

Respiratory syncytial virus and asthma: still no final answer

Renato T Stein,¹ Fernando D Martinez²

During the past two decades, a large number of studies have addressed the association of viral respiratory events in early life and the subsequent development of recurrent wheezing and asthma later in life.^{1–4} Investigations performed both in animal models and in humans have provided new insights into potential pathogenetic mechanisms discernible during acute and convalescent stages of viral events and their potential association with the long-term consequences of these events.^{5,6} Retrospective analysis of clinical trials has suggested that the use of anti-respiratory syncytial virus (RSV) antibodies may decrease the incidence of subsequent asthma-like symptoms,⁷ but prospective data are lacking.

The strongest data for the association between early RSV events and asthma comes from longitudinal studies. The Tucson Children's Respiratory Study was based on a healthy and representative population, and its results, if not automatically applicable to all communities given the peculiarities of the Arizona desert, have been replicated in other population-based studies. The main findings from the Tucson study indicated that RSV, independent of other known risk factors for asthma, was significantly associated with recurrent wheeze in the first decade of life.¹ The results of a larger birth cohort, also population based, the ALSPAC study from Bristol points in the same direction as the Tucson study: children with a RSV bronchiolitis admission in the first year of life were more likely to have asthma at age 7 years, compared with controls and there was no relation with RSV infection and the development of atopy at this age.⁸ The issue of a possible relation between early life RSV bronchiolitis and the later development of

atopy has been entertained by a series of studies, and the disparities of findings seem to be related to the methodology used in selecting the subjects.

A major strength of these two above-mentioned birth cohort studies is that they are population based, and are powered adequately enough to study asthma and atopy as main outcomes, in a scenario in which a great number of other independent risk factors were also ascertained. Valuable information comes from a subset of children in the Tucson study who had infant lung function testing before any viral event was detected; these children were more likely to wheeze with lower respiratory illnesses if they had lower lung function values as measured by maximal expiratory flow at functional residual capacity [$V_{\text{max}}\text{FRC}$].⁹ Infant lung function data were not evaluated in relation to severe bronchiolitis or RSV bronchiolitis in the Tucson study, but this was done in birth cohort from Perth, in which 253 healthy infants were followed from birth and had lung function measured at 1, 6 and 12 months of life. Similarly to the Tucson findings, infants in Perth who had bronchiolitis were in the lowest quartile for premorbid lung function values.¹⁰ When this cohort was re-evaluated years later, children with bronchiolitis were shown to be at an increased risk of wheezing and, more interestingly, their expiratory flows at age 11 years were significantly lower compared with the rest of the cohort, and these levels tracked with the lower expiratory flows observed in the first months of life.¹¹ These findings indicate that premorbid lung function predicts low lung function that may not (at least not significantly) be affected by the acute viral bronchiolitis event.

In this issue of *Thorax*, Sigurs and collaborators¹² (see page 1045) offer new insights into mechanisms relating early life severe viral bronchiolitis and later asthma. These investigators revisit their cohort, for which almost 18 years ago they originally enrolled two groups of children: one admitted to hospital and diagnosed with severe RSV bronchiolitis and another consisting of healthy

controls. A series of previous publications by the same group has established not only that children in the bronchiolitis group were at greater risk of subsequent wheeze in later years, when compared with healthy controls, but that they were also at greater risk of atopy. This latter finding has not been confirmed by most other studies, perhaps due to specific characteristics of the Swedish population, or a bias that might have been introduced in the selection of cases and controls at the beginning of the study.¹³

In the current study, Sigurs and colleagues¹² confirm their earlier findings now at age 18 years, indicating, as the long-term prospective studies mentioned previously, that the combination of RSV bronchiolitis and early sensitisation is a major risk factor for persistent wheeze. They also report that children with RSV bronchiolitis, independently of asthma at age 18 years, but not the asthmatic controls, had lower levels of lung function, thus suggesting that severe RSV may directly affect lung development. It is worth mentioning again that the main limitation of these conclusions is that no premorbid data are available for these children. The observation that small airway dysfunction, as measured by the lung clearance index, at age 18 years was associated with current asthma, enhanced airway responsiveness, and Fraction of exhaled nitric oxide (FeNO) but not with bronchiolitis points to the need for sensitive measures of small airways function and markers of inflammation to detect changes in children with milder disease. All these conclusions are based on the evaluation of a small number of subjects (after stratification for subgroups), with functional differences that may not mean much clinically. More data are needed, especially considering that the lung clearance index is a new method with some limitations, especially when used on the evaluation of children with asthma.¹⁴

Recent twin studies further support the idea of a shared heritability between asthma and RSV bronchiolitis. Using a large registry of twins in Denmark and sophisticated statistical modelling, Thomsen and coworkers¹⁵ concluded that severe RSV bronchiolitis is an early indicator of a shared genetic predisposition for asthma, and not that asthma is the consequence of having had RSV bronchiolitis. We take a step further to suggest that, for most children presenting with severe RSV bronchiolitis, the most frequent risk factor is premorbid low lung function and that, in the absence of

¹Pediatric Respirology, Department of Pediatrics, Pontifícia Universidade Católica RGS, Rio Grande do Sul, Brazil; ²Arizona Respiratory Center and BIO5 Institute, University of Arizona Health Sciences Center, Arizona, USA

Correspondence to Dr Fernando D Martinez, Arizona Respiratory Center and BIO5 Institute, University of Arizona Health Sciences Center, Arizona, USA; fernando@resp-sci.arizona.edu

a predisposition for asthma, most of these children do not go on to develop the disease. The association with asthma is observed for a subgroup of children in whom the persistence of asthma-like symptoms after RSV is due to genetically determined alterations in airway and immune responses that predisposes them to having both RSV and asthma.

What these alterations may be is still unknown, but an atopic predisposition seems to play a major role. In studies in which the population was selected based on a family history of asthma or allergies, such as the COAST cohort,¹⁶ respiratory illnesses in the first years of life in which RSV was isolated and, to a greater extent, those in which human rhinovirus was identified, were associated with asthma later in life. It is plausible to speculate that whenever an atopic predisposition is present, respiratory viruses can trigger an atopy-dependent cascade of immunoinflammatory events in the airways.¹⁷ However, atopy does not seem to be the whole story. It was recently shown that, even during the preschool years and independent of atopy, children with recurrent wheezing show evidence of airway wall remodelling that is not clearly distinguishable from that of classic asthma.¹⁸ These findings suggest that the factors that determine the deficits in airway growth observed in chronic asthma may predate any evidence of allergic sensitisation. Reduced interferon gamma production of stimulated mononuclear cells was identified in infants, before any wheezing—lower respiratory illness, as a significant risk factor for subsequent wheezing into the school years.¹⁹ Deficits in interferon types I and III responses by airway-derived cells have been reported in adults with asthma^{20 21} and in children with asthma with spirometric evidence of airflow limitation.²² It is thus possible that the dysregulation of innate immune airway responses may be the connecting link between viral

infection in early life and subsequent persistent asthma.²³

Observational studies such as those by Sigurs and coworkers¹² that evaluate functional and molecular mechanisms associated with long-term outcomes of RSV bronchiolitis can offer valuable insights. However, the final word on the role (or lack thereof) of RSV in the inception of childhood asthma can only come from randomised, placebo-controlled clinical trials in which the prevention of RSV—lower respiratory illness is shown to be associated with the decreased incidence of subsequent asthma. The time to conduct such trials is now.

Funding FDM was funded by grants from the National Heart, Lung and Blood Institute.

Competing interests None to declare.

Provenance and peer review Commissioned; not externally peer reviewed.

Accepted 6 August 2010

Published Online First 26 October 2010

Thorax 2010;**65**:1033–1034.

doi:10.1136/thx.2009.133967

REFERENCES

1. **Stein RT**, Sherrill D, Morgan WJ, *et al*. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999;**354**:541–5.
2. **Kusel MM**, de Klerk NH, Holt PG, *et al*. Role of respiratory viruses in acute upper and lower respiratory tract illness in the first year of life: a birth cohort study. *Pediatr Infect Dis J* 2006;**25**:680–6.
3. **Lemanske RF Jr**, Jackson DJ, Gangnon RE, *et al*. Rhinovirus illnesses during infancy predict subsequent childhood wheezing. *J Allergy Clin Immunol* 2005;**116**:571–7.
4. **Sigurs N**, Gustafsson PM, Bjarnason R, *et al*. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med* 2005;**171**:137–41.
5. **Sly PD**, Kusel M, Holt PG. Do early-life viral infections cause asthma? *J Allergy Clin Immunol* 2010;**125**:1202–5.
6. **Bartlett NW**, McLean GR, Chang YS, *et al*. Genetics and epidemiology: asthma and infection. *Curr Opin Allergy Clin Immunol* 2009;**9**:395–400.
7. **Simoes EA**, Groothuis JR, Carbonell-Estrany X, *et al*. Palivizumab prophylaxis, respiratory syncytial virus and subsequent recurrent wheezing. *J Pediatr* 2007;**151**:34–42.
8. **Henderson J**, Hilliard TN, Sherriff A, *et al*. Hospitalization for RSV bronchiolitis before 12 months of age and subsequent asthma, atopy and wheeze: a longitudinal birth cohort study. *Pediatr Allergy Immunol* 2005;**16**:386–92.
9. **Martinez FD**, Wright AL, Taussig LM, *et al*. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;**332**:133–8.
10. **Young S**, O'Keefe PT, Arnott J, *et al*. Lung function, airway responsiveness, and respiratory symptoms before and after bronchiolitis. *Arch Dis Child* 1995;**72**:16–24.
11. **Turner SW**, Young S, Landau LI, *et al*. Reduced lung function both before bronchiolitis and at 11 years. *Arch Dis Child* 2002;**87**:417–20.
12. **Sigurs N**, Aljassim F, Kjellman B, *et al*. Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. *Thorax* 2010;**65**:1045–52.
13. **Mallia P**, Johnston SL. Respiratory viruses: do they protect from or induce asthma? *Allergy* 2002;**57**:1118–29.
14. **Horsley A**. Lung clearance index in the assessment of airways disease. *Respir Med* 2009;**103**:793–9.
15. **Thomsen SF**, van der Sluis S, Stensballe LG, *et al*. Exploring the association between severe respiratory syncytial virus infection and asthma: a registry-based twin study. *Am J Respir Crit Care Med* 2009;**15**:1091–7.
16. **Jackson DJ**, Gagnon 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;667–72.
17. **Subatra LS**, Bizantino J, Mamessier E, *et al*. Interactions between innate antiviral and atopic immunoinflammatory pathways precipitate and sustain asthma exacerbations in children. *J Immunol* 2009;**183**:2793–800.
18. **Sagani S**, Payne DN, Zhu J, *et al*. Early detection of airway wall remodeling and eosinophilic inflammation in preschool wheezers. *Am J Respir Crit Care Med* 2007;**176**:858–64.
19. **Stern DA**, Guerra S, Halonen M, *et al*. Low IFN-gamma production in the first year of life as a predictor of wheeze during childhood. *J Allergy Clin Immunol* 2007;**120**:835–41.
20. **Wark PA**, Johnston SL, Bucchieri F, *et al*. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. *J Exp Med* 2005;**201**:937–47.
21. **Contoli M**, Message SD, Laza-Stanca V, *et al*. Role of deficient type III interferon-lambda production in asthma exacerbations. *Nat Med* 2006;**12**:1023–6.
22. **Bosco A**, Ehteshami S, Stern DA, *et al*. Decreased activation of inflammatory networks during acute asthma exacerbations is associated with chronic airflow obstruction. *Mucosal Immunol* 2010;**3**:399–409.
23. **Smyth RL**. The airway epithelium in health and disease: 'calm on the surface, paddling furiously underneath'. *Thorax* 2009;**64**:277–8.