



Release Date: June 2007
Valid Until: August 2007

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

Participants who wish to receive CME credit for this educational activity should do the following: (1) read the current issue; (2) complete the post-test and evaluation form. To apply for CME credit, return the completed post-test and evaluation form to:

Professional Postgraduate Services[®]
CME Dept. T314
150 Meadowlands Parkway
Secaucus, NJ 07094-2304

You may also fax the completed materials to 1 (201) 430-1441. If you have any questions, please call 1 (800) 606-6106 Ext. 8892.

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 form and post-test.

Learning Objectives

After studying the literature presented in this issue, participants will be able to:

- Differentiate the immune responses caused by RSV or influenza virus in infants surviving lower respiratory tract infection (LRTI)
- Describe the criteria for characterization of severe infantile RSV LRTI and influenza virus LRTI
- Assess the relationship between the robust inflammatory response and the severity of RSV bronchiolitis

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.

Professional Postgraduate Services[®] is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Professional Postgraduate Services[®] designates this educational activity for a maximum of 0.50 *AMA PRA Category 1 Credit*[™]. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This CME activity is supported by an educational grant from MedImmune, Inc.

Clinical Insights, Pediatric Respiratory Care Initiative, and PRCI are trademarks used herein under license.

Off-Label Disclosure

Some of the drug treatments discussed in this issue may note uses not approved by the Food and Drug Administration. Articles containing such uses will be noted at the end of the article.

Copyright © 2007 **Professional Postgraduate Services**[®]. All rights reserved.

PEDRO A. PIEDRA, MD,* EDITOR-IN-CHIEF; JAY M. LIEBERMAN, MD,[†] REVIEWER; KATHLEEN M. MAJOR,[‡] GRACE L. MCBRIDE,[§] SENIOR MANAGING EDITORS; CHING-LING C. CHEN, PhD,^{||} MEDICAL WRITER

Severe Lower Respiratory Tract Illness Caused by RSV and Influenza Virus Is Characterized by Inadequate Cytotoxic Lymphocyte Responses

Respiratory syncytial virus (RSV) and influenza virus are common causes of lower respiratory tract infection (LRTI) in young children. In infants, RSV and influenza LRTI can be severe, and RSV infection is the most frequent cause of hospitalization of infants in the United States. Both viral replication and inappropriately enhanced immune responses (particularly lymphocyte responses) are believed to contribute to disease severity. Welliver and colleagues conducted the present study to elucidate the pathogenesis of LRTI caused by RSV and influenza virus infections in infants.

Two population groups of children were included in the study. One group consisted of surviving infants <12 months of age with RSV (n=36) or influenza virus (n=36) infection of the upper respiratory tract (URTI) or LRTI, and a second group of infants had fatal LRTI infected with RSV (n=9) or influenza virus (n=11). Nasopharyngeal secretions were collected from infants surviving RSV and influenza virus infections for measurement of cytokines and chemokines. Lung tissues obtained from infants with fatal cases of RSV and influenza virus LRTI were used to assess the types of inflammatory cells and to detect the presence of lymphotoxin granzyme and the apoptosis marker caspase 3.

Surviving infants with RSV bronchiolitis had longer duration of hospitalization (4.8 versus 2.4 days; $P=0.004$) and lower oxygen saturations (93% versus 95%; $P=0.0002$) than those with influenza virus bronchiolitis. For both types of viral infection, none of the cytokines measured was found in higher concentrations in infants with LRTI compared to those with URTI.

Most of the 17 cytokines and chemokines measured in nasopharyngeal secretions were present in lower quantities ($P<0.0001$) or less frequently detected in infants with RSV infection than in those with influenza virus infection. For instance, T lymphocyte-derived cytokines, interleukin-2 (IL-2), IL-4, IL-17, and interferon (IFN)- γ were nearly undetectable in infants with RSV LRTI. In contrast, these mediators were all at higher concentrations or frequently detected in infants with influenza virus LRTI. Furthermore, although only one specimen was obtained from each patient, the concentrations of T lymphocyte cytokines in infants with RSV LRTI declined with time after onset of wheezing, therefore, there was no evidence of lymphocyte activation by RSV infection was detected over this interval.

Additionally, cytokines released by other cell types, such as macrophage-associated IL-12, macrophage chemotactic protein (MCP)-1 and IL-6, as well as IL-1 β , IL-7, and IL-10, were all in reduced concentrations ($P<0.0001$) in infants with RSV infection, as compared to those with influenza virus infection. In contrast, cytokines granulocyte-macrophage colony-stimulating factor (GM-CSF), G-CSF, tumor necrosis factor (TNF)- α , and macrophage inflammatory protein (MIP)-1 (notably released from epithelial cells) were present in comparable concentrations in children with RSV and influenza virus infection.

Viral replication was evaluated in lung tissues from infants with fatal LRTI. Influenza viral antigen was detectable primarily in the epithelium of larger airways, whereas RSV viral antigen was more extensively present in both epithelium and exfoliated epithelial cells

Continued

Disclosures:

- * Dr Piedra is 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.
- † Dr Lieberman is Chief, Pediatric Infectious Diseases at Miller Children's Hospital, Long Beach, California. He has indicated relevant financial relationships as noted: he receives grant/research support and is a retained consultant and speaker for MedImmune and Merck, and is a speaker for Sanofi-Pasteur and GlaxoSmithKline.
- ‡ Ms Major is a senior managing editor for Professional Postgraduate Services[®]. She has indicated no relevant financial relationships.
- § Ms McBride is a senior managing editor for Professional Postgraduate Services[®]. She has indicated no relevant financial relationships.
- || Dr Chen is a medical writer for Professional Postgraduate Services[®]. She has indicated no relevant financial relationships.



Severe LRTI Caused by RSV and Influenza Virus *(Continued)*

obstructing the lumen of small airways. Damage to the bronchiolar epithelium was also greater in the lung of fatal RSV bronchiolitis.

Immunohistochemical staining of lung tissue revealed a low frequency of CD4, CD8 (cytotoxic T cells), and CD56 (natural killer cells) antigen-positive lymphocytes in fatal RSV and influenza virus bronchiolitis. Granzymes, a lymphotoxin product of lymphocytes, were also rarely detected in the lung of bronchiolitis. In contrast, strongly positive signals for neutrophils and macrophage antigen CD16 and apoptosis marker caspase 3 were observed in lung tissue of infants with fatal RSV and influenza virus bronchiolitis.

Welliver and colleagues concluded that fatal LRTI caused by RSV and influenza virus was

characterized by low cytotoxic T lymphocyte responses, robust viral application, and increased apoptosis. The authors proposed that the pathogenesis of fatal RSV and influenza virus LRTI results from the absence of T lymphocyte activation, which is required for eradication of virus-infected respiratory epithelial cells, and replacement with cellular apoptosis as a mechanism for clearing virus.

Welliver TP, Garofalo RP, Hosakote Y, et al. Severe human lower respiratory tract illness caused by respiratory syncytial virus and influenza virus is characterized by the absence of pulmonary cytotoxic lymphocyte responses. *J Infect Dis.* 2007;195:1126-1136.

COMMENTARY

JAY M. LIEBERMAN, MD, Chief, Pediatric Infectious Diseases, Miller Children's Hospital, Long Beach, California.

This interesting and important report from Welliver and colleagues challenges the widely held belief that the severity of RSV infection is related to the degree of the host's immune response. This concept, to a large degree, derives from experience with the investigational, formalin-inactivated RSV vaccine that was evaluated in the 1960s. Vaccinated children developed more severe lower respiratory tract illness when they were subsequently infected with RSV than did control subjects, and two otherwise healthy infants died of RSV infection. Autopsies on these infants showed a prominent eosinophilic and lymphocytic infiltration. However, the pathogenesis of lower respiratory tract RSV infection has not been well described or understood. In this study, US infants who survived RSV LRTI had significantly lower quantities of lymphocyte-derived cytokines detected in their nasopharyngeal secretions that did infants with influenza virus LRTI. Similarly, lung tissue from infants from Chile with fatal RSV infection demonstrated high quantities of viral antigen, but a near absence of cytotoxic T cells, findings that were markedly different than those of infants who had died from influenza. The idea that the development of RSV bronchiolitis is dependent on over-responsiveness of cytotoxic lymphocytes has led to efforts to decrease this response with the use, for example, of corticosteroids. However, corticosteroids have not been found to positively impact the course of disease. The findings reported in this paper, if confirmed, suggest that greater efforts should be spent on developing effective anti-viral agents.

RSV concentrations were significantly higher in children who presented to the emergency department earlier in their illness than those who presented later during their disease process.

Inflammatory Response Is Not Associated With Severity of RSV Bronchiolitis

Bronchiolitis, a virus-induced respiratory disease, is the number one health problem in children younger than 2 years in the United States. Approximately 300,000 children are hospitalized annually because of this disease. Respiratory syncytial virus (RSV) is the most common pathogen in bronchiolitis and in lower respiratory tract disease in children. Both proinflammatory and anti-inflammatory mediators have been shown to be involved in the RSV infection. To gain insight into the immunopathogenesis of RSV bronchiolitis, Bennett and colleagues conducted a prospective cohort study to evaluate the relationship between RSV infection and inflammatory mediators, cytokines and chemokines, and the impact of these factors on the severity of RSV-infected bronchiolitis.

Children <24 months old who presented to the emergency department with clinical symptoms of bronchiolitis during a 17-week RSV outbreak between November 2004 and February 2005 were enrolled in the study. Nasal-wash

samples were collected for identification of viral pathogens, as well as for measurement of RSV and cytokine/chemokine concentrations. Severe cases of bronchiolitis, defined as those requiring hospitalization, and further determined on the basis of the duration of supplemental-oxygen and/or intravenous-fluid (IVF) therapy, were evaluated in children with RSV bronchiolitis or with non-RSV bronchiolitis.

Among 101 children enrolled, 63 children were infected with RSV, 13 children were infected with other respiratory viruses (5 with picornavirus, 3 with adenovirus, 2 with human metapneumovirus, and 1 with cytomegalovirus, 1 with influenza type B, and 1 with parainfluenza virus), and in 22 children there was no virus detected. The impact of age on infection status and outcome measures was studied in 4 age groups; 0≤3, 3≤6, 6≤12, and 12≤24 months. Children at younger age, <6 months, had higher risk for RSV infection ($P<0.05$), as well as higher need for hospitalization ($P<0.05$), than those at

Continued



Participate in a quick 12-question survey on educational needs, visit www.ppscme.org and go to Respiratory Care.

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.

Inflammatory Response (Continued)

6≤24 months of age. There was a significant positive correlation between age and RSV concentration ($r = 0.26$; $P = 0.04$). Additionally, RSV concentrations were significantly higher in children who presented to the emergency department earlier in their illness than those who presented later during their disease process ($P = 0.04$).

When compared with children with non-RSV bronchiolitis ($n = 34$), children with RSV bronchiolitis ($n = 62$) had a robust inflammatory response. A significantly profound increase in the concentrations of nasal-wash cytokines and chemokines, including interleukin-6 (IL-6), IL-8, IL-1 β , interferon (IFN)- γ , macrophage inflammatory protein (MIP)-1 β , tumor necrosis factor (TNF)- α , granulocyte-macrophage colony-stimulating factor (GM-CSF), and G-CSF, were observed in children with RSV bronchiolitis ($P \leq 0.01$ and $P \leq 0.05$). However, the greater inflammatory response observed in children with RSV bronchiolitis was not associated with more severe bronchiolitis. The frequency of hospitalization, supplemental oxygen therapy for >24 hours, and need for IVF for >24 hours were not significantly different between children with RSV and non-RSV bronchiolitis.

Furthermore, evaluation of the relation between the levels of inflammatory mediators and the severity of the disease in 63 RSV-infected children also showed that the concentrations of cytokines and chemokines in these children were not significantly different with respect to the need for hospitalization or the duration on IVF therapy. Interestingly, the concentrations of proinflammatory mediators, such as IL-6, IL-8, IFN- γ , and MIP-1 β , as well as IL-10, were inversely associated with the duration of supplemental-oxygen therapy ($P \leq 0.05$).

The authors concluded that in children with RSV bronchiolitis, the robust inflammatory response caused by the infection was not associated with more severe bronchiolitis. On the contrary, an early elevated proinflammatory response (IL-6, IL-8, IFN- γ , and MIP-1 β), as well as of the regulatory cytokine (IL-10), may be protective against hypoxia in RSV bronchiolitis.

Bennett BL, Garofalo RP, Cron SG, et al. Immunopathogenesis of respiratory syncytial virus bronchiolitis. *J Infect Dis.* 2007;195:1532-1540.

Clinical Insights® in Pediatric Respiratory Care Post-Test

- Which of the following statements is **false** regarding immune responses and fatal infantile LRTI caused by RSV or influenza virus?
 - Lymphocyte-derived cytokines, such as IL-2 and IL-4, are present in higher concentrations in respiratory secretions of infants with influenza virus LRTI than in those with RSV LRTI
 - CD8 antigen is detected in very low numbers of lymphocytes in lung tissues of infants with fatal RSV LRTI and fatal influenza virus LRTI
 - Cytokines from epithelial cells are present in equal concentrations in children with RSV and influenza virus infection
 - Lymphocyte-derived cytokines are more frequently detected in the secretions of infants with RSV LRTI than in those with influenza virus LRTI
- Which of the age groups has the highest risk for RSV bronchiolitis requiring medical evaluation in the emergency department?
 - 0≤6 months
 - 6≤12 months
 - 12≤24 months
 - 24≤36 months

- Children at <6 months of age have the highest risk for RSV-infected bronchiolitis.
- Infants with RSV LRTI.
- Lymphocyte-derived cytokines, such as IL-2, IL-4, IL-17, and IFN- γ , are less frequently detected in

For more information about upcoming PRCI® CME activities, visit us at www.ppscme.org.

You have received this email because we believe it may be of interest to you. If you would like your name to be removed from the PRCI Clinical Insights® in Pediatric Respiratory Care newsletter email list, please click on the following prci@ppscme.com.

If you have any friends or colleagues who would like to receive this newsletter via email, please fill in their information on the lines below and fax this page to us at 1 (201) 430-1295 so they can be added to our subscriber list.

Name: _____
 Specialty: _____
 Email Address: _____

