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This educational activity is conducted as a part of the *Pediatric Respiratory Care Initiative™* (PRCI™), sponsored by Thomson Professional Postgraduate Services® (PPS), Secaucus, NJ.

Issue No. 10, June 2006, is part of a 12-part CME/CE activity (September 2005 – August 2006).

Participants who wish to receive CME/CE credit for this educational activity should do the following: (1) read each of the 12 monthly issues in the series and retain them for future reference; (2) review the original articles discussed in their entirety; and (3) complete the post-test that accompanies the last issue in the series (August 2006). The post-test may also be obtained by calling 1 (800) 223-8978. You will receive the post-test and CME/CE Activity Evaluation/Registration Form by fax. To receive CME/CE credit, the participant must complete the 12-part series, post-test, and CME/CE Activity Evaluation/Registration Form and return the completed forms to: Thomson Professional Postgraduate Services, Attn: CME Dept. T304, PO Box 1505, Secaucus, NJ 07096-1505 (Fax: 1 [201] 430-1441).

Applicants will receive a certificate of participation from PPS by return mail within 6 to 8 weeks of the date of receipt of the completed evaluation/registration form.

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 Impact of Viral Respiratory Infections in Cystic Fibrosis

The hallmarks of cystic fibrosis (CF) are chronic inflammation and recurrent infections of the lungs. Van Ewijk and colleagues report that viral respiratory infections in the setting of CF are associated with greater short-term and long-term morbidity. Viruses are frequently detected in CF patients with lower respiratory tract symptoms, and a higher percentage occurs in younger people. Moreover, interactions have been noted between viral and bacterial infections in CF.

Among CF patients, viral infection has been detected in 40% of individuals with pulmonary exacerbation vs only 9% of individuals with stable disease. Various viruses have been isolated in CF

patients, most commonly respiratory syncytial virus (RSV), influenza A and B, parainfluenza, and adenovirus. Other viruses, such as rhinovirus, might be underreported because of technical limitations in detection methods.

Although viral respiratory infections occur with equal frequency in CF patients and healthy controls, the clinical impact is much worse in CF patients. Viral respiratory infections in CF patients result in an increase in

respiratory symptoms, deterioration of Shwachman and radiological scores, prolonged hospitalizations, increased antibiotic use, and a higher frequency of exacerbations. Furthermore, several studies have shown that viral respiratory infections in CF patients are associated with diminished pulmonary function, including decreases in forced expiratory volume in 1 second and forced vital capacity.

Results of several clinical studies suggest an interaction between viruses and bacteria in

CF. It has been estimated that 60% to 68% of cases of new bacterial colonization occur during the viral season. Additionally, new bacterial colonization was found to primarily occur within 3 weeks after a viral upper respiratory tract

infection. New colonization with *Pseudomonas aeruginosa*, one of the most important pathogens in CF, followed a viral upper respiratory tract infection within 3 weeks in 85% of cases. Moreover, 35% of patients who were hospitalized for a viral lower respiratory tract infection had colonization with *P aeruginosa* within 12 to 60 months.

Experimental data, although limited, suggest virus infection facilitates bacterial

Viral respiratory infections in the setting of CF are associated with greater short-term and long-term morbidity.

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Disclosures:

- * Dr Piedra is an associate professor of molecular virology and microbiology, and pediatrics at Baylor College of Medicine. He has indicated relevant financial relationships as noted: he receives grant/research support from MedImmune, Inc.; is a speaker for MedImmune, Inc.; is an expert witness for Sanofi-Pasteur; and is an ad hoc consultant for GlaxoSmithKline, MedImmune, Inc., and Sanofi-Pasteur.
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Clinical Impact of Viral Respiratory Infections in Cystic Fibrosis

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colonization and causes destruction of the epithelial barrier, with loss of cilia and tight junctions. Bacteria might also use viral glycoproteins and other virus-induced receptors to adhere to host cells.

Insights into the pathophysiology of viral respiratory infections in CF might lead to new therapeutic strategies. Annual influenza vaccination is currently recommended for all CF patients, although the effectiveness of this approach has not been clearly established. Passive immunization against RSV might be achieved with palivizumab,* but data on this strategy are currently lacking. Active immunization against RSV in CF patients is being investigated.

Effective antiviral agents for influenza virus infection include amantadine, zanamivir,

and oseltamivir. Ribavirin* can possibly be used against RSV. Emerging evidence suggests that interferon and statins might interfere with virus replication. Low-threshold administration of antibiotics during viral infections in CF patients might prevent secondary bacterial infections, although supporting data are lacking for such use.

The paucity of data regarding specific options for treating viral respiratory infections in patients with CF underscores the need for more studies.

van Ewijk BE, van der Zalm MM, Wolfs TFW, van der Ent CK. Viral respiratory infections in cystic fibrosis. *J Cyst Fibros*. 2005;4(suppl 2):31-36.

*Not FDA approved for this indication.

COMMENTARY

JAIME E. FERGIE, MD, Director, Pediatric Infectious Disease, Driscoll Children's Hospital, Corpus Christi, Texas.

Children with cystic fibrosis (CF) are infected as often as healthy children with community respiratory viruses, but the consequences of these infections are more significant and long lasting. Unfortunately, the number of therapeutic interventions is very limited, with the exception of antiviral agents for influenza infection. Of particular concern is the association between respiratory viral infection and the development of bacterial colonization in children with CF. From a practical point of view, diagnosing a viral respiratory infection in a child with CF may not avoid the use of antibiotics if the child has developed lower respiratory tract symptoms.

Clearly, prevention is the goal. These children in particular need the development of a viral respiratory vaccine that would protect against most of the usual respiratory viruses. But here also we have limited options, with yearly influenza vaccination being the only standard one. Alcohol-based hand sanitizers in the health-care setting and at home can help control the spread of viral respiratory viruses and other infectious agents.

Short-Term, High-Dose Oral N-acetylcysteine Reduces Airway Inflammation in Cystic Fibrosis

Cystic fibrosis (CF) is an inherited disorder that causes widespread dysfunction of the exocrine glands, resulting in chronic lung disease. CF is the most common recessive genetic disease among Caucasians, and its incidence is approximately one in 2,500 live births. Most children with CF are diagnosed by their first birthday.

The respiratory disorder results from mutations in the CF transmembrane conductance regulatory protein expressed in exocrine epithelia. CF is characterized by neutrophilic airway inflammation. Airway neutrophils produce oxidants that are believed to contribute to a systemic redox imbalance manifested by an extracellular deficiency in the antioxidant

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Short-Term, High-Dose Oral *N*-acetylcysteine Reduces Airway Inflammation in Cystic Fibrosis

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In addition to regular issues of Clinical Insights® in Pediatric Respiratory Care, look for a CME monograph, Respiratory Syncytial Virus and Bronchiolitis: Risk Factors for a Possible Link to Asthma, to be published soon.

glutathione (GSH). In turn, systemic redox stress might recruit more circulating neutrophils into the lungs. Current therapies, which focus primarily on the palliative treatment of airway inflammation, include inhaled corticosteroids, high-dose ibuprofen, and azithromycin.

Attention has recently been given to use of oral *N*-acetylcysteine (NAC),* a pro-drug for GSH, in CF patients. Tirouvanziam and associates conducted a phase 1, unblinded, dose-escalation trial of high-dose oral NAC (0.6 g, 0.8 g, and 1.0 g given 3 times daily for 4 weeks) in 18 patients with stable CF (mean age, 25 years; age range, 11-44 years). The study group was divided into 3 cohorts of 6 patients based on daily dose (1.8 g/day, 2.4 g/day, 3.0 g/day). At baseline, a deficiency in GSH was found among the 18 patients compared with 9 healthy controls ($P=0.003$).

Over the 4-week period, overall study drug compliance was 93%. NAC administration significantly increased intracellular neutrophil GSH (+23%; $P=0.025$) as well as whole blood GSH (+12%, $P=0.031$). There were no significant differences in effects on GSH between the 3 doses. NAC administration also significantly reduced airway neutrophil count measured by sputum samples ($P=0.003$).

Furthermore, NAC administration was associated with a significant decrease in the activity of sputum elastase ($P=0.006$), considered the best predictor of pulmonary function in patients with CF. As expected

with short-term treatment, pulmonary function (measured by forced expiratory volume in 1 second and forced vital capacity) did not improve. The number of airway neutrophils actively releasing elastase-rich granules was also significantly reduced with NAC treatment ($P=0.005$). However, primary granule release on airway neutrophils was not changed by NAC treatment, indicating that the decrease in elastase activity might be caused by a decrease in the overall neutrophil count.

These results indicate that high-dose

oral NAC has the potential to ameliorate redox imbalances and possibly counter the self-amplifying inflammatory process in CF. Notably, this study was the first to use NAC doses in excess of 1.8 g/day. NAC was well tolerated, with no adverse effects.

The study investigators suggested that oral NAC could be used in combination with other CF treatments, including antibiotics. However, they warned against uncontrolled use of this drug, which is available as over-the-counter nutraceutical formulations that may not be subject to proper quality control. Further studies are needed to evaluate the long-term efficacy and safety of high-dose oral NAC in treating CF.

...oral NAC could be used in combination with other CF treatments, including antibiotics.

Tirouvanziam R, Conrad CK, Bottiglieri T, et al. High-dose oral *N*-acetylcysteine, a glutathione prodrug, modulates inflammation in cystic fibrosis. *Proc Natl Acad Sci USA*. 2006;103:4628-4633.

*Not FDA approved for this indication.

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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