

# Bronchiolitis and asthma in infancy and early childhood

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*Introductory article*

## Asthma and wheezing in the first six years of life

FD Martinez, AL Wright, LM Taussig, CJ Holberg, M Halonen, WJ Morgan and the Group Health Medical Associates

**Background.** Many young children wheeze during respiratory infections, but the pathogenesis of these episodes and their relation to the development of asthma later in life are not well understood. **Methods.** In a prospective study, we investigated the factors affecting wheezing before the age of three years and their relation to wheezing at six years of age. Of 1246 newborns in the Tucson, Arizona area enrolled between May 1980 and October 1984, follow-up data at both three and six years of age was available for 826. For these children, assessments in infancy included measurement of cord-serum IgE levels (measured in 750 children), pulmonary-function testing before any lower respiratory illness had occurred (125), measurement of serum IgE levels at nine months of age (672), and questionnaires completed by the children's parents when the children were one year old (800). Assessments at six years of age included measurement of serum IgE levels (in 460), pulmonary-function testing (526), and skin allergy testing (629). **Results.** At the age of six years, 425 children (51.5 percent) had never wheezed, 164 (19.9 percent) had had at least one lower respiratory illness with wheezing during the first three years of life but had no wheezing at six years of age, 124 (15.0 percent) had no wheezing before the age of three years but had wheezing at the age of six years, and 113 (13.7 percent) had wheezing both before three years of age and at six years of age. The children who had wheezing before three years of age but not at the age of six had diminished airway function (length-adjusted maximal expiratory flow at functional residual capacity [V<sub>max</sub> FRC]) both before the age of one year and at the age of six years, were more likely than the other children to have mothers who smoked but not mothers with asthma, and did not have elevated serum IgE levels or skin-test reactivity. Children who started wheezing in early life and continued to wheeze at the age of six were more likely than the children who never wheezed to have mothers with a history of asthma ( $P < 0.001$ ), to have elevated serum IgE levels ( $P < 0.01$ ), to have normal lung function in the first year of life, and to have elevated serum IgE levels ( $P < 0.001$ ) and diminished values for V<sub>max</sub>FRC ( $P < 0.01$ ) at six years of age. **Conclusions.** The majority of infants with wheezing have transient conditions associated with diminished airway function at birth and do not have increased risks of asthma or allergies later in life. In a substantial minority of infants, however, wheezing episodes are probably related to a predisposition to asthma. (N Engl J Med 1995;332:133-8)

Probably the two most common questions which the parents of a wheezy infant ask their paediatrician are "has he got asthma, doctor?" and "will he grow out of it, doctor?" As we approach the end of the 20th century the honest answer to both questions is usually that we have no idea, but research of the kind described by Martinez *et al*<sup>1</sup> is helping us to obtain a better understanding of the problem.

### Do infants who wheeze stop wheezing in early childhood?

Interest in this subject goes back a long way and there

have been many surveys which have attempted to follow up wheezy infants in order to see what becomes of them as they grow older. Over 40 years ago Boesen<sup>2</sup> published the results of a questionnaire sent to the parents of children who had been admitted to hospital several years earlier with "chronic cough, prolonged expiration and characteristic rales". Of particular interest in the present context is that only 3-7% of infants who had been admitted under one year of age were considered to be asthmatic in later childhood compared with 42% who were over three years old on admission, while a family history of allergy was also much commoner in

**Table 1** Summary of findings in study of Martinez *et al*<sup>1</sup>

	No. of infants	Percentage of total
Total cohort studied	826	100.0
Never wheezed <6 years	425	51.5
Wheezy <3 years and stopped	164	19.9
Wheeze >3 years only	124	15.0
Wheeze <3 years and continued	113	13.7
All wheezing >3 years	237	28.7

the older group (55% versus 33%). More recent studies have reached similar conclusions – namely, that the younger the child when wheezing begins the less likely is it to continue. Most older studies were based on the follow up of children admitted to hospital because of wheezing and hence the population was clearly biased in favour of those who were sick enough to come to hospital. A more informative approach has been the study of cohorts of children who were selected before they ever began to wheeze. Thus, Sporik *et al*<sup>3</sup> followed a cohort of 67 children from birth who were selected as potential wheezers because at least one parent had a history of hay fever or asthma. By the age of 11 years the lifetime prevalence of wheezing was 63% but, of the 21 who first wheezed when under two years of age, only five (24%) were wheezing at the age of 11 years compared with 17 of 21 (81%) who first wheezed after the age of two years. Brooke *et al*<sup>4</sup> undertook an unselected community based survey of a cohort of preschool Leicestershire children and then followed 68 whose parents had reported that the child wheezed, 70 who reported coughing, and 175 controls. Almost half the wheezers and over half the coughers were symptom free when reviewed an average of three years later. In the study of Martinez *et al*<sup>1</sup> a birth cohort of 826 children was available for evaluation at both three and six years of age (table 1). This cohort was not apparently selected on the basis of a parental predisposition to respiratory disease although it is common knowledge that many families move to the Tucson area for health reasons. Of the total cohort 51.5% had never wheezed by the age of six years and, of the 277 who first wheezed before the age of three years, 164 (59%) had stopped wheezing by six years of age. Given that the evaluation in the other studies was carried out at different ages,<sup>3,4</sup> the trend for early wheezers to stop wheezing is similar in all three studies.

#### **Do infants who wheeze and stop have the same disease as those who continue?**

Many infants who wheeze stop having symptoms in early childhood and the question arises as to whether these wheezing infants differ from those who continue to wheeze. The cohort study of Martinez *et al*<sup>1</sup> provides some evidence to suggest that those children who wheezed before the age of three years and stopped wheezing were different from those who continued to wheeze. Those who began to wheeze earlier and who stopped wheezing by six years of age had low values of forced expiratory flow at resting lung volume (V<sub>max</sub>-FRC) at a mean age of 2.4 months and before they had begun to wheeze. Moreover, although their mothers were likely to be smokers, they were unlikely to be asthmatic. The infants who began to wheeze early and continued to wheeze did not have reduced lung function in infancy, did have elevated serum IgE levels at nine months of age, and were more likely to have mothers

who smoked or had asthma and other atopic diseases. Thus, there appears to be a difference in premorbid lung function and in an association with atopic diseases between those who continue to wheeze and those who stop early. Another approach to this problem was used by Young *et al*<sup>5</sup> in Perth who studied a birth cohort of children to see whether there were differences between those who wheezed with viral bronchiolitis and those who did not. They also noted a trend for the infants who subsequently developed viral bronchiolitis in the first year of life to have lower values of V<sub>max</sub>FRC before their first respiratory illness. These children with bronchiolitis also tended to stop wheezing by the end of the first year (78%) and not to have positive skin tests for allergy. Those who began to wheeze in their second year of life did not have reduced lung function in early infancy but did have an increased incidence of positive skin tests for allergy and a trend for a positive family history of asthma. Thus, there are obvious similarities between the bronchiolitic infants of Young *et al*<sup>5</sup> and the wheezy infants of Martinez *et al*<sup>1</sup> who stopped wheezing in early childhood. However, some bronchiolitics continue to wheeze<sup>6</sup> and, in studies of lung function in such patients, we noticed that over half had surprisingly low values of lung volume which we originally thought was related to problems of whole body plethysmography<sup>7</sup> since we did not find this in infants with cystic fibrosis or in normal infants. It now seems quite possible that these bronchiolitic infants had small lung volumes even before their viral infection. Thus, several studies now suggest that those infants who wheeze very early in life may be predisposed to wheeze with viral bronchiolitis because their airways are narrower, while others wheeze because of a family or personal background of atopy. Older infants who begin to wheeze are also more likely to have the allergic background of asthmatic subjects but do not have reduced lung function as a predisposing factor.<sup>1</sup>

#### **Do infants with proven viral bronchiolitis develop asthma?**

Another approach to the problem of the wheezy infant has been to follow infants with viral bronchiolitis to see whether or not they become asthmatic. This type of research has been plagued by ambiguous definitions of bronchiolitis and by the inclusion of infants with recurrent wheezing and older infants who might well have already been asthmatic. However, a particularly well controlled study was undertaken some years ago by Pullen and Hey<sup>6</sup> who followed 130 infants admitted to hospital at a mean age of 14 weeks with proven respiratory syncytial virus (RSV) bronchiolitis and compared them with matched controls. At the age of 10 years 6.2% of the RSV group and 4.5% of the control group were wheezing, bronchial hyperreactivity to exercise and histamine was a little more common in the RSV group (16% versus 5% and 19% versus 6%, respectively) but the prevalence of positive skin tests for allergy was actually less in the group with RSV (15% versus 27%). During the first four years of life 38% of the infants with RSV had repeated episodes of mild wheezing compared with 15% of the controls. Lung function was not measured in infancy in this study which began almost 30 years ago. The conclusion was that RSV bronchiolitis resulted in an acute episode of airways obstruction with repeated milder attacks in some 38% of infants over the early years of life, but did not significantly increase the incidence of true asthma in later childhood even though it left some children with

bronchial hyperreactivity. The finding of bronchial hyperreactivity has often been equated with the presence of asthma, but care is needed since it has been shown that children with other types of chronic lung disease often have hyperreactivity to methacholine but only asthmatic subjects are hyperreactive to exercise and adenosine monophosphate.<sup>8,9</sup> It is therefore quite possible that the bronchial hyperreactivity found by Pullen and Hey<sup>6</sup> in some of the children in the RSV group at the age of 10 was not due to asthma. More recent follow up studies of bronchiolitic infants, albeit with rather smaller numbers, have shown a similar pattern of episodes of wheezing in the early years after the initial attack, but with only a small excess of overt asthma in later childhood and persistence of bronchial hyperreactivity to methacholine or histamine.<sup>10,11</sup>

### Is there a genetic difference between bronchiolitis and asthma?

From what has been discussed so far it appears that wheezing in early infancy may be due to two distinct diseases – acute viral (usually RSV) bronchiolitis of early infancy on the one hand, which is preceded by lower levels of lung function and is followed by recurrent wheezing in some 40% of subjects during early childhood and, on the other, bronchial asthma which may begin at any age but is almost always associated with atopy in children. There is increasing evidence to support an important genetic component in childhood asthma although it is far from obvious as to how this operates. Studies of twins in Finland<sup>12</sup> found a heritability estimate of about 36% for asthma while we noted concordance for asthma, atopy, and exercise induced asthma of 57–71% in identical twins compared with 0–19% in fraternal twins.<sup>13</sup> Recent studies of the children and grandchildren of asthmatic subjects from Holland have produced strong evidence that a gene governing bronchial hyperresponsiveness is located near a major locus of genes governing cytokine production and the ability to produce high levels of IgE on chromosome 5q31–33.<sup>14</sup> At the same time, studies in Oxford and Melbourne have indicated a link between atopy and a gene for a high affinity IgE receptor on chromosome 11q13 which may also be linked to bronchial hyperreactivity.<sup>15,16</sup> These studies suggest a close genetic link between childhood asthma, bronchial hyperreactivity, and allergy and would therefore cast doubt on the diagnosis of asthma in a child without an atopic genetic background.\* There have not been any similar studies of genetic linkage between atopy and bronchial hyperreactivity in infants with viral bronchiolitis or in infants with reduced lung function before developing respiratory symptoms. However, the data of Martinez *et al*<sup>1</sup> and the other studies that have looked at family background<sup>2,5,6</sup> strongly suggest that there is no link between early wheezing which stops and a personal or family background of atopy.

One of the problems with studying the genetics of asthma is that, even in identical twins, the concordance for asthma is far from complete<sup>13</sup> and it is therefore possible that the genetic factor requires an environmental inducing agent before it becomes operative. Could viral bronchiolitis serve to activate a latent gene or genes resulting in bronchial hyperreactivity and atopy? Some studies have suggested that the production of IgE

**Table 2 Wheezing in childhood if bronchiolitis and asthma are unrelated**

	% all children	% bronchiolitics	% asthmatics
<b>Predisposition to bronchiolitis</b>			
(? small lungs)	5–10	100	
Wheeze once only	2.75	55	
Short term wheeze	1.50	30	
With asthma	0.75	15	
<b>Predisposition to asthma</b>			
(? genetic)	10–20		100
With bronchiolitis in infancy	0.75		5
With wheeze <3 years	2.25		15
With wheeze only >3 years	12.00		80

is enhanced by RSV infection<sup>17,18</sup> but, on the whole, it seems that those infants who continue to wheeze after RSV bronchiolitis and also produce IgE are those with a family background of atopy and hence the viral infection may indeed be unmasking latent asthma in such children.

Another problem with any attempt to distinguish between viral bronchiolitis and asthma is that they are both common conditions in early childhood. While it is difficult to obtain reliable data since those infants who require admission to hospital are not representative of the community at large, there have been some community based studies. In the birth cohort study of Martinez *et al*<sup>1</sup> 19.9% of infants wheezed only in the first three years. In an earlier publication from Tucson the incidence of bronchiolitis in the first year of life was given as about 20%.<sup>19</sup> In the cohort study of Sporik *et al*<sup>3</sup> the incidence of wheezing in early infancy was also about 20%, although their cohort was chosen on the basis of a predisposition to atopy. It may be that respiratory illnesses are particularly prevalent in the Tucson area and that both these estimates are on the high side since earlier community based studies of bronchiolitis from general paediatric practice suggest a much lower incidence of bronchiolitis of 1.3–6% in infants under two years.<sup>20,21</sup> Estimates of prevalence of asthma in childhood range from about 10% to 25%, depending upon how it is defined and the methods used in the survey.<sup>22–25</sup> In a study we conducted at an army recruiting base in Israel<sup>22</sup> nearly all the men aged 17 in the area were screened by trained physicians aided by tests of lung function and bronchial reactivity. The lifetime prevalence of asthma up to age 17 was 9.6%. If there is no genetic linkage between susceptibility to viral bronchiolitis (which may be related to possessing narrower airways) and susceptibility to bronchial asthma (which usually implies a linkage to atopy), then by chance one would expect about 15% of infants with viral bronchiolitis to carry the genes for asthma, to have personal or family atopy, and to continue to wheeze for some years during childhood. The approximate proportions of wheezing of different types in children with bronchiolitis and asthma if there is no causative linkage between them is shown in table 2. The fact that some 41% of wheezy infants in the study of Martinez *et al*<sup>1</sup> fitted this pattern may support the suggestion that asthmatic genes are common in the Tucson population.

### Does getting the diagnosis correct matter?

The paediatrician obviously would like to be able to tell the parents why their infant is wheezing and also what is likely to become of him or her in the future. From

\* This subject is discussed in more detail in the review by Boguniewicz and Hayward on pp S55–S59.

## LEARNING POINTS

- \* Reduced lung function predisposes to wheezing in early infancy probably due to viral infection which is unassociated with atopy and unlikely to persist into childhood.
- \* Personal or family atopy is associated with persistence of wheezing in early infancy as childhood asthma which may be genetically determined.
- \* Viral bronchiolitis and asthma are probably independent causes of wheezing in early childhood but about 15% of children with bronchiolitis are likely to be potential asthmatics.
- \* Most wheezing in early infancy is poorly responsive to treatment whatever its origin, while older infants and children respond well.
- \* About 1–6% of all infants under one year of age in a community setting are likely to develop viral bronchiolitis while about 10–15% of children have asthma at some time during childhood.

### The chances are that the infant has viral bronchiolitis and not asthma if

- it is known that the infant had reduced lung function before starting to wheeze (an unlikely piece of information outside the Tucson area)
- the infant is aged less than about one year at the time of the initial attack
- there is a positive identification of RSV
- there is no family history of atopic disease
- the infant does not possess asthma genes (still awaiting definitive location and characterisation)

### The chances are that the child has asthma if

- the child is over about one year of age at the time of the initial attack
- there is a strong atopic family background
- IgE is elevated
- the initial attack is not associated with RSV infection

what has already been discussed in relation to the study by Martinez *et al*<sup>1</sup> and the other studies, the chances can be summarised as in the box.

Even if the infant with bronchiolitis wheezes on and off for a few months, persistence of wheezing into childhood with typical asthma is unlikely except in perhaps 10–15% of bronchiolitic subjects who also possess the genes for asthma. While the prognosis of asthma in childhood is generally good and most children seem largely or completely to lose their asthma during childhood, some continue to wheeze into adult life and some who stop wheezing start again as adults.<sup>26–29</sup>

Just to add to the problems of the paediatrician, it is by no means clear that the response to treatment with medications for asthma helps in the differential diagnosis. There is no good evidence that  $\beta_2$  adrenergic bronchodilator drugs, sodium cromoglycate, or corticosteroids result in improvement in most young wheezy infants with acute bronchiolitis, post-bronchiolitic wheezing, or in those destined to continue to wheeze as childhood asthmatics.<sup>30–34</sup> Undoubtedly the occasional very young wheezy infant does respond and the fact that most older infants who have continued to wheeze also respond may simply mean that these are the asthmatic subjects in the group.

So – when all is said and done – does it really matter? From the intellectual point of view it certainly does, and

the type of study being undertaken by the investigators in Tucson and elsewhere is leading us towards an understanding of the basic pathophysiology of wheezing in infancy and childhood. From the practical point of view it probably does not matter very much. I always tell the parents of my patients that I have bad news and good news – the bad news is that I cannot tell them for certain what is the matter with their baby but the good news is that it doesn't really matter. Either the baby has bronchiolitis or post-bronchiolitic wheezing and will in all probability stop having a problem over the next few months, or else the baby really does have asthma and – if not now then over the next few months – will respond very well to the excellent treatments available for childhood asthma until he or she “grows out” of it.

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