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The calculated risk of childhood asthma from severe bronchiolitis

Jonathan M. Gaffin, MD, MMSc[1,2] and **Wanda Phipatanakul, MD, MS**[2,3]

[1]Division of Respiratory Diseases, Boston Children's Hospital, Boston, USA

[2]Harvard Medical School, Boston, USA

[3]Division of Allergy and Immunology, Boston Children's Hospital, Boston, USA

That there is a risk of school age asthma following severe bronchiolitis in early life is almost indisputable[1], but the quantification of that risk is debated. Estimates have ranged as widely as 20 – 60%; however variations in definitions of the predictor and outcome, bronchiolitis and asthma, the populations studied, and the time constraints placed around the assessment of events, lead to inherent difficulty in generalizability of individual study findings. In this issue of *The Journal of Allergy and Clinical Immunology: In Practice*, Balekian, et al.[2] report on the prevalence of asthma following severe bronchiolitis in a nested birth cohort study of children attending a single center in Massachusetts. In this report, 27% of children hospitalized with severe bronchiolitis developed asthma by age 5 years old, compared to the population prevalence of 11.5%. Furthermore, while several known clinical characteristics were also found to be associated with asthma, such as prematurity, low birth weight, early atopic dermatitis, maternal asthma and cesarean delivery, there was no interaction of atopic dermatitis with bronchiolitis. This is an important distinction from prior work which has identified early atopy as a key factor in this pathway from bronchiolitis to asthma[3]. The strengths of this study are the large sample size and prospective nature of follow-up. As a birth cohort, the population estimates for severe bronchiolitis events and subsequent asthma outcomes can more naturally be compared to the general population than with case control studies and case series that dominate this body of literature. However, the granularity with which predictors of risk can be determined is limited by the study design in which claims data is the source of comorbid conditions. For example, the absence of billing code for atopic dermatitis is far from determining that an individual is truly non-atopic. Specific testing for atopy, which could be better determined by serum IgE level or skin prick test, may identify a risk group interaction for atopy that is unable to be elicited when atopic dermatitis billing codes are used as a surrogate marker.

So, what are the implications of this work? This study provides further evidence of the strong relationship between severe bronchiolitis and subsequent development of early childhood asthma. The point estimate in prevalence of asthma, or recurrent wheeze, as many studies have measured, after severe bronchiolitis ranges widely. Case control studies of RSV bronchiolitis in Sweden found a 23% prevalence of asthma at age 7, though the background

Corresponding Author: Wanda Phipatanakul, MD, MS, Children's Hospital Boston, Division of Immunology, Fegan 6, 300 Longwood Ave., Boston, MA 02115;Phone: 617-355-6117; Fax: 617-730-0310; wanda.phipatanakul@childrens.harvard.edu.

rate of asthma was quite low at 3%[4]. Ecological studies in the US have demonstrated similar rates of asthma after hospitalization for bronchiolitis in infancy (22%) [5]. Interventional studies following bronchiolitis with larger inclusion timeframes for bronchiolitis report up to 50%[6]. Variability in these estimates may be inherently due to focus on a specific viral etiology, differences in population mix and medical culture. However, undoubtedly the greatest etiology of variation in the estimates is the precision of measure of both the predictor – bronchiolitis – and the outcome – asthma – both of which lack exactness and subject to misclassification bias. For example, allowing inclusion of bronchiolitis for 2 or 3 years of life increases the likelihood that the population is enriched for a predisposition to asthma. An outcome of recurrent wheeze rather than diagnosis of asthma may also inflate the prevalence. In this report, the estimate is 27% and 2.6 times the odds of developing asthma by age 5 years following hospitalized bronchiolitis within the first year of life in a large cohort of the northeastern US population attending an urban medical center. It is not surprising that the risk estimate is on the lower end compared to other studies considering bronchiolitis was only considered in the first year of life, and that asthma was defined by diagnosis in the medical record or 2 or more asthma medication events. Whatever the true point prevalence of asthma following bronchiolitis, the summation of evidence leads to the same conclusion, whether measured by study clinicians, medical record review, ecologic associations[7], or health system claims data, as in this case: severe bronchiolitis is associated with childhood asthma.

Previous work[8, 9] has more specifically identified that RSV and rhinovirus associated bronchiolitis and atopic predisposition are enhanced predictors of later wheeze and asthma development for children with severe bronchiolitis. Further work to understand the mechanisms leading from one respiratory insult to the other continue to be needed as understanding the risk profile will offer specific therapeutic targets to intervene.

The holy grail of pediatric asthma research is to find a way to prevent the disease from developing. Determining a reliable antecedent event, such as severe bronchiolitis, that predicts asthma in a substantial proportion of affected children offers the hope that the development of asthma is a process that may be prevented or interrupted. Strategies to leverage this relationship may either focus on the prevention of severe bronchiolitis (primary prevention) or intervention following the bronchiolitis event as a secondary prevention effort to interrupt the progression to asthma.

Primary prevention efforts in the form of vaccination with palivizumab for RSV in high risk populations defined by prematurity have shown promise. Simoes and colleagues identified that late preterm infants had nearly half the incidence of recurrent wheeze if they received RSV prophylaxis than their unvaccinated counterparts[10]. A prospective randomized trial of palivizumab in healthy late preterm infants demonstrated promising results in the first year of life – a 10% lower rate of recurrent wheeze, and 50% fewer wheezing days[11]. Long term follow-up is needed to see if the benefit is sustained. To date, successful interventions to prevent rhinovirus-related bronchiolitis are lacking. More general strategies of using probiotics to attempt to minimize TH2 stimulation of the immune system have largely not met with success. However, evidence of mitigation of recurrent lower respiratory tract infections with a product containing multiple bacterial lysates[12] as an immunostimulant may

be promising and is currently being studied for recurrent wheeze (clinicaltrials.gov: NCT02148796).

The identification of children with severe bronchiolitis likely to develop asthma additionally holds the promise of secondary prevention of asthma. Montelukast has not been shown to prevent recurrent wheeze following RSV bronchiolitis[13]. However, early studies suggest that azithromycin may have efficacy in this situation[14]. As allergic sensitization preceding viral wheeze may be key in the causal pathway[3], interrupting the atopic march following early life wheezing illnesses may be an effective secondary prevention measure as well. In fact, binding the FcεR1 receptor may reduce viral symptoms[15]. A prevention of asthma trial is currently underway using omalizumab in young children that may capitalize on this mechanism (clinicaltrials.gov: NCT02570984).

Balekian, et al.[2] lend further evidence of the strong link between severe bronchiolitis and asthma development in a large, prospective US cohort, confirming that severe bronchiolitis is a precursor to asthma in a substantial number of children. Identifying targets in the pathway preceding bronchiolitis through the development of asthma offers opportunities to intervene. Leveraging this early life event for primary or secondary prevention of asthma may of paramount importance.

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