Acute decompensation occurred within less than 24 h prior to admission with clinical changes including tachypnea, use of accessory respiratory muscles and decreased aeration on clinical exam with reported chest tightness. Mental status change occurred in two patients: one exhibited agitation, and the second increased somnolence. Of note, these two patients had the most severe hypoxemia of all reviewed children, 74% and 80% oxygen saturations on room air. All were tested for viruses using viral PCR nasal swabs and found to be positive for rhinovirus. Initial venous (four) and arterial (one) blood gas values are depicted in Table 3. Primary

Table 4. Spirometry values (pre-bronchodilator) after follow up from hospitalization.

Case	FEV ₁ %	FEF 25%–75%
1	85	41
2	91	55
3	91	43
4	88	65
5	69	44

interventions included the use of non-rebreather oxygen mask in two cases, continuous positive airway pressure in one case, and supplemental oxygen in two cases. Worsening clinical distress led to endotracheal intubation in all cases in conjunction with mechanical ventilation. Due to ongoing hypoxia and worsening acidosis, all patients underwent ECMO cannulation within 24 h of admission. In four cases, venous/venous ECMO was employed and in one case venous/arterial ECMO. Patients remained cannulated on ECMO for a mean duration of 4.2 days, ranging from three to seven days.

Invasive ECMO therapy coincided with continued medical management of SA. In all cases, continuous albuterol was maintained and weaned post ECMO decannulation to every four hours before hospital discharge. Ipratropium was employed as an adjunctive therapy in four of five cases. All patients received a terbutaline infusion, tapered after ECMO decannulation. All patients received systemic corticosteroids, which were completed enterally after discharge. Antibiotic coverage was provided for at least 48 h in all patients because of their initial acuity; however, none of the patients were diagnosed with a ventilator-associated pneumonia, and only one patient had positive bronchial aspirate results (specifically methicillin-sensitive *Staphylococcus aureus*). This patient received seven days of antibiotics for possible pneumonia; however, subsequent growth of this organism several months later may suggest airway colonization without acute bacterial infection. Upon further improvement and transfer to the medical floor, three patients started combination inhaled corticosteroid/long-acting bronchodilator therapy for home management. One patient was discharged on inhaled corticosteroids alone; this patient re-presented five months later and required a second course of ECMO for the same infectious trigger. Follow-up in the outpatient office occurred after a variable period, averaging 16.7 weeks (range 5–32 weeks) post ECMO. In the Pulmonology office, pre-bronchodilator spirometry was performed as documented in Table 4. Although most patients showed normal FEV₁, patients showed persistently decreased FEF_{25–75} after discharge.

Discussion

This case series demonstrates life-threatening respiratory failure associated with SA and HRV infection in a group of patients with underlying persistent asthma, the majority of which also demonstrated atopy.

Research into viral associated hospitalizations in asthmatic patients has previously focused on respiratory syncytial virus (RSV) as one of the most common respiratory pathogens of childhood; a 10-year population study found more than 34% of hospitalizations were due to RSV or influenza [6]. Recent studies now suggest that HRV causes up to 60% of pediatric asthma-associated hospitalizations [4]. Furthermore, literature suggests patients with asthma may have decreased host immunity to HRV during an asthma exacerbation. Proposed mechanisms include apoptosis of host immune cells leading to unchecked viral replication. Type 1-interferon cells in the bronchial epithelium may also have a blunted response during asthma exacerbations leading to unchecked viral replication and a robust inflammatory response [1]. An additional study reviewing microscopic changes to the asthmatic airway during exposure to HRV showed a 50-fold increase in viral replication in the first 48 h of asthmatic patients compared with otherwise healthy children [7].

The presented cases reflect the virulence of HRV infection in childhood as four of the eight children required ECMO at this institution over a five-year period due to SA exacerbated by HRV. This differs from other etiologies such as RSV where ECMO is used predominantly for bronchiolitis in a younger population: children under two years of age and premature infants with bronchopulmonary dysplasia [8] in the first five to seven days of bronchiolitis [9]. HRV affects children of all ages, potentially suggesting it serves as a significant concern with increased severity in a broader pediatric population.

All children with HRV who required ECMO were African American and used Medicaid insurance in this cohort. This finding is consistent with data that black children have not only increased prevalence of asthma but also greater morbidity and mortality (including ED visits, hospitalizations and death) [10]. The majority of patients had atopy with elevation in serum IgE levels, suggesting that underlying genetic and environmental mechanisms also play an important role in the susceptibility to severe disease caused by HRV. Our findings are similar to those of a population study in which patients with atopy and asthma had a six-fold increase in hospital admission rates if diagnosed with HRV-C [5].

Considering the severity of the episode of SA, lung function at the time of Pulmonology follow up showed maintenance of large airway function with a normal FEV₁. However, abnormal small airway function (FEF_{25–75}) was seen in all patients with mild-to-moderate obstruction. This persistent small airway obstruction may be an indicator of ongoing small airway inflammation and risk for further exacerbations in the setting of viral or other environmental triggers. Literature evaluating lung function in pediatric asthma patients post ECMO is scarce and serves as an area of interest for future outcome studies.

Limitations of this study include the inability to differentiate species of HRV based on testing methods used by our laboratory. There are hundreds of HRV subtypes within three species, HRV-A, HRV-B and HRV-C. Of note, HRV-C has been associated with more severe respiratory symptoms and rates of hospital admission in children with asthma [4,5,11]. Furthermore, this study presumes these episodes were related to an acute infection with HRV. Patients had recent symptom development, but there was no evaluation for viral illness by PCR testing in the preceding months as documented in available medical records, and therefore, it is possible, though unlikely, these patients were recovering from a prior infection as HRV may be shed for prolonged periods.

In summary, with increased availability of rapid viral testing, knowledge regarding the importance of various viral pathogens has grown and their clinical implications will continue to expand [12]. While prior studies have demonstrated that HRV in children is associated with increased respiratory symptoms, rates of subsequent wheeze and increased health care use in children, this case series demonstrates that HRV is an important pathogen in cases of severe and life-threatening asthma exacerbations and ECMO initiation.

Disclosure statement

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