



Release Date: Nov. 14, 2008
CME Credit Valid Through: Jan. 14, 2009

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

- Describe the effects of palivizumab on respiratory syncytial virus (RSV) hospitalization rates in infants and young children with congenital heart disease (CHD)
- Explain the effects of ribavirin therapy on the risk for developing asthma and allergen sensitization in high-risk children hospitalized with 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.

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

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Clinical Insights® in

PEDIATRIC RESPIRATORY CARE

VOLUME 4, NUMBER 10, 2008

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Palivizumab Use With Congenital Heart Disease: 2000–2004 Palivizumab Outcomes Registry

In the United States, respiratory syncytial virus (RSV) is the leading cause of hospitalization due to bronchiolitis in children <1 year of age. Certain groups of children are at increased risk of severe or fatal RSV infection, including infants with cyanotic or complicated congenital heart disease (CHD). Young children with CHD hospitalized for RSV infection often times have a complicated prolonged hospital course. Palivizumab, a humanized neutralizing IgG1 monoclonal antibody directed against the F protein of the RSV, is recommended by the American Academy of Pediatrics (AAP) for RSV prophylaxis in children ≤24 months of age with hemodynamically significant cyanotic or acyanotic CHD.

The Palivizumab Outcomes Registry prospectively collected data on 19,548 subjects who received ≥1 dose of palivizumab during 4 consecutive RSV seasons between 2000 and 2004 at 256 sites across the United States. Cohen and colleagues recently evaluated the characteristics of enrolled registry subjects with congenital heart disease (CHD). This was the first prospective epidemiologic analysis involving subjects with CHD receiving palivizumab outside of a clinical trial.

Pediatricians were the primary healthcare provider in most of the subjects (89.5%–93.0%) and most often recommended use of palivizumab (61.5%–73.4%). At the time of first

injection, 47.1% of subjects with CHD were younger than 6 months of age. Compliance with the palivizumab injection regimen increased from 72.0% in the first season to 85.4% the fourth season. Across all 4 RSV seasons, 83.4% of subjects were compliant with the palivizumab injection regimen.

A total of 1,500 subjects with CHD were enrolled during the registry period, representing 7.7% of the entire registry cohort of 19,548. Of the subjects with CHD, 71% had acyanotic CHD. The percentage of children with CHD more than doubled across the 4 seasons, from 4.8% in the first season to 11.4% in the last season. Further, the proportion with cyanotic CHD increased from 19.6% to 37.5%. The three most common primary diagnoses were patent ductus arteriosus, ventricular septal defect, and atrial septal defect.

The cumulative RSV hospitalization rate was significantly higher among subjects with CHD than among those without CHD (1.9% vs 1.2%; $P=0.003$), reflecting the higher risk associated with CHD. Among subjects with cyanotic and acyanotic CHD, hospitalization rates were 2.6% and 1.6%, respectively. Across the 4 seasons, a decreasing trend was evident in the proportion of RSV hospitalizations for all subjects with CHD ($P=0.0215$) as well as for subjects with acyanotic CHD ($P=0.0046$). The decrease in

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Disclosures:

Dr Piedra is professor of pediatrics and molecular virology and microbiology at Baylor College of Medicine, Houston, Texas. He has indicated that he receives grant/research support from Juvaris BioTherapeutics, Inc., MedImmune, Inc., Sanofi Pasteur, and Novartis Pharmaceuticals; is a speaker for MedImmune, Inc.; and is an ad hoc consultant for MedImmune, Inc., Sanofi Pasteur, Novartis Pharmaceuticals, Hoffmann-La Roche Inc., and Merck & Co., Inc.

Dr DeVincenzo has indicated that he receives grant/research support and is a retained consultant for Arrow Pharmaceuticals Inc., Novartis, and MedImmune Inc.; he receives grant/research support from Alnylam Pharmaceuticals, Inc.; and he is a retained consultant for Tibotec, Inc.

PPS Staff: Mark Palangio, senior medical writer; Terri Setteducato, senior program director; and Elizabeth Ward, CME director, have indicated no relevant financial relationships. Jennifer Nisita, senior editor, has indicated that her spouse is a salaried employee of Merck & Co, Inc.



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Palivizumab Use With Congenital Heart Disease (Continued)

hospitalization rates was temporally associated with increased compliance with monthly palivizumab injections.

Prospective data from the Palivizumab Outcomes Registry show low hospitalization rates among children with CHD receiving palivizumab and suggest that physicians, primarily pediatricians, prescribe palivizumab to infants and young children with CHD consistent with

the AAP guidelines and labeled indications. These results are consistent with earlier randomized controlled trials that show the efficacy of prophylaxis with palivizumab.

Cohen SA, Zanni R, Cohen A, et al. Palivizumab use in subjects with congenital heart disease: results from the 2000-2004 Palivizumab Outcomes Registry. *Pediatr Cardiol*. 2008;29(2):382-387.

COMMENTARY

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Because this study lacks a control group, conclusions cannot be drawn from it regarding the efficacy of palivizumab. Despite this major limitation, the registry provides other interesting insights on RSV management, notably with respect to compliance.

Although compliance tended to improve across the seasons evaluated in the outcomes registry (72% to 85% across the 4 seasons of the study), it is still inexcusable to have almost 20% of patients non-compliant—especially when one considers that the drug is already paid for by the insurance company. Moreover, the definition of compliance used in this paper was such that compliance was only measured after the first dose of palivizumab was received. Children who failed to receive their first dose of palivizumab on time, yet were being exposed to RSV, were nonetheless counted as being compliant. Thus, this report actually overestimates the compliance rates.

Compliance rates for this study cannot be extrapolated to other health care providers. The practices participating in the registry were chosen because they had high volume of “high RSV risk” patients. For the general pediatrician or other health care groups with smaller numbers of “high RSV risk” infants, the compliance rates could likely be substantially lower than those observed here.

The increase in compliance over the 4 years of the study likely represents improvements in individual offices’ infrastructure and the perfection of techniques to identify and track patients and missed doses. Other healthcare practices would benefit from similar advancements. Physicians need to establish better systems for patient identification and tracking to assure that the injections, especially the first dose of palivizumab, are administered in a timely fashion.

The Effects of Ribavirin for RSV Bronchiolitis on the Risk of Asthma and Allergen Sensitization

Accumulating evidence indicates that respiratory syncytial virus (RSV) bronchiolitis in early life is associated with the later development of asthma, recurrent wheezing, and atopy. Ribavirin is the only antiviral agent currently available for treating children with acute RSV bronchiolitis and its use in immunocompetent children with RSV bronchiolitis is controversial. However, the long-term effects of ribavirin therapy remain uncertain, and the cost of ribavirin therapy is relatively high.

To investigate the effects of ribavirin therapy on the risk for developing asthma and allergen sensitization, Chen and associates studied a cohort of children hospitalized with RSV bronchiolitis before 2 years of age and followed until a mean age of 6.2 years at the National Taiwan University

Hospital. The surveillance period lasted 4.5 years (January 1997–June 2001).

A total of 175 of the 224 evaluable children were included in this study. High-risk young children with congenital heart disease or chronic lung disease with RSV bronchiolitis hospitalization were either treated with ribavirin (n=40) or did not receive this agent (n=44). The controls were otherwise healthy RSV-hospitalized children who did not receive ribavirin. They were divided into control group A (n=49) and control group B (n=42). Control group A was matched for date and age at hospitalization to high-risk children treated with ribavirin. Control group B was matched to high-risk children not treated with ribavirin. In addition to wheezing and asthma assessment,

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The Effects of Ribavirin for RSV Bronchiolitis on the Risk of Asthma and Allergen Sensitization (Continued)

serum levels of allergen-specific IgE antibodies were measured for 8 common inhaled allergens, including *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Blomia tropicalis*, cat dander, dog dander, cockroach, Bermuda grass, and ragweed.

Demographic and background data were similar between groups except that high-risk children treated with ribavirin and their controls (Group A) were significantly younger at follow-up compared with high-risk children not treated with ribavirin and their controls (Group B). The cumulative prevalence of asthma was significantly lower in the high-risk ribavirin group than in control group A (8% vs 33%; $P=0.004$) but not in the high-risk no ribavirin group and control group B (21% vs 36%; $P=0.15$). The combined rate of cumulative asthma/recurrent wheezing was significantly lower in the high-risk ribavirin group compared with either control group A (15% vs 43%; $P=0.005$) or the high-risk no ribavirin group (15% vs 34%; $P=0.049$). No significant differences in the rate of cumulative asthma/recurrent wheezing, however, were found between the high-risk no ribavirin group and control group B, or between control groups A and B. Further, a multivariate logistic analysis showed that ribavirin therapy was an independent factor in reducing the risk for developing asthma (odds ratio, 0.2;

95% confidence interval, 0.1-0.7; $P<0.01$) and asthma/recurrent wheezing (odds ratio, 0.3; 95% confidence interval, 0.1-0.7; $P<0.01$).

Rates of allergen sensitization were significantly lower in the high-risk ribavirin group than in control group A (26% vs 75%; $P=0.002$), and not significantly different between the high-risk no ribavirin group and control group B (33% vs 60%; $P=0.128$). Additionally, sensitization rates to *D pteronyssinus*, *D farinae*, and *B tropicalis* were significantly reduced in the high-risk ribavirin group compared with control A group ($P=0.001$, $P<0.001$, and $P=0.043$, respectively). There were no significant differences in sensitization rates with the 8 allergens between the high-risk no ribavirin group and control group B.

These results suggest that ribavirin therapy for high-risk children hospitalized with RSV bronchiolitis decreased the risk for developing asthma and allergen sensitization. In light of these findings, the study authors indicated that the long-term effects of ribavirin for acute RSV bronchiolitis merit further investigation.

Chen C-H, Lin Y-T, Yang Y-H, et al. Ribavirin for respiratory syncytial virus bronchiolitis reduced the risk of asthma and allergen sensitization. *Pediatr Allergy Immunol.* 2008;19(2):166-172.

Clinical Insights® in Pediatric Respiratory Care Post-Test

- In the Palivizumab Outcomes Registry, which of the following best describes RSV hospitalization rates in infants with CHD receiving palivizumab prophylaxis?
 - Hospitalization rates decreased across the 4 seasons
 - Hospitalization rates increased across the 4 seasons
 - Hospitalization rates remained stable across the 4 seasons
 - Hospitalization rates fluctuated across the 4 seasons
- In the study by Chen et al, ribavirin therapy for children hospitalized with RSV bronchiolitis was associated with which of the following?
 - An increase in the rate of asthma and allergen sensitization
 - A decrease in the rate of asthma and allergen sensitization
 - An increase in the rate of asthma and a decrease in the rate of allergen sensitization
 - A decrease in the rate of asthma and an increase in the rate of allergen sensitization

ANSWERS

Question 1 answer: a. Prospective data from the Palivizumab Outcomes Registry show low hospitalization rates among children with CHD receiving palivizumab. A decreasing trend was evident in the proportion of RSV hospitalizations across the 4 seasons.
Question 2 answer: b. In the study by Chen et al, ribavirin therapy for children hospitalized with RSV bronchiolitis decreased the risk for developing asthma and allergen sensitization.

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