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Early Life Wheezing and Respiratory Syncytial Virus Prevention

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Wheezing illnesses in preschool children have perplexed clinicians for decades in terms of their differential diagnosis, acute and chronic treatment, and prognosis regarding their ability to foreshadow the subsequent development of asthma. Although wheezing illnesses have been described in more than fifty percent of preschool children, many eventually “outgrow” this problem.¹ A major concern with using wheezing to define an illness is the subjectivity in assessing this symptom in terms of caregiver recognition, agreement between parental and physician assessment, and recognition of the degree of severity that portends subsequent administration of systemic corticosteroids or hospitalization.² Nonetheless, since more objective pulmonary function studies are difficult to perform in the majority of preschool children, wheezing has been used as a surrogate marker to identify clinically relevant lower airway obstruction.

Viral respiratory tract illnesses, particularly those due to infections with respiratory syncytial virus (RSV)³ and human rhinovirus (HRV)⁴, have been frequently associated with the development of persistent wheezing and/or childhood asthma, indicating that prevention of infection with either virus would have the potential of reducing risk of developing either or both of these outcomes.

Based on these relationships, it seems plausible that currently available anti-RSV therapy could reduce recurrent wheezing risk secondary to RSV infections. Using a retrospective and non-randomized study design, Simoes et al. treated premature infants with palivizumab and compared them to an untreated cohort matched for chronological and gestational age. During a 24-month follow-up period, physician-diagnosed recurrent wheezing was significantly less frequent in the treated group.⁵ Interestingly, this reduction in wheezing frequency was seen only in those children who did not have an atopic family history.⁶

In this issue, Blanken and colleagues extend these observations in a randomized double blind placebo controlled trial using total number of wheezing days in the first year of life as the primary outcome.⁷ Remarkably, premature infants treated with palivizumab had a significant 61% relative decrease in total number of wheezing days during the first year of life. Moreover, the effect of RSV prevention on the number of wheezing days persisted in the post-prophylaxis period, i.e. from two months after the last injection. As anticipated, palivizumab treatment reduced hospitalizations related to RSV infection; in addition, the

data indicate that treatment had a significant effect on reducing rates of medically attended non-hospitalized RSV infections.

Given the limitations inherent with using wheezing as a primary outcome measure discussed previously, these data rather convincingly demonstrate that palivizumab treatment can reduce both RSV infection rates and subsequent recurrent wheezing in preterm infants. These relationships were noted despite rather low nasopharyngeal swab sample procurement (30%) and respiratory pathogen detection (approximately 60%) rates obtained during wheezing illnesses by the parents or caregivers. However, study coordinator and investigator oversight of the trial was excellent as adherence to scheduled injections in both the placebo and palivizumab groups occurred more than 85% of the time.

With the potentially strong association between early life wheezing and the development of childhood asthma, what do these data mean in terms of predicting future asthma risk in this population of high-risk infants? Two of the most important risk factors for the development of asthma in children are the presence of allergic sensitization⁸ and wheezing during both viral and bacterial respiratory tract illnesses⁹ in the first few years of life. Recent data generated in the COAST cohort indicate that allergic sensitization may be causative in the subsequent development of viral-induced wheezing.¹⁰ One proposed mechanistic pathway to explain these sequential relationships involves impairment of innate responses to viral pathogens due to IgE receptor cross-linking that results in increased airway inflammation and subsequent loss of lung function in sensitized individuals.¹¹

It is important to recognize, however, that other asthma risk “pathways”, which are independent of allergic sensitization, may also contribute. One such pathway may involve genetic variation within the 17q21 locus and viral-induced respiratory wheezing illnesses. In recent studies, variants at this locus were associated with HRV wheezing illnesses in early life, but not with RSV wheezing illnesses. The associations of 17q21 variants with asthma were restricted to children who previously had HRV wheezing illnesses, resulting in a significant interaction effect with respect to the risk of asthma. Interestingly, these associations were independent of the presence or absence of allergic sensitization.¹²

In the current study, the effect of RSV prevention with palivizumab on the total number of wheezing days was similar regardless of parental history of atopy. As stated previously, Simoes et al.⁶ found that palivizumab reduced wheezing only in children without atopic family histories. The fact that an atopic genetic background did not further influence wheezing frequency in both studies suggests that palivizumab treatment, while decreasing morbidity in infancy, may have limited effects on at least some future *asthma* risk pathways. Whether more definitive evaluations of both allergic sensitization (i.e., allergen-specific IgE testing) and 17q21 locus variation, or treatment of term infants would alter these findings, improve risk predictions, and/or influence the natural history of asthma, warrants further study.

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References

1. Martinez FD, Wright AL, Taussig LM, et al. Asthma and wheezing in the first six years of life. *N Engl J Med.* 1995; 332:133–8. [PubMed: 7800004]
2. Skytt N, Bonnelykke K, Bisgaard H. "To wheeze or not to wheeze": That is not the question. *J Allergy Clin Immunol.* 2012; 130:403–7. e5. [PubMed: 22766098]
3. Wu P, Hartert TV. Evidence for a causal relationship between respiratory syncytial virus infection and asthma. Expert review of anti-infective therapy. 2011; 9:731–45. [PubMed: 21905783]
4. Jackson DJ, Gangnon RE, Evans MD, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med.* 2008; 178:667–72. [PubMed: 18565953]
5. Simoes EA, Groothuis JR, Carbonell-Estrany X, et al. Palivizumab prophylaxis, respiratory syncytial virus, and subsequent recurrent wheezing. *J Pediatr.* 2007; 151:34–42. e1. [PubMed: 17586188]
6. Simoes EA, Carbonell-Estrany X, Rieger CH, et al. The effect of respiratory syncytial virus on subsequent recurrent wheezing in atopic and nonatopic children. *J Allergy Clin Immunol.* 2010; 126:256–62. [PubMed: 20624638]
7. Blanken MO, Rovers MM, Molenaar JM, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *N Engl J Med.* 2013 In Press.
8. Sly PD, Boner AL, Bjorksten B, et al. Early identification of atopy in the prediction of persistent asthma in children. *Lancet.* 2008; 372:1100–6. [PubMed: 18805338]
9. Bisgaard H, Hermansen MN, Bonnelykke K, et al. Association of bacteria and viruses with wheezy episodes in young children: prospective birth cohort study. *BMJ.* 2010; 341:c4978. [PubMed: 20921080]
10. Jackson DJ, Evans MD, Gangnon RE, et al. Evidence for a causal relationship between allergic sensitization and rhinovirus wheezing in early life. *Am J Respir Crit Care Med.* 2012; 185:281–5. [PubMed: 21960534]
11. Durrani SR, Montville DJ, Pratt AS, et al. Innate immune responses to rhinovirus are reduced by the high-affinity IgE receptor in allergic asthmatic children. *J Allergy Clin Immunol.* 2012; 130:489–95. [PubMed: 22766097]
12. Caliskan M, Bochkov YA, Kreiner-Moller E, et al. Rhinovirus wheezing illness and genetic risk of childhood onset asthma. *N Engl J Med.* 2013 In press.