

Enterovirus 68 Infection—Association with Asthma



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A previously sporadic virus called enterovirus 68 (EV-D68) appears to have been associated with asthma-like illness with a predisposition for asthmatics after an outbreak that occurred in North America in 2014. Clinicians should be aware of the clinical associations with EV-D68 particularly its predilection with pre-existing asthma or asthma-like illness as well as the potential association with acute flaccid myelitis. Further elucidation and development of diagnostic and treatments modalities are warranted to better understand and limit the potential public health impact of future outbreaks of EV-D68 infection. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:226-8)

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CASE PRESENTATION

A 5-year-old boy with a history of intermittent asthma presented to the emergency department (ED) with 24 hours of worsening cough and difficulty breathing unresponsive to short-acting bronchodilator agonist (SABA). His mother noted the child appeared to be warm for the past 12 hours, and was also concerned about his difficulty breathing and coughing. On examination, the patient was noted to be hypoxic on room air ($\text{SaO}_2 = 89\%$), wheezing, and had retractions with a fever of 101.2°F . The patient was unresponsive to additional SABA treatments in the ED, and admitted to the pediatric intensive care unit (PICU). In the PICU, the patient was treated with corticosteroids, continuous bronchodilator therapy, and noninvasive positive pressure ventilation (bilevel positive airway pressure). A chest x-ray revealed nonfocal infiltrates that suggested the potential for an infectious component. A nasopharyngeal swab was sent to the hospital laboratory for the PCR-based standard respiratory viral panel testing. The results of the panel from the hospital laboratory came back positive for human rhinovirus (RV). Another sample was sent to the state public health laboratory for respiratory virus sampling. The patient's clinical condition improved rapidly and he was discharged home.

The results of the state laboratory respiratory test came back positive for enterovirus 68.

2014 OUTBREAK OF ENTEROVIRUS 68

A number of respiratory viruses have been studied that contribute to asthma-like illness.¹ A relatively unknown sporadic virus called enterovirus 68 (EV-D68) has been associated with an outbreak in North America during the summer of 2014 that resulted in asthma-like illness. From 2014 to 2015, a total of 1153 EV-D68 infections were confirmed, although this number may underestimate the number of true cases because of limited specific testing.² Our understanding of EV-D68 is evolving, and only preliminary virology, epidemiology, and clinical pathology studies are available. Clinicians should be aware of the clinical manifestations of EV-D68, particularly its association with asthma or asthma-like illness as well as the potential association with acute flaccid myelitis (AFM).

EV-D68 has features of both enterovirus and RV, which, as discussed later, creates some diagnostic challenges. EV-D68 is a species D enterovirus belonging to the *Picornaviridae* family of small nonenveloped developed viruses with a single-stranded positive-sense RNA genome.³ However, in contrast to other enteroviruses, EV-D68 is biologically more like RV. Interestingly, EV-D68 target receptor is represented by the α -2-6 sialic acids, similar to influenza and parainfluenza viruses that infect the respiratory tract.⁴

In the middle of August 2014, the Centers for Disease Control and Prevention (CDC) was notified by clinicians from Children's Mercy Hospital in Kansas City, Mo, of a dramatic increase in pediatric patients with severe respiratory illness requiring intensive care treatment.⁵ Several weeks after, the CDC was notified of similar increases in respiratory illness from Children's Hospitals in Chicago, Ill, and Aurora, Col, respectively. Sequencing of samples from selected cases suggested that the predominant isolated pathogen was a virus known as EV-D68. Although a member of the enterovirus family, this virus had been associated primarily with respiratory asthma-like illness. Interestingly, the virus shows some biological activity similar to RV and cannot be distinguished from RV by commonly used PCR assays' pathogen panels.⁶ In September 2014, clusters of severe respiratory illness were also reported in Canada.⁷ An increase in ED visits was noted in Alberta, Canada, for patients with symptoms of influenza-like illness, shortness of breath, and cough that were associated with EV-D68 detection.⁸ Enterovirus 68 was first isolated in 1962 from respiratory specimens from 4 Californian children with lower respiratory tract disease.⁹ Epidemiological data on EV-D68 have accumulated primarily from passive surveillance, as specific molecular testing had not been widely available. From 1970 to 2005, only 26 cases of EV-D68 were identified in the USA. Small clusters of

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infection were noted in the USA, Asia, and Europe from 2008 to 2010, and an expanded number of clusters were reported between 2010 and 2014 in Europe, Asia, Oceania, and Africa. Clinicians in Japan had reported that children with well-controlled asthma developed severe asthma exacerbation when infected with EV-D68 in 2011.^{10,11}

CLINICAL PRESENTATIONS ASSOCIATED WITH ASTHMA-LIKE ILLNESS

The clinical and epidemiological aspects of the North American EV-D68 outbreak are just being characterized. A descriptive epidemiological study revealed common symptoms among 614 EV-D68 positive patients admitted to the hospital in the USA from June 1 to November 1, 2014.¹² In this cohort, the median age was 5 years (range, 3-92 years). Thus, although the virus commonly targets young children, older adults can also be infected with EV-D68. Common symptoms included dyspnea (84%), cough (81%), and wheezing (70%), similar to RV virus. A total of 48% of these patients had fever, 59% of the cohort were admitted to intensive care units, 28% required ventilator support, and 52% had a history of asthma or reactive airway disease. Interestingly, of those patients with asthma or reactive airway disease, 66% required intensive care compared with 51% with no history of asthma ($P = .0004$). Patients infected with EV-D68 with a history of asthma or reactive airway disease were more likely to require ventilator support (32%) compared with those patients with no history (24%, $P = .04$). This study thus strongly suggests that a history of asthma or reactive airway disease may be associated with illness severity of EV-D68 infection. Of the hospitalized pediatric patients with EV-D68 in the USA, most were admitted to PICUs (59%). This is in contrast to the Canadian cohorts where only 6.8% required intensive care treatment.⁸ It is unclear why this Canadian cohort had perhaps milder clinical sequelae and required less intensive care treatment from the same viral infection. A recent study by Schuster et al¹³ summarized the clinical characteristics of patients at Children's Mercy who required the PICU. Pediatric patients admitted to the PICU with EV-D68 were more likely to have a history of asthma or recurrent wheeze (68%) compared with patients who were negative for EV-D68 (42%, $P = .03$). In addition, those patients were experiencing more cough (90%) compared with non-EV-D68 patients (63%, $P = .009$). They were also more likely to receive albuterol (95% vs 79%, $P = .04$), continuous albuterol (89% vs 68%, $P = .06$), magnesium (75% vs 42%, $P = .004$), and aminophylline (25% vs 4%, $P = .004$). Patients in the EV-D68 cohort were treated with heliox (10%), epinephrine (24%), and corticosteroids (86%). Noninvasive ventilation was required in 44% of those children in the PICU.

POTENTIAL ASSOCIATION OF EV-D68 AND AFM

In addition to the strong association with asthma, there has been a potential association of patients with EV-D68 and those with AFM. In September 2014, 12 children with acute flaccid paralysis and cranial nerve dysfunction were noted.¹⁴ Of 11 children, 5 had detectable EV-D68 from the nasopharynx samples. The US CDC conducted a national surveillance of AFM and noted that between 2014 and 2015, 118 children had developed this debilitating neurologic syndrome. EV-D68 had been isolated in nasopharynx in 7 of 19 children who had

SYMPTOMS

- Cough
- Cyanosis
- Dyspnea

SIGNS

- Retractions
- Hypoxia
- Decreased Breath Sounds
- Fever (may present <50%)
- Cranial nerve dysfunction and paralysis

RADIOGRAPHY

- Non-focal infiltrates

LABS

- Elevated absolute neutrophil count

HISTORY

- Can present as asthma exacerbation
- History of asthma or recurrent wheeze not required

DIAGNOSIS

- NP Swab for PCR
- Respiratory Virus Panel (PCR) cannot differentiate from rhinovirus
- EV-D68 specific RT-PCR required (Consider sending specimen to CDC or state public health)

FIGURE 1. Clinical and diagnostic features of enterovirus 68 infection.

samples within 14 days of a prodromal respiratory illness. However, the virus had not been isolated from the cerebral spinal fluid (CSF) of any of these cases. It should be noted that so far EV-D68 has been isolated from the CSF of 2 other patients with central nervous disease, which had been reported previously before the more recent outbreak.¹⁵ Thus, the potential association of EV-D68 and paralysis remains an area of investigation but yet unproven. Interestingly, an association between asthma and acute flaccid paralysis has been reported previously and is known as Hopkins syndrome.¹⁶ In several cases of Hopkins syndrome described in the literature, EV-D68 was not tested but poliovirus was ruled out.

In addition to cohorts of asthmatics, patients with hematologic malignancy and hematopoietic cell transplant were also infected with EV-D68 during the 2014 North American outbreak.¹⁷

The clinical presentation in this cohort ranged from mild upper respiratory symptoms to respiratory failure. The authors of this study suggest that these immunocompromised adult patients' infections may be associated with more severe respiratory symptoms compared with immunocompetent patients.

VIROLOGICAL DIAGNOSIS AND ANTIVIRALS

EV-D68 can be detected in respiratory secretions of both the upper and lower respiratory tract, but the diagnostic dilemma is that most commercially available assays cannot differentiate it from RV. More widespread availability of EV-D68-specific RT-PCR assays will make diagnosis more applicable to the better understanding of the pathogenesis of this virus. None of the three antivirals in the clinical development for enterovirus or RV infections were observed to have *in vitro* activity against EV-D68 when tested by the US CDC.¹⁸ Pleconaril was shown to inhibit the 1962 Fermon strain for EV-D68 but had limited activity against the 2014 EV-D68 strain. Like influenza virus, these results exemplify the potential impact that genetic changes in the virus from year to year may have on the susceptibility to pathogen-directed antivirals. Two compounds had significant

in vitro activity against 2014 EV-D68 strain including fluoxetine and DAS181. DAS181 is a nebulized drug in clinical development for influenza and parainfluenza infections and cleaves α -2, 6-linked sialic acids, the receptor for EV-D68.¹⁹

CLINICAL IMPLICATIONS

It is imperative that clinicians be familiar with the potential for another EV-D68 outbreak, particularly as it appears to be associated with an asthma-like illness, similar to other respiratory viruses. In 2014, EV-D68 caused widespread respiratory illness with a greater propensity for severe illness in asthmatics. A summary of clinical and diagnostic considerations is shown in Figure 1. Of note, unlike influenza or other viruses, many patients were afebrile. Current experience suggests that supplemental oxygen, bronchodilators, systemic corticosteroids, and ventilator support were employed with generally good outcomes. However, this novel infection merits further evaluation in both patients with a previous history of asthma and those without a history of asthma. Clearly, the potential association between asthma symptoms and AFM needs further study and clarification and is of great interest. Further elucidation and development of diagnostic and treatments modalities are warranted to better understand and limit the potential public health impact of future outbreaks of EV-D68 infection.

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