Deciphering the Importance of Host and Environmental Factors that Influence the Genesis of Asthma During Childhood

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(See the major article by Gern et al, on pages 1342–9.)

Identifying host and environmental factors that promote the development of asthma during childhood has been an area of intense investigation for years. Most early studies focused on the role of respiratory syncytial virus (RSV) infections and the development of asthma, especially among infants hospitalized for severe bronchiolitis [1, 2]. More recent studies, however, have demonstrated that young children who wheeze with rhinovirus (HRV) have an even greater risk for developing asthma by age 6 years than those who wheeze with RSV [3]. Additionally, advances in respiratory tract virus detection indicate that different strains of viruses may be more virulent and possibly “asthmagenic” than other strains (eg, a chimeric A2 strain of RSV in mice and possibly group C strains of HRV in humans) [4, 5]. These studies are of great interest and are relevant to the identification of new targets for antiviral treatments [6].

In this issue of the Journal of Infectious Diseases, Gern and colleagues provide a detailed study of viral detection in nasal washes collected from infants during episodes of respiratory illness and compare the results in 2 cohorts of subjects: 515 infants enrolled from 4 inner-city areas (Urban Environment and Childhood Asthma [URECA] study) and 285 infants from families living in suburban Madison, Wisconsin (Childhood Origins of Asthma [COAST] study) [7]. Because infants from these cohorts were exposed to different environmental conditions, the investigators recognized a unique opportunity to compare and contrast results regarding the detection of viral pathogens associated with flares of respiratory symptoms experienced by these infants during the first year of life. In longitudinal studies, the investigators plan to evaluate the impact of these infections on the development of asthma as the children grow older. A significant strength of the study is that the enrollment criteria and methods used for evaluating the infants from both cohorts were similar.

The scoring system used to determine when nasal washes would be collected from infants in both studies included points for upper and lower respiratory tract symptoms. Virus detection and data analyses were based on samples collected from infants who had a symptom score ≥5. Although we do not know for sure how the virus results relate to exacerbations of wheezing or the need for urgent care, the inner-city infants from all 4 urban sites had significantly higher rates of adenovirus detected in their nasal washes (varying from 10% to 21% in the 4 cities) than the infants from Madison (6%). The authors note that crowded conditions favor the spread of adenovirus, which may in part account for the higher rates of adenovirus detected in washes from the inner-city infants who, by contrast, had lower rates of positive tests for HRV and RSV.

The extent to which adenovirus infections in the URECA cohort will influence the development of asthma remains to be determined. Overall, the proportion of washes testing positive only for adenovirus (ie, without evidence for coinfection) was 4.8% among infants in the URECA study and 0.7% among infants in the COAST study. These percentages were substantially lower than the proportion of nasal washes testing positive for HRV alone in these cohorts (24.1% and 36%, respectively). Additionally, the strains of adenovirus detected were mostly group C (94% group C in the URECA study and 100% in the COAST study). As the authors note, group C strains are more frequently associated with upper, rather than lower, respiratory tract symptoms, and the potential for these strains to influence the development of asthma or other
respiratory illnesses will only become clear from longitudinal follow-up.

An important finding in this study was that the inner-city infants, again from all 4 urban locations, had lower overall rates of virus detection than the infants from Madison. Reasons for this observation are of considerable interest because of the high prevalence, morbidity, and mortality associated with asthma in poor urban communities [8]. This problem heightens interest in early life events that may contribute to the increased burden of asthma in the inner city. Thus, the lower rate of virus detected in washes from the urban infants when they were symptomatic was unexpected and was also observed among these infants when they were asymptomatic. Because the methods of specimen collection and viral diagnostics used for both cohorts were similar, the authors mention that a higher frequency of undetected (or currently undetectable) viral infections among the urban infants might partially account for the difference, although this is not likely to be the sole explanation. Alternatively, the authors cite recent compelling investigations that suggest that bacterial pathogens associated with respiratory and wheezing illnesses during infancy (e.g., Streptococcus pneumonia, Haemophilus influenza, and Moraxella catarrhalis) deserve further evaluation [9, 10]. Sensitive diagnostic techniques are now available for evaluating the microbiota of the airways, gut, and skin as potential immune modulating factors that might also influence the development of allergic disorders, including asthma [11]. Non-infectious exposures (e.g., air pollutants and environmental tobacco smoke) may also be relevant to the persistence and severity of symptoms and deserve further investigation.

In addition to virus-induced wheezing during infancy, the roles of atopic host characteristics and allergen exposures in promoting the development of asthma have been highlighted in many previous reports. Several studies have demonstrated that there is a strong association between atopy and asthma after 3 years of age and that allergen-specific immunoglobulin E (IgE) responses and elevations in total IgE (>200 IU/mL) are present in more than 75%–80% of children who are hospitalized or treated in the emergency room for asthma during their school-age years [12, 13]. Evidence that allergic inflammation underlies the risk for wheezing provoked by viral infections, predominantly by HRV, after age 3 comes from studies that show that more than 90% of school-age children and young adults who wheeze with HRV are atopic, have elevated levels of expired nitric oxide prior to their infection, and have high levels of allergen-specific IgE antibody, which significantly increases their risk for an HRV-induced attack of wheezing [13-15]. Consistent with this, family history for allergy, the presence of atopic dermatitis during infancy, sensitization to food allergens, increased levels of total serum IgE at 9 months, and high levels of exposure to dust mite allergen among infants born to allergic parents have all been associated with the development of asthma [16-20]. Further highlighting the importance of atopy at an early age, the risk of having asthma at age 5 years among children with virus-induced wheeze during the first year of life was restricted to children who were sensitized to aero-allergens by 2 years of age [21]. More recent data from the COAST study have also shown that allergen sensitization by 3 years of age increased the risk for asthma by age 6 and that allergen sensitization is likely to precede the first episode of virus-induced wheeze among those who developed persistent wheeze [22]. In the URECA and COAST subjects, the rates of allergen-specific IgE were low during the first 12 months of life; however, infants from both cohorts came from families with at least 1 parent who had self-reported allergies or asthma. Objective tests for sensitization among parents from both cohorts will make it easier to compare parental risk factors for allergy in these cohorts and to learn how the atopic background of the infants relates to the development of asthma as they grow older.

Together, viral respiratory tract infections and allergic inflammation (an interaction between the 2 is most likely) appear to be the dominant risk factors for developing asthma during childhood. To what extent other environmental exposures can modulate this process will be easier to judge from these and other prospective studies, followed by intervention studies in the future. Improved diagnostic methods should also improve our understanding of the “virus conundrum” wherein studies indicating that virus-induced wheezing in infancy may promote asthma contrast to other studies that suggest that viral infections might have a protective effect and decrease the risk for asthma among infants who attend day care where they are presumably exposed more often to viral pathogens (and probably also to bacterial pathogens and different levels of allergen exposure) than they are at home [23]. Looking to the future, more comprehensive assessments of environmental exposures and infections using improved diagnostics will help to decipher the relative importance of risk factors associated with the development of asthma during the early school-age years and determine whether these risk factors are similar to those that influence the development of asthma after puberty when a gender shift (more females than males) is observed.

Gern and colleagues should be congratulated for demonstrating the importance of comparing data from 2 distinct demographic cohorts. Both the URECA and COAST studies were designed to identify environmental factors that may influence the subsequent development of asthma and respiratory allergy [24, 25]. The results clearly show differences in the detection of viral infections during the first year of life. This approach is likely to provide novel insights that will serve to guide the development of treatment interventions to decrease the
prevalence and severity of asthma during childhood.

Notes

Financial support. This work was supported by NIH grants R01 AI020565 and U19 AI070364.

Potential conflicts of interest. The authors certify no potential conflicts of interest. The authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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