EV-D68: Not your usual enterovirus

by Mary Anne Jackson, M.D., FAAP

Pediatricians recognize the seasonal certainty and characteristic clinical manifestations of viruses like respiratory syncytial virus and influenza that appear each winter. Similarly, during summer and early fall, providers know that many children presenting with febrile illnesses, rashes like hand, foot and mouth disease, and viral meningitis likely are infected with enteroviruses, usually a Coxsackie virus or echovirus.

In August, a less-recognized enterovirus — enterovirus D68 — emerged, and cases of severe respiratory tract infection in children have been reported across the United States.

How does EV-D68 differ from other enteroviruses?

An estimated 10 million to 15 million cases of enteroviral infection occur in U.S. children each year. At least 100 enteroviruses are described, typically classified into one of five groups: polioviruses, Coxsackie A viruses, Coxsackie B viruses, echoviruses and enteroviruses, and four different species (A-D) based on RNA-related sequencing.

Enterovirus 68 was first described in four California children with respiratory tract infection in 1962 and was classified in 1967 as enterovirus species D. Over the next 36 years, disease caused by EV-D68 was reported infrequently, and it was thought to be one of the rarest subtypes. Between 2008 and 2010, small clusters of disease were reported in the United States, United Kingdom, Japan, the Netherlands and the Philippines. All cases were associated with significant respiratory tract infection.

When did EV-D68 emerge most recently in the U.S.?

In mid-August, a surge in cases of respiratory virus infection resulting in severe respiratory distress was recognized in children who presented at two geographically distinct children’s hospitals. Review of microbiologic records showed an unexpected peak in EV/rhinovirus positivity in nasopharyngeal specimens tested by respiratory panel polymerase chain reaction (PCR). This respiratory panel is used at many children’s hospitals and can identify 20 different pathogens. In the case of EV/rhinovirus detections, however, the test does not discriminate between the many different types of each of these virus groups.

Further typing was undertaken by the Centers for Disease Control and Prevention (CDC) in 22 critically ill children in Kansas City and 14 from Comer Children’s Hospital in Chicago who were EV/rhinovirus positive. Thirty were confirmed to have EV-D68 on Aug. 26.

To date, 10 additional states have confirmed EV-D68 cases, and many more are reporting similar disease, with cases yet to be typed. It is estimated that this will be the largest EV-D68 outbreak ever reported in the world.

What are the clinical manifestations and approach to care for children with EV-D68?

Preliminary data show children with confirmed EV-D68 ranged in age from 6 weeks to 16 years. Most were school aged. Many had a history of asthma, but one-third had no prior history of wheezing. In both Kansas City and Chicago, disease was recognized in outpatient and inpatient settings; there was a high rate of hospital admission; and intensive care was necessary for a substantial number.

Clinical manifestations for the first 30 children with confirmed EV-D68 were similar. Most presented with cough and rhinorrhea, usually without fever. Significant difficulty breathing within a day or two of onset prompted presentation to the emergency department (ED), where tachypnea and hypoxemia generally were noted. While one-third of children wheezed, many just did not move air effectively.

In Kansas City, most children had chest radiographs typical of lower respiratory viral infection showing perihilar infiltrates, hyperinflation, atelectasis but without lobar consolidation. Continuous albuterol was utilized in the vast majority of children, and virtually all required oxygen and intravenous corticosteroids, with escalation of asthma interventions for those admitted to the pediatric intensive care unit (PICU). No effective antivirals are available for EV-D68.

Burden of disease in ensuing weeks

In both locales, a substantial burden of disease was on the outpatient side, resulting in an increased number of children presenting to the ED or urgent care clinics. In Kansas City, upwards of 700 children were seen daily at the apparent peak of activity — an estimated 100–150 children more than the number normally seen daily in the ED/urgent care clinic in late summer.

Higher acuity of illness and a greater risk for hospitalization also was noted. By the second week of the Kansas City outbreak, 100% of 300 beds were occupied compared to an average census of about 240 in weeks 32-34 in the prior two years. In addition, four to five children each day required admission to the PICU.

Cases appeared to peak in Kansas City during the fourth week of the outbreak. By week six, approximately 600 children had a positive result on PCR for EV/rhinovirus, the majority of whom required hospitalization. Typing is under way to determine how many had EV-D68 infection.

Daniel C. Johnson, M.D., FAAP, estimated that at the peak of the outbreak, 80% of children admitted to the general pediatric service at Comer Children’s Hospital during the EV-D68 outbreak were hospitalized because of respiratory tract infection.

Lessons learned so far

• An outbreak of severe respiratory illness caused by EV-D68 is ongoing across the United States, and many states likely will have confirmed cases.
• EV-D68 infection likely causes a spectrum of infection from mild upper respiratory infection to severe bronchospasm with respiratory failure.
• Typing of specimens from patients with severe respiratory illness thought to be caused by EV-D68 is available through the CDC.
• The burden of disease resulting in hospitalization has been substantial at many sites, and a team-based approach to care is essential for patients.
• Providers should recognize that other respiratory pathogens are circulating concurrently and should consider other infectious and non-infectious causes of respiratory symptoms in children.
• Providers should be on the lookout for unusual EV-D68 manifestations, disease in vulnerable hosts and the potential for post-infectious manifestations of EV-D68.

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