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LEARNING OBJECTIVES

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

- Discuss the association between early childhood wheezing and adulthood wheezing and asthma
- Describe the relationship between early childhood RSV infection and the later emergence of wheezing and asthma

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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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.

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Early Childhood Wheezing Is Linked to Adulthood Wheezing and Asthma

Wheezing is common in early childhood. In fact, approximately 30% of children develop wheezing during respiratory infection before their third birthday. Although most children outgrow such symptoms by school age, a substantial proportion eventually develop adult asthma—even after many symptom-free years. In a recent review article, Piippo-Savolainen and Korppi presented evidence from long-term postbronchiolitis Swedish and Finnish follow-up studies linking early childhood wheezing to persistent wheezing and asthma later in life.

As discussed in this article, infants and children with wheezing comprise a heterogeneous group with different outcomes. The Tucson birth cohort study identified 3 main phenotypes of early childhood wheezing: transient wheezers (60%), atopic persistent wheezers (20%), and nonatopic persistent wheezers (20%). Transient wheezers experience symptoms only during respiratory infections before 3 years of age and have subnormal lung function throughout childhood. Atopic persistent wheezers usually experience their first wheezing episode during their second or third year of life followed by repeated wheezing throughout childhood. They also have allergic sensitization and subnormal lung function throughout childhood. Nonatopic persistent wheezers begin wheezing before 1 year of age, typically resulting from respiratory syncytial virus (RSV) infection. In this group, wheezing occurs only during respiratory infections, and lung function remains subnormal throughout childhood.

Children younger than 24 months with wheezing that is severe enough to require hospitalization are at increased risk for asthma and other respiratory disorders later in life. In prospective cohort studies, 14% to 40% of children hospitalized with bronchiolitis subsequently developed asthma during the adolescent or teenage years. Permanent loss of lung function was evident after bronchiolitis. Later lung function abnormalities were apparent after severe bronchiolitis in infancy, after mild early-life wheezing, and for years after cessation of wheezing.

> *Children younger than 24 months with wheezing that is severe enough to require hospitalization are at increased risk for asthma and other respiratory disorders later in life.*

Recurrent wheezing and asthma are common in children for years after hospitalization for RSV bronchiolitis. However, some studies suggest that subsequent wheezing and asthma appear to be more prevalent after bronchiolitis caused by viruses that are less severe than RSV. The authors of this article speculated that viral infection early in life may alter normal lung development.

Early childhood risk factors for teenage or

Continued

Disclosures:

* Dr Piedra indicated that he receives grant/research support from 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 Belshe indicated that he receives grant/research support from MedImmune, Inc. and Merck & Co., Inc.; is a retained consultant for MedImmune, Inc., Merck & Co., Inc., and Novartis Pharmaceuticals; and is a member of the speakers bureau for MedImmune, Inc., Sanofi Pasteur, and Merck & Co., Inc.

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Early Childhood Wheezing *(Continued)*

adult asthma include parental asthma, family atopy, female gender, sensitization to food or inhaled allergens, eosinophilia, early atopy (eg, atopic dermatitis), repeated wheezing at 24 months of age or younger, and parental smoking. The Swedish prospective case-control postbronchiolitis study recognized 3 independent factors leading to adult asthma after bronchiolitis hospitalization in infancy: an allergic pathway from family atopy through allergy, early passive smoking through bronchial hyperreactivity, and later active smoking through bronchial hyperreactivity.

The Tucson study group developed an algorithm for identifying wheezing children at risk for subsequent asthma. Based on the information revealed in this review, Piippo-Savolainen and Korppi revised this algorithm to define those children who are at particular risk for ensuing asthma after hospitalization for early childhood wheezing. In this revision, major criteria include: (1) physician-diagnosed asthma in a parent, (2) parental, especially maternal, smoking, and (3) physician-diagnosed atopic dermatitis and/or food allergy. Minor criteria include: (1) sensitization to inhaled allergens, (2) wheezing induced by viruses other than RSV, and (3) blood eosinophilia or lack of eosinophilic response during viral infection.

In conclusion, most wheezing infants and children outgrow their symptoms by school age. However, long-term follow-up studies indicate that many of these wheezing children go on to develop adult asthma, and that history of parental asthma, maternal smoking, and wheezing induced by viruses other than RSV are predictive of developing adult asthma. Identifying infants and children with bronchiolitis who are at risk for persistent wheezing and asthma in later life could potentially avoid complications associated with undertreatment, such as permanent lung function impairment, as well as side effects associated with overtreatment with corticosteroids or other medications for the treatment of asthma.

Piippo-Savolainen E, Korppi M. Wheezy babies—wheezy adults? Review on long-term outcome until adulthood after early childhood wheezing. *Acta Paediatr.* 2008;97(1):5-11.

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COMMENTARY

ROBERT B. BELSHE, MD, Dianna and J. Joseph Adorjan Endowed Professor of Infectious Diseases and Immunology, Professor of Medicine, Pediatrics, and Molecular Microbiology, Saint Louis University School of Medicine, Missouri.

The articles presented in this issue focus on the association between respiratory viral infections in infants, subsequent wheezing in children, and long-term effects resulting in wheezing in adults. There is no question that respiratory viruses remain the single major target for additional vaccine development. Respiratory viruses are the most common cause of hospitalization of infants, and a handful of viruses led by respiratory syncytial virus (RSV), parainfluenza, and human metapneumovirus are the cause of most lower respiratory illnesses in infants and young children. If we prevented these viral infections with vaccine, what proportion of asthma would be prevented? The review by Piippo-Savolainen and Korppi guide us in this answer. We expected that one of the 3 main phenotypes of early childhood wheezing would likely be prevented by immunization against RSV. The authors estimate that perhaps 20% of children develop recurrent wheezing and persistent lung function abnormalities because of RSV and other common respiratory viruses. The remaining causes include environmental allergens, parental smoking, and genetics, suggesting that an RSV vaccine would not prevent asthma in those other cases. However, prevention of serious lower respiratory disease in infants would clearly have profound benefit, not only in the prevention of 20% of asthma cases, but also in preventing the most common cause of hospitalizations in infants.

Early Childhood RSV Infection Is Associated With Long-Term Wheezing and Asthma

Respiratory syncytial virus (RSV), a paramyxovirus, is the main respiratory pathogen among infants and young children worldwide. As the most frequent cause of bronchiolitis in infants, RSV infects virtually all children by 3 years of age. Yet, the association between early RSV infection and the later emergence of wheezing and asthma has not been clearly delineated. As such, Pérez-Yarza and colleagues carried out a systematic review of studies examining the association between RSV infection in the first 36 months of life and the subsequent development of asthma and bronchial hyperreactivity.

This review involved a literature search for original studies on RSV infection published in English or Spanish between 1985 and 2006 using Medline, Embase, and Indice Médico Español, and in The Cochrane Library. The criteria for article selection included: (1) original

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Early Childhood RSV Infection *(Continued)*

article, (2) RSV infection defined by virologic diagnosis, (3) maximum age of infection of 3 years, (4) defined outcome variables, and (5) any design, sample size, or follow-up period. Article quality was assessed according to the Hadorn criteria.

A total of 12 articles were identified that met the selection criteria and the objective of this review. All of these articles described longitudinal studies with a control group of healthy children and involved follow-up periods of longer than 6 months. In these studies, RSV lower respiratory tract infection was associated with an increased risk of subsequent development of recurrent wheezing or asthma. Moreover, this association became progressively smaller with increasing age.

The authors concluded that there is an association between RSV infection and the emergence of different asthma phenotypes, with a progressive disappearance of this effect with increasing age.

Parent-reported recurrent wheezing was evaluated in 8 articles, 3 of which demonstrated an association with early RSV infection. Physician-diagnosed recurrent wheezing was evaluated in 3 articles, among which all 3 found an increased incidence of wheezing among RSV-infected children. Physician-diagnosed asthma was evaluated in 8 articles, 6 of which showed a relationship between RSV and this condition. For example, in one of the evaluated studies, RSV-infected children, compared with controls, had a greater incidence of physician-diagnosed recurrent wheezing (48% vs 14%, respectively) and asthma (60% vs 7.8%, respectively). Allergic sensitization, which was defined by a positive skin prick test result and by measuring pneumoallergen-specific and/or food-specific immunoglobulin E levels, was evaluated by 8 articles, 5 of which demonstrated a relationship between RSV infection and allergic sensitization. The relationship, however, was not consistent, with one study reporting a significantly lower probability of skin test positivity in children with a history of RSV infection.

According to the information compiled in this systematic review, the authors concluded that there is an association between RSV infection and the emergence of different asthma phenotypes, with a progressive disappearance of this effect with increasing age. However, the authors acknowledged the limited methodologic quality of the articles and that additional investigation is needed, ideally with specific therapeutic approaches intended to reduce RSV replication.

Pérez-Yarza EG, Moreno A, Lázaro P, Mejías A, Ramilo O. The association between respiratory syncytial virus infection and the development of childhood asthma: a systematic review of the literature. *Pediatr Infect Dis J*. 2007;26(8):733-739.

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.

Post-Test

1. Based on the findings of this review, which of the following is not a childhood risk factor for teenage or adult asthma?
   a. Female gender
   b. Parental asthma
   c. Maternal smoking
   d. Repeated wheezing at <24 months of age
   e. Exposure to food and inhalant allergens

2. Based on the findings of this review, there is an association between early childhood respiratory syncytial virus (RSV) infection and the subsequent development of which of the following?
   a. Recurrent wheezing
   b. Asthma
   c. Allergic sensitization
   d. Recurrent wheezing and asthma only
   e. Recurrent wheezing, asthma, and allergic sensitization

ANSWERS

Answer: e. Exposure to food and inhalant allergens does not mean sensitization.

Answer: d. In these studies, RSV lower respiratory tract infection was associated with the subsequent development of recurrent wheezing and asthma. The relation with allergic sensitization was inconsistent.

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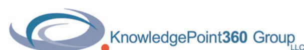

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I have participated in this activity as designed and am claiming _______ *AMA PRA Category 1 Credit*™ (maximum .50)

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Overall Program

	Strongly Disagree		Disagree	Agree		Strongly Agree
1. The activity met the stated objectives in such a way that I am better able to:						
a. Discuss the association between early childhood wheezing and adulthood wheezing and asthma	1	2	3	4	5	6
b. Describe the relationship between early childhood RSV infection and the later emergence of wheezing and asthma	1	2	3	4	5	6
2. Please rate the following statements:						
a. Activity provided clear evidence to support the content	1	2	3	4	5	6
b. Activity was presented in a way that facilitated learning	1	2	3	4	5	6

3. Did the activity present a balanced view of therapeutic options available for the disease state(s)? ☐ Yes ☐ No*
   * If you checked "No," please explain. ____________

4. Did the activity present content that fairly represented, and was based on a reasonable and valid interpretation of the information available on the subject? ☐ Yes ☐ No*
   * If you checked "No," please explain. ____________

5. Did the activity appear to place an unreasonable emphasis on one particular product/service? ☐ Yes* ☐ No
   * If you checked "Yes," please explain. ____________

6. In reflecting on your practice, what type of impact will this educational activity have? *(Select all that apply.)* I will:
   - ☐ Help identify infants and children with bronchiolitis who are at risk for persistent wheezing and asthma in later life.
   - ☐ Help focus my attention on prevention of serious lower respiratory disease in infants via prophylaxis and parent behavior, thus reducing the risk of asthma and preventing hospitalization.
   - ☐ Other *(please specify)* ____________

7. What topics should be dealt with in more detail? *(List topics.)* ____________

8. What is the most important thing you learned from this activity? ____________

Thank you for your participation