



Release Date: September 2005
CME Credit Valid Until: February 2007
CE Credit Valid Until: January 31, 2007

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Issue No. 12, August 2006, is part of a 12-part CME/CE activity (September 2005 – August 2006).

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Learning Objectives

After studying the literature presented in this Pediatric Respiratory Care series, participants will be able to:

- Identify respiratory disorders in pediatric patients
- Summarize risk factors for respiratory disorders in pediatric patients
- Select an appropriate therapeutic regimen for patients with pediatric respiratory disorders

Target Audience

This educational activity is designed for pediatricians, primary care physicians, pediatric and family nurse practitioners, neonatologists, infectious disease specialists, allergists, pulmonologists, immunologists, and other healthcare professionals involved in the care and management of pediatric respiratory patients.

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Clinical Insights[®] in

PEDIATRIC RESPIRATORY CARE

VOLUME 1, NUMBER 12 • AUGUST 2006

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Pathologic Features of Fatal Influenza Virus Infection in Children

During the 2003-2004 influenza season, the Centers for Disease Control and Prevention (CDC) enhanced national surveillance for influenza-associated deaths among children because of early reports of pediatric deaths. As a result of this enhanced surveillance, 153 influenza-associated deaths in children were reported. Influenza-associated death is now a reportable condition.

Guarner and colleagues recently described the pathologic changes in tissue specimens obtained from 47 children with fatal influenza virus infection during the 2003-2004 season. Lung and upper airway specimens were processed using hematoxylin and eosin, special stains for bacteria and fungi, and immunohistochemical (IHC) assays for influenza A and B viruses and other potential viral and bacterial respiratory pathogens.

Among the 47 patients, 19 (40%) were ≤2 years old, 26 (55%) were female, and 6 had a chronic medical condition that increased the risk for influenza complications. The most common

histopathologic findings in samples from the major airways (n=40) were submucosal congestion (36 patients [90%]), submucosal mononuclear inflammation (29 patients [73%]), necrosis of bronchial epithelium (20 patients [50%]), and submucosal hemorrhage (20 patients [50%]).

The most common findings in lung samples (n=46) were mononuclear interstitial inflammation (31 patients [67%]), hyaline membranes (31 patients [67%]), intraalveolar hemorrhage (25 patients [54%]), and neutrophilic bronchopneumonia (21 patients [47%]). Hemophagocytosis was present in 18 (50%) of 36 children who succumbed from influenza.

Significant life-threatening pathologic conditions that could be considered the cause of death were found in 36 patients (77%). These conditions included diffuse alveolar damage (12 cases), extensive secondary pneumonia (11 cases), extensive intraalveolar hemorrhage (10 cases), viral pneumonitis (10 cases), myocarditis (6 cases), and meningoencephalitis (1 case).

These results reaffirm the importance of IHC assays for the diagnosis of influenza and bacterial pneumonia, and emphasize the value of performing autopsies to identify cause of death in influenza-infected patients.

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Disclosures:

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Pathologic Features of Fatal Influenza Virus Infection in Children

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Influenza IHC testing was positive in 27 patients (57%), of whom 26 patients had type A antigens and 1 patient had type B antigens. IHC assays were the only confirmatory diagnostic test for 5 patients (11%). Influenza antigens were observed focally in bronchoepithelial cells of 25 patients, including 8 patients with staining of mucous glands of trachea, bronchi, and larger bronchioli. Six patients had viral antigen staining in single cells in the alveoli. Review of medical records showed that patients with positive IHC assay results had been ill for a median of 3 days, and patients with negative IHC assay results had been ill for a median of 5 days. Evidence of pneumonia was noted in 21 (47%) of the 46 lung tissue samples. A bacterial or fungal etiology was determined by IHC assay for 9 patients with secondary pneumonia (3 with *Staphylococcus aureus* infections, 3 with group A streptococci infections, 1 with *Streptococcus pneumoniae*, 1 with *Bordetella pertussis*, and 1 with *Aspergillus*).

This is the first pathologic study of influenza-associated deaths in children during an

interpandemic season; most published reports involve pandemic cases. In contrast to the very high incidence (~75%) of secondary pneumonia found in fatal cases during the 1957-58 H2N2 pandemic, secondary pneumonia was found in only 47% of the fatal cases in children studied during the 2003-04 influenza season. Inflammation and hemorrhage around major airways were common pathologic features of fatal influenza virus infection. The study authors recommend that at least 5 blocks be prepared from bronchi or centrally located lung containing large bronchioli to increase the likelihood of detecting a positive result with IHC assay.

These results reaffirm the importance of IHC assays for the diagnosis of influenza and bacterial pneumonia, and emphasize the value of performing autopsies to identify cause of death in influenza-infected patients.

Guarner J, Paddock CD, Shieh WJ, et al. Histopathologic and immunohistochemical features of fatal influenza virus infection in children during the 2003-2004 season. *Clin Infect Dis*. 2006;43:132-140.

COMMENTARY

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Every year is a potential pandemic influenza year for young children. Young children generally have little immunity to influenza and children younger than 2 years of age are hospitalized at a rate that exceeds that for all other age groups when they are infected with influenza. The pathologic features of fatal influenza described by Guarner et al foreshadow what would happen in all ages when a novel pandemic virus strikes. Primary viral pneumonia was responsible for approximately one half of the fatal infections and was characterized by mononuclear interstitial inflammation and intraalveolar hemorrhage. The hemorrhagic pneumonia described in some patients is reminiscent of the hemorrhagic pneumonia described in young healthy adults who died in 1918. Other deaths were due to secondary pneumonias; some of the secondary etiologies were identified and included Group A streptococcus, Streptococcus pneumoniae, Staphylococcus aureus, and one case with Bordetella. Unlike most older patients who die from influenza, the majority of children did not appear to have severe underlying conditions identifying them as high risk for death from influenza. Prevention of influenza in children has taken on increased importance in public health decision making and, in part, this is driven by the observations during the 2003-2004 season, for which fatal influenza infections in children were carefully described.

New Insights Into Respiratory Syncytial Virus Disease

Moore and Peebles recently reviewed the disease mechanisms in primary RSV infection and new therapeutic options. Among infants in the United States, respiratory syncytial virus (RSV) is the leading cause of bronchiolitis, pneumonia, the need for

mechanical ventilation, and respiratory failure. By 2 years of age, almost all children have been infected with RSV, with more than half being infected twice. Approximately 1% of RSV-infected children have to be hospitalized. In the United States, more than 100,000 infants per year are

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New Insights Into Respiratory Syncytial Virus Disease

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hospitalized because of RSV-induced bronchiolitis and RSV infection is a major cause of respiratory illness among high-risk adults and the elderly.

There are a number of risk factors for RSV disease including age <1 year, age <3 months at the start of RSV season, bronchopulmonary dysplasia, congenital heart disease, and prematurity. RSV occurs as a yearly epidemic, peaking in January or February in most parts of the United States and occurring slightly earlier in the Southeast.

The pathophysiology of severe RSV disease involves virus-induced airway dysfunction and inflammation. Genetic variation in certain genes (surfactant protein A, surfactant protein D, Toll-like receptor 4, IL-4, IL-8, IL-10, and chemokine receptor 5) are likely to contribute to disease severity and outcome in RSV infection. Further complicating our understanding of RSV pathologic mechanisms is a wide range of RSV disease phenotypes. Among infants with RSV infection, T-helper type 1 (Th1), T-helper type 2 (Th2), or

mixed Th1/Th2-type immune responses might be evident. Recent evidence suggest that T cells are associated with clearance of infectious RSV as well as RSV immunopathology. However, the exact role of neutrophils for clearance and immunopathology in RSV infection

is unknown. Human studies, in vitro systems, and murine models have implicated RANTES (regulated on activation normal T-cell expressed and secreted) chemokines and IL-8, which are important for recruitment of T cells and neutrophils, respectively.

RSV strain differences determine RSV disease severity. Through the use of monoclonal antibody panels, 2 RSV strains have been identified: antigenic subtype A and antigenic subtype B. Subtype A strains are associated with greater virulence than subtype B strains. Although subtype A and B strains circulate together, subtype A strains usually predominate. The predominating strain changes from year to year and can vary between communities.

Researchers are examining the possible link between RSV infection and asthma. Long-term longitudinal studies suggested that early

RSV infection increases the risk of wheezing and asthma later in life. Clinical evidence also suggests that acute asthma exacerbations might be related to RSV infection.

Currently, there is no RSV vaccine. Several obstacles have hampered the development of live attenuated RSV vaccines, such as targeting of neonates (first few weeks of life) for vaccination, the immunologic immaturity of neonates, interference of immunogenicity by maternal antibodies, and incomplete or failed immunity to RSV. Promising live vaccine candidates awaiting clinical trials include recombinant RSV strains with defined attenuating mutations and gene deletions.

Because RSV disease occurs after peak viral replication, development of anti-RSV therapies is challenging. There are currently no effective post-infection therapies for RSV disease, other than supportive care.

Corticosteroid therapy has not been shown to be effective for RSV infection, and the use of ribavirin therapy for RSV remains controversial. New antiviral drugs for RSV are being developed by traditional screening of compounds. Small molecules are under investigation that inhibit virus-cell fusion. In addition, antiviral drugs known as short interfering RNA (siRNA) that bind to viral mRNA targets are being evaluated.

Anti-RSV monoclonal antibody treatment is an effective prophylactic strategy for high-risk infants. Palivizumab is a humanized anti-RSV monoclonal antibody (mAb) that binds to the F protein epitope of the RSV and has been shown to be effective in preventing hospitalization due to severe RSV infection. Mutation of mAb genes has led to the development of a new ultra-potent, RSV-specific mAb exhibiting a greater neutralizing capacity and, for the first time, the ability to reduce RSV replication in the upper respiratory tract in animal models.

New insights into the pathologic mechanisms of RSV infection have led to the identification of several therapeutic targets. Promising therapeutic approaches include new vaccine candidates, antiviral agents, and prophylactic mAbs.

Moore ML, Peebles RS Jr. Respiratory syncytial virus disease mechanisms implicated by human, animal model, and in vitro data facilitate vaccine strategies and new therapeutics. *Pharmacol Ther* [Epub ahead of print]. July 1, 2006.

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Because RSV disease occurs after peak viral replication, development of anti-RSV therapies is challenging. There are currently no effective post-infection therapies for RSV disease, other than supportive care.



Clinical Insights® in Pediatric Respiratory Care Post-test

- Compared with influenza, RSV infection is responsible for more deaths in children
 - <1 year of age
 - 10 to 17 years of age
 - 5 to 9 years of age
 - 1 to 4 years of age
- Serogroups are important in host defense and a major target in immunoprophylaxis against meningococcal disease.
 - True
 - False
- Transmission of avian H5N1 influenza is normally carried out by
 - Contact with an actively infected person
 - Inhalation of infectious droplets
 - Fomites
 - Contact with infected animals
 - All of the above
- Which of the following is a comorbidity of invasive community-acquired methicillin-resistant *Staphylococcus aureus* infection in children?
 - Metastatic pulmonary disease
 - Primary pneumonia with complicated effusions
 - Bacterial pulmonary disease
 - All of the above
- Recurrent wheezing episodes occurring in the first 2 years of life are related to
 - RSV infections
 - Other respiratory viruses
 - The percentage of minorities in a population
 - The number of children vaccinated against RSV
 - a and b
 - c and d
- With regard to outbreaks of hMPV infections
 - Only group A strains can cause outbreaks
 - Only group B strains can cause outbreaks
 - Strains from both groups may be present
 - Group B2 strains are entirely responsible
- Primary treatment for a *Bordetella pertussis* infection is
 - Antibiotics
 - Intravenous immunoglobulin
 - Supportive therapy
 - Corticosteroids
- Currently recommended prophylactic treatment of viral respiratory infections in cystic fibrosis includes the use of
 - Influenza vaccine
 - Ribavirin
 - Albuterol
 - Palivizumab
 - a and d
 - b and c
- In children infected by rhinovirus (RV) or respiratory syncytial virus (RSV), prednisolone therapy had which of the following effects?
 - Reduction in number of wheezing relapses in children with RV
 - Reduction in number of wheezing relapses in children with RSV
 - Reduction in number of wheezing relapses for both RSV- and RV-infected children
 - No effect
- Of the 2 RSV strains that have been identified, which has been found to be the most virulent?
 - Antigenic subtype A
 - Antigenic subtype B
 - Both types are equally virulent

PRCI MISSION STATEMENT

The PRCI is a multicomponent educational program on pediatric respiratory disorders designed for pediatricians, primary care physicians, pediatric and family nurse practitioners, neonatologists, infectious disease specialists, allergists, pulmonologists, immunologists, and other healthcare professionals involved in the care and management of pediatric respiratory patients. PRCI programs address issues concerning asthma, respiratory syncytial virus, and other respiratory tract infections and disorders. Methods to prevent, control, and treat respiratory illnesses in children are also evaluated.

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