CQ

CASE QUIZ

E.P.C.M.S.

"Just a Virus"

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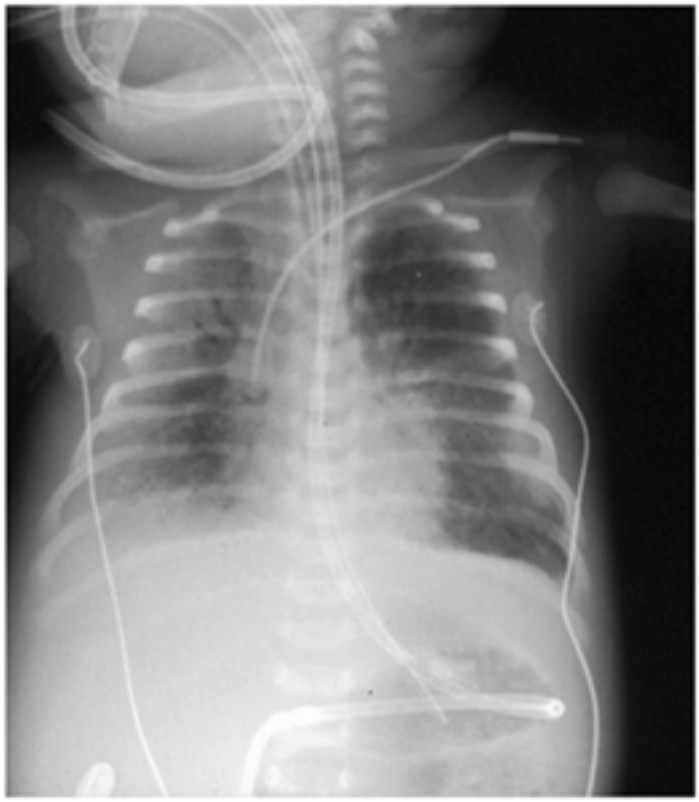
A 10-month-old boy presents to the hospital with a 1-week history of worsening cough and fever. He has no significant medical history. Recently, an older sibling had "pink-eye." The child lives in El Paso and has no recent travel history. During the past few hours, his mother states that she has noticed that he is "breathing harder" and that he "turned blue" en route to the hospital. In the emergency department, the infant is noted to be in severe respiratory distress with cyanosis, grunting respirations, and decreased responsiveness. Initial pulse oximetry saturation is 68% while breathing room air and increases to 84% with bag-valve mask ventilation with fraction of inspired oxygen of 1.0. Emergent endotracheal intubation is performed successfully, after which copious pink, frothy tracheal secretions are suctioned. Chest radiography reveals an extensive bilateral interstitial infiltrate with patchy bilateral alveolar consolidation (Figure). The patient is admitted to the pediatric intensive care unit and is initially stabilized with sedation, neuromuscular blockade, and a lung-protective mechanical ventilation strategy with a tidal volume of 5 mL/kg and positive end-expiratory pressure of 15 cm H_2O. Laboratory examination results are notable for an elevated C-reactive protein level and mild elevation of levels of transaminases. Test results for respiratory syncytial virus and influenza are negative both by rapid test and, ultimately, by viral culture.



Which of the following organisms is the MOST likely cause of this infant's pneumonia and respiratory failure?

A. Adenovirus
B. Coronavirus
C. Human metapneumovirus
D. parainfluenza virus
E. rhinovirus

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CASE QUIZ

"Just a Virus" (Continued)

A: The child described in the vignette has severe hypoxemic respiratory failure secondary to a viral pneumonia. According to recent estimates, approximately 100 million cases of viral community-acquired pneumonia occur yearly in children worldwide, with approximately 1.6 million deaths in children younger than 5 years. Most of these fatalities occur in resource-limited, developing countries. Of the choices given, the most likely cause of an overwhelming viral pneumonia in a previously healthy infant is adenovirus.

Most respiratory viruses that cause pneumonia appear to first infect the upper, or larger, airways of the respiratory tract and then to spread to the alveoli. These viruses target and have a cytopathic effect on respiratory epithelial cells. This process results in ulceration of the mucosa and severe damage to ciliated epithelial cells, with resultant dysfunction of normal mucociliary clearance. Desquamation of cells into the bronchial lumen occurs, which, along with increased mucous production, leads to bronchiolar obstruction and distal air trapping. Obstruction of the small airways results in distal atelectasis, with resultant hypoxemia from intrapulmonary shunt and V/Q mismatch. In severe cases of viral pneumonia, such as the one described in the vignette, a necrotizing alveolar inflammation may occur and may include alveolar hemorrhage. This process results in decreased lung volumes and decreased lung compliance. A serious complication of viral pneumonia is secondary bacterial infection, such as is often seen with *Staphylococcus aureus* infections superimposed on influenza pneumonia.

Differentiating a viral pneumonia from a bacterial pneumonia is not always straightforward. Epidemic patterns of disease outbreaks tend to suggest a viral cause of pneumonia. The most common cause of viral pneumonia in children remains respiratory syncytial virus (RSV), which tends to occur in yearly outbreaks starting in late autumn. Historically, influenza epidemics occur in late autumn or winter and may cause viral pneumonia in children and adults. However, the recent global pandemic of influenza A (H1N1) did not follow a typical seasonal pattern. Rapid diagnostic tests, particularly those using polymerase chain reaction (PCR) technology, are extremely useful for isolation and cohorting of hospitalized patients and for early institution of specific antiviral therapy, such as oseltamivir for influenza pneumonia. Both seasonal influenza and pandemic influenza can cause severe respiratory failure in children, particularly in children with comorbid conditions. In general, a younger age, temperature less than 38.5°C, the presence of wheezing on examination, and interstitial as opposed to alveolar infiltrates on chest radiography are thought to be suggestive of a viral rather than a bacterial cause for pneumonia. It should be emphasized, however, that none of these findings carry a high sensitivity or specificity. Marked elevations in serum leukocyte count, C-reactive protein concentration, and procalcitonin concentration are often believed to be more indicative of a bacterial pneumonia rather than a viral pneumonia. Use of elevations in procalcitonin concentrations as a guide to antibiotic therapy is an area of active investigation. Regarding radiographic findings, a frank lobar con-

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solidated infiltrate is suggestive of a bacterial pneumonia, such as *Pneumococcus*. Although viral pneumonia typically causes bilateral interstitial infiltrates, one study of children with viral pneumonia found alveolar changes on chest radiography in 49% of cases. Adenovirus is believed to account for 2% to 12% of cases of viral pneumonia in children, with the wide range of prevalence likely related to both geographic differences in study population and differences in assay techniques used for viral identification. PCR testing of respiratory secretions yields much higher sensitivities for adenovirus detection compared with older, antigen-based assays. Adenovirus is well known for potentially causing a severe, necrotizing pneumonia, particularly if infection is with serotype 3, 7, or 14. Adenovirus serotype 14 has been responsible for recent outbreaks in the United States, including outbreaks among military recruits, with some cases of severe hypoxemic respiratory failure. Adenovirus is the most common cause of postinfectious bronchiolitis obliterans in children, a chronic necrotizing process of the small airways, which ultimately results in airway fibrosis and obliteration. Postinfectious bronchiolitis obliterans caused by adenovirus carries a very high mortality rate. Adenovirus unfortunately can cause this severe spectrum of disease in previously healthy children. A recent study from Argentina, where adenovirus is the second-most prevalent viral lower respiratory tract pathogen in young children, demonstrated that 80% of children with adenoviral pneumonia were previously healthy. In this same retrospective study of 415 children, the mortality rate was 15%, with 84% of the deaths in the acute phase of respiratory failure and the remainder occurring from chronic progressive respiratory failure, including bronchiolitis obliterans. Hypoxemic respiratory failure caused by adenoviral pneumonia can be severe enough to require support with extracorporeal membrane oxygenation (ECMO), with some patients surviving even after prolonged ECMO support, as reported by Allibhai et al. At this point, treatment for pneumonia caused by adenovirus is largely supportive, although the antiviral drug cidofovir is becoming more widely used in patients with life-threatening adenoviral infections and in immunocompromised patients with adenovirus. In addition to pneumonia, adenovirus may cause conjunctivitis, as alluded to in the vignette by a history of the child having contact with a sibling with "pink-eye." Adenovirus is also known for causing hepatitis, which may be life-threatening in some cases.

Many different viruses are capable of causing pneumonia in children. A partial listing is given in the **Table**.

Table: Causes of Viral Pneumonia in Children

Respiratory syncytial virus	Mostly in infants and young children
Influenza A, B, C	Seasonal or pandemic
Rhinovirus	
Human metapneumovirus	
Human bocavirus	
Parainfluenza viruses	
Adenovirus	
Coronaviruses	Novel coronavirus cause of severe acute respiratory syndrome
Herpes simplex virus	Infants and immunocompromised
Hantavirus	In United States, most likely in Southwestern states
Varicella-zoster virus	Predominantly immunocompromised
Cytomegalovirus	Predominantly immunocompromised
Measles	Predominantly in developing countries

Worldwide, the predominant cause of viral pneumonia in young children remains RSV. Human metapneumovirus (hMPV) is an RNA virus that, although not a newly emerged virus, was only first discovered in 2001. It appears to have a wide distribution and high prevalence, particularly in late winter and spring. Some investigators have found it to be the second-leading cause of bronchiolitis behind RSV, and one large study identified hMPV in respiratory tract secretions of children with lower respiratory tract infection (LRTI) symptoms and no other identified cause. LRTI caused by hMPV appears to be more common in infants younger than 1 year, those born prematurely, and those with underlying pulmonary disease. On the basis of studies thus far, hMPV is more likely to cause bronchiolitis or a milder form of pneumonia than an overwhelming acute hypoxemic respiratory failure, as described in the vignette. However, it has been associated with severe and even fatal disease in immunocompromised hosts, such as hematopoietic stem cell transplant recipients.Because of PCR technology, rhinovirus is being detected more frequently from the respiratory tract of patients with pneumonia. However, the role of rhinovirus as a causative agent in pneumonia is debated because it is frequently detected in the respiratory tract of asymptomatic individuals. Rhinovirus infection more commonly causes asthma exacerbation or bronchiolitis in children than it does pneumonia. Although case series have identified rhinovirus types as sole causative agents of community-acquired pneumonia, it may often be a coinfection with another virus or with bacteria. Fulminant, acute respiratory failure, as described in the vignette, does not appear to be a usual presentation of rhinovirus infection. Likewise, although the human parainfluenza viruses (types 1-3) are not uncommonly identified with respiratory tract infections and community-acquired pneumonia, they do not typically produce fulminant hypoxemic respiratory failure in an otherwise healthy infant.

The coronaviruses are increasingly recognized as causes of viral community-acquired pneumonia. In a recent study from Seattle, Washington, of respiratory secretions from more than 1000 patients with respiratory symptoms, 4 coronavirus subtypes were detected in approximately 6% of specimens. In that study, RSV was the most common virus detected, followed by parainfluenza viruses, influenza A, hMPV, and adenovirus. In this study, infection with a coronavirus alone was not frequently associated with disease severe enough to require intensive care. Patients with coronavirus alone and no coinfections were much more likely to have underlying conditions, such as congenital heart disease. Six immunocompromised children from this study, including patients with malignant neoplasms and neutropenia and a renal transplant recipient, were found to have respiratory disease associated with coronavirus.

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