

Recurrent Wheezing in Infants and Young Children and Bronchial Hyperresponsiveness

A Perspective

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Abstract

Epidemiological studies report a 50% incidence of at least one wheezing episode in young children. If we can argue that 10% of children have asthma sometime during their pediatric years, it still leaves a significant percentage of children with an unexplained cause for their wheezing. Other recognized phenotypes of recurrent wheezing include young children exposed to excessive environmental tobacco smoke (ETS), while other infants wheeze recurrently following a significant episode of bronchiolitis. Bronchial hyperresponsiveness (BHR) is a universally recognized phenomenon of asthma, but its presence in young children with recurrent wheezing is not as well studied. Currently available studies demonstrate that BHR is also seen in young pediatric asthmatics, paralleling what is well recognized in adolescent or adult asthma. In those children with post-bronchiolitis wheezing, BHR appears to be present to a degree; while infants and young children exposed to ETS have increased BHR, as a group. If exaggerated BHR in recurrent wheezing children without asthma has the same inherent disadvantage as it does in asthmatic children, additional studies looking directly at this issue in a longitudinal fashion need to be designed. A hypothesis of BHR in non-asthmatic children is presented that could be studied prospectively.

Index Entries:

Children; asthma; wheezing; bronchial hyperresponsiveness; recurrent wheezing; post-bronchiolitis; wheezing phenotypes.

Introduction

A review of a pediatric pulmonary textbook generally provides an extensive list for the differential diagnosis of wheezing in infants and children (1). In a recurrently wheezing infant or young child, each specific diagnosis must be considered. In many clinical situations, the classic examples of diseases that cause wheezing—such as cystic fibrosis or a foreign body—have been excluded. If the first few months of life have already passed without wheezing, a congenital cause can probably be excluded. Although helpful, the “traditional” textbook causes for wheezing, other than asthma, are rarely diagnosed.

Over the past 5 yr, there have been many published studies on wheezing in young children and infants. These published reports have greatly assisted the understanding of who is at risk for wheezing, and why. Unfortunately, this information is largely epidemiological in nature, has not yet been included in standard pediatric textbooks, and is not part of the common body of information taught in medical schools, or in the continuing education of primary care physicians. In our experience, the misunderstanding of wheezing-related conditions results in the common use of the misnomer “reactive airway disease.”

With this perspective, we attempt to outline and describe common causes of recurrent wheezing (wheezing phenotypes), as currently described in the literature, and review what is known about the bronchial hyperresponsiveness (BHR) of these clinical conditions. BHR is considered a primary phenomenon of asthma in all age groups, and reports of its presence (or absence) in different childhood wheezing phenotypes would be valuable clinical and prognostic information. A recent review of the development of BHR during childhood provides valuable reference information on this topic (2).

In infants and young children, the usual precipitating event for the first wheezing event

is with a viral respiratory illness, often respiratory syncytial virus (RSV). With or without laboratory confirmation, the initial event is usually labeled as “bronchiolitis” and treated accordingly. The clinical dilemma presents itself when the child is young, then returns with subsequent episode(s) of wheezing. A review of the concepts of the “wheezy infant” was discussed in a brief article by Godfrey (3) in 1985, and further reviewed by Wilson (4). In our article, we attempt to delineate the wheezing phenotypes, based on published studies, and review what is known about BHR for each entity, previously a topic of editorial comment by Taussig (5).

Numerous studies have examined “wheezing infants” and BHR, but the underlying reason for the wheezing is *undefined*, and statistical associations of the child’s atopy, family atopy, and parental BHR are suggested as etiologies. In this article, we use studies with definable etiologies for the wheezing phenotype, and present findings on BHR testing.

Lessons from Epidemiological Studies on Wheezing Phenotypes

Overall Wheezing Trends

There are a number of well-executed epidemiological studies that provide insight into the issue of recurrent wheezing in infants. The lessons arising from these studies have direct implications in clinical medicine. Published in 1995, the study of Martinez et al. (6) provides impressive epidemiological evidence into the patterns of recurrently wheezing infants. From a group of 1246 infants enrolled in an HMO, 826 were prospectively followed for 6 yr. Incredibly, over this period of time, 49% of the followed subjects had a wheezing episode. The authors retrospectively divided these wheezing children into three groups: *transient early wheezers*, *late wheezers*, or *persistent wheezers*.

Using odds-ratio analysis, the characteristic of these three groups of wheezers was defined and compared to the 425 children who had not

wheezed by age 6. *Transient early wheezers* had wheezing within the first 3 yr, but not at 6 yr of age. In these children, maternal smoking was significantly associated with wheezing. These children also had lower length-adjusted pulmonary function, suggesting a deleterious effect of the passive smoke exposure. The children who developed wheezing after age 3 (*late-onset wheezers*) were more likely to have mothers with asthma, to be male, and to have had rhinitis in the first year of life. (Although not stated, these would be common characteristics of young asthmatics.) Children who wheezed throughout the 6 yr of the study (*persistent wheezers*) had a significant incidence of maternal asthma, wheezing often or very often, wheezing without colds, eczema, Hispanic background, and maternal smoking. Twenty-five percent of these children had been labeled asthmatic by age six.

Small Airways (Reduced Pulmonary Function)

A study by Martinez et al. (7) examined pulmonary function in 124 children at a very early age, prior to any respiratory illness. Longitudinal observations of their wheezing patterns revealed that those infants with reduced pulmonary function were significantly more likely to have wheezing associated with a lower respiratory-tract illness. In this study, maternal smoking did not further influence the predictability of wheezing.

A study of 97 infants by Tager et al. (8) provides additional evidence of the effect of diminished lung function and wheezing in the first year. In their studied infants, the level of lung function measured before 6 mo predicted a wheezing episode.

Smoke Exposure

The literature on passive smoke exposure and infantile lung function has been reviewed (9). In particular, a report by Young et al. (10) revealed in 63 infants that either a family history of asthma or parental smoking were more

likely to result in increased airway reactivity to inhaled histamine. BHR is a hallmark of all asthmatics, and the presence of increased BHR at an early age might be permissive for recurrent wheezing, especially at younger ages.

This group subsequently reported that in utero smoke exposure is associated with a significant reduction in pulmonary function in infants measured within 1 wk of birth (11). Infants with a family history of asthma also had significantly diminished lung function.

Another group of investigators have reported supporting evidence to the deleterious effect of intrauterine smoke also (extrauterine) exposure, post-birth pulmonary function, and the onset of wheezing in the first year of life (8,12).

A recent report documented diminished lung function in premature infants exposed to in utero smoke, but prior to hospital discharge, eliminating the effect of post-uterine smoke exposure on lung mechanics (13).

Post-Bronchiolitis Wheezers

There is a general acceptance that an episode of bronchiolitis, generally caused by RSV, can be followed by recurrent wheezing episodes (14,15).

It is our opinion that RSV adversely affects the airway in a percentage of children who will subsequently develop recurrent wheezing. As a group, these children are non-atopic, but some post-RSV wheezers develop traditional "asthma," and may have been programmed to develop asthma in any case. These children would also become (or be) atopic, as are most other pediatric asthmatics.

The epidemiological evidence supporting the development of the post-RSV wheezing phenotype is largely based on the work of Stein et al. (16).

Unclassified Wheezing

The pediatric pulmonary literature is replete with publications—some using measures of BHR—that classify the study infants or children,

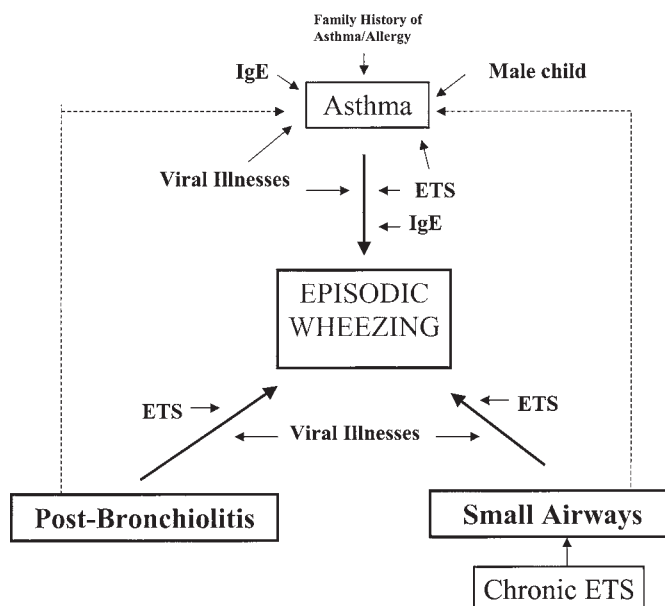


Fig. 1. A schema of likely and known associations in young children with recurrent wheezing episodes. ETS: environmental tobacco smoke.

as “infants who wheeze,” or “wheezy infants.” Close review of their inclusion criteria fails to provide enough criteria to further classify these children into a recognizable “diagnosis” classification. This further points out the dilemma of clinically based diagnosis and therapy, especially when as shown by Martinez et al. (6), 49% of children have wheezing episodes by 6 yr of age.

Overlapping Types

In clinical practice, the presentation of a recurrently wheezing young child raises the possibility of a long differential diagnosis. As previously mentioned, many traditional reasons for wheezing can be excluded by age, history, physical examination, or by selected diagnostic procedures. In considering other causes for wheezing, as presented here, it would be convenient to have a single explanation for the parents. However, in many circumstances, the child is in day care, and is re-exposed to many viruses, and the initial episode was called “bronchiolitis,” but no laboratory confirmation was obtained. The child was or is exposed to a smoking parent, and a grandparent has asthma

or allergic problems. These situations are all too common, and quickly expose the limitations of translating epidemiological information to the examination room.

Epidemiologically Recognized Wheezing Phenotypes

The lessons gleaned from epidemiologic studies suggest three common themes in many wheezing infants. For the sake of this discussion, each pattern can be considered independently, although overlap and interaction often occur. These patterns are: i) infantile asthma; ii) post-bronchiolitis wheezing; and iii) small airways with or without passive smoke exposure (intrauterine +/– extrauterine). These three patterns are schematically represented in Fig. 1.

In clinical practice, the most commonly associated medical condition seen with recurrent wheezing children is an intercurrent viral illness. It is likely that the episodic wheezing that occurs in each of the three patterns is adversely influenced by a new viral illness. The exact cause of viral-triggered wheezing in asthma is poorly defined (15), and yet similar

reasons for wheezing in the other two patterns can be postulated.

In clinical situations, a theme for the recurrent wheezing episodes may be evident; however, the “non-asthmatic” patterns may evolve to clinical asthma, especially post-bronchiolitis wheezing. Clearly, recurrent wheezing is not a static process with a “totally benign” end point. Longitudinal assessment is often necessary (17).

BHR and Wheezing Phenotypes

Overview

Originally found to be a characteristic of the asthmatic phenotype, BHR is now believed to exist to some degree in all infants, and to be exaggerated in children with specific pulmonary conditions, especially asthma. There have been limited studies looking at BHR in wheezing children, or in the longitudinal evaluation of wheezing children. We have used the previously outlined wheezing phenotypes as a conceptual framework to discuss what is known about BHR in the different recurrent wheezing phenotypes.

Overall Wheezing Trends and BHR

Although the original description of early childhood wheezing by Martinez et al. was determined by clinical presentation (6), the children were subsequently tested using methacholine at age 11 (18). Children were divided by wheezing presence or absence at 3 and 6 yr of age, and further stratified by no atopy or atopy at the same study periods. The results, as extracted from the publication (18), are summarized in Table 1. Atopy appears to be more closely associated with BHR than wheeze.

Young Asthmatic Children and BHR

Published reports in older children using methacholine or histamine (both direct-challenge methods), cold air, exercise, or distilled water (indirect-challenge methods), using standard-challenge methods, have shown exagger-

Table 1
Follow-Up Results

	Total children seen at age 11	McH + * atopy – age 11	MCH + * atopy + age 11
No wheeze age 3			
No wheeze age 6	188	14%	32%
Yes wheeze age 3			
No wheeze age 6	80	10%	32%
No wheeze age 3			
Yes wheeze age 6	47	7%	39%
Yes wheeze age 3			
Yes wheeze age 6	33	11%	52%

* MCH+ (Yan method) (18a) defined as being below the 10% percentile of a healthy control group.

ated air responsiveness, consistent with what would be expected of an adult asthmatic.

Studies of direct or indirect bronchial challenges in very young asthmatics have been published, although modifications are necessary in the challenge protocol and measurement of airway responses to accommodate the limitations imposed by the children’s ages. Although not a comprehensive list of studies in young asthmatic children, selected results are summarized in Table 2.

ETS Exposed Infants/Children and BHR

In a report published in 1991 (10) by investigators experienced in infant lung studies, 63 infants, 2–10 wk of age were challenged with histamine, and their pulmonary function was measured using the forced expiratory flow method. Infants who had one or both parents smoking during pregnancy (ETS) were compared to three other groups: no smokers and no immediate family asthma history; immediate family asthma history, smoke exposure, and asthma histories. Nonsmoking parents were so during and after pregnancy. The results, extracted from the publication (10), are presented in Table 3.

Overall, only five of the 63 infants challenged did not respond by the top histamine dose. The infants with asthma in their family

Table 2
Young Asthmatic Children and BHR

Journal	Ages	Methods	Results
Annals of Allergy 1988 (19)	2–5 years <i>n</i> = 141	TcPO ₂ change With MCH = Dmin-PO ₂	Asthma = 4.47 + 7.91 Controls = 33.1 + 20.7 <i>p</i> < .01
AJRCCM 2000 (20)	2–5 years <i>n</i> = 38	Cold air Specific airway resistance changes = SRaw	26/38 asthmatics > 3 SD change in SRaw 2/29 controls > 3 SD change in SRaw
J Asthma 1999 (21)	1–5 years <i>n</i> = 137	TcPO ₂ change With MCH = Dmin-PO ₂	Asthmatics significantly more responsive than controls at each age 1–5 years (except age 3).
AJRCCM 2000 (20)	2–5 years <i>n</i> = 38	MCH Specific airway resistance changes = SRaw	36/38 developed a 50% increase in SRaw
Pediatr Pulmonol (22)	2–4 years <i>n</i> = 23	Compared response techniques in asthmatic children using methacholine	Asthmatic children responded to methacholine using various response measures

A recent report examined BHR, lung function, and clinical parameters at 1 mo and 6 yr of age. BHR at 1 mo was significantly associated with physician-diagnosed asthma and wheeze at 6 yr of age (23).

Table 3
ETS Exposed Infants/Children and BHR

Group	Background	<i>n</i>	Histamine challenged	Responders (≤ 8 g/L)	Mean PD ₄₀ * 95% C.I.	P value of BHR
1	No asthma No ETS	11	11	10	2.75 g/L (1.48–4)	
2	Asthma	19	17	16	.78 g/L (.44–1.15)	2 > 1 < 0.01
3	No asthma ETS	13	13	12	.52 g/L (.43–5.40)	3 > 1 < 0.05
4	Asthma ETS	20	19	17	.69 g/L (.37–2.10)	4 > 1 < 0.05

* PD₄₀ is the dose of histamine causing a 40% decrease in V_{maxFRC}.

were more responsive to histamine than the control infants. The infants with smoke exposure had significantly greater BHR than those infants who had no smoke exposure. These smoke-exposed infants did not have wheezing histories (yet?) The article also emphasizes the phenomenon of early infant (native) BHR, and how prenatal and/or genetic factors can influence its intensity.

At least two studies have examined BHR and environmental tobacco smoke exposure in children 7–11 yr of age. Martinez et al. (24),

using carbachol, demonstrated a significant increase in BHR in males, 9-yr-old children, (O.R. 4.2, *p* < .009) who were exposed to any parental smoke, compared to boys who were not exposed. No difference was seen in girls. In contrast, a study of methacholine challenge tests in 1215 children, 7–11 yr of age, showed significant BHR in girls in those exposed to maternal and/or paternal smoke, but only for boys if smoke exposure and high household crowding were considered together (25). Of additional interest is a study showing longitu-

dinal persistence of BHR ($\geq 10\%$ fall in FEV_1) as measured by distilled water challenge in 539 children 8 yr of age at the initial challenge, and exposed to maternal smoke throughout life. Asthma diagnosis exclusion did not change the smoke-exposure results (26).

To date, there are no studies of BHR in young children with recurrent wheezing and intrauterine and/or post-uterine smoke exposure. Studies show that these children have decreased airway diameter (11,12), as measured by infant lung function, which is likely to be directly related to their propensity to wheeze. The question is whether ETS exposure would further exacerbate BHR in young children.

Suggested Studies

1. A population of infants selected for maternal intrauterine smoke exposure, with baseline early-life lung function. Children would they be followed with BHR measures using methacholine, and stratified by wheeze, no wheeze, urinary cotinine levels, atopy, and family histories of asthma over a 2–5-yr period.

Post-RSV Wheezing and BHR

Probably the most influential publication involving RSV and post-RSV wheezing was published by Stein et al. in 1999 (16). Using a well-known pediatric study population, children with lower respiratory illness before 3 yr of age were stratified into five groups depending on the etiology of the infection, and studied to 13 yr of age. When children who had RSV were compared to children with no lower respiratory illnesses in the first 3 yr, the RSV-infected group were more likely to have infrequent or frequent wheeze at ages 6 and 11, but not at 13 yr of age.

Furthermore, increased atopy and IgE were not features of the post-RSV wheezers. Baseline FEV_1 and bronchodilator response were measured at 11 yr of age. These measures were significantly different, with lower FEV_1 and more vigorous bronchodilator responsiveness in the

post-RSV wheezers compared to the controls (not infected in the first 3 yr).

It is important to note that in an earlier report (18), children from the *same* cohort were examined for BHR at 11 yr of age, depending on the presence or absence of wheezing at age 3, 6, and 11 yr of age. The children at *age 11 and skin-test-negative* (presumably many of the same children described in the manuscript published by Stein in Lancet in 1999 [16]) had a range of 0–8% for BHR (four groups stratified by wheeze presence/absence at 6 and 11 yr of age). Of those who were *11 yr of age and skin-test-positive*, the four stratified groups ranged from 18–65% positive for BHR.

A comparison of the results of the two reports from the same cohort, although it described different phenomenon (*wheezing* vs *RSV positivity*) revealed that the number of children who wheezed at age 3 ($n = 113$) (18) and the children who had a +RSV screen ($n = 207$) (16) were not overlapping groups, at least based on the results. Thus, making conclusions about the phenomenon: i) recurrent wheezing after RSV, and ii) the presence of BHR as a consequence of RSV, remains somewhat tenuous based on this cohort of children. (*We would speculate that the authors could re-analyze the data evaluating the following: RSV positivity before age 3 + wheezing at age 11 + BHR at age 11.*)

The study by Stein et al. (16) clearly substantiates a report by Mok and Simpson (27) that is probably overlooked as to its relevance to this issue. Children with RSV and hospitalization (obviously a sicker group) had a 47% risk for subsequent wheeze. Among RSV children not hospitalized, at 8 yr of age there was a 2.34 odds risk ($p < .001$) for wheezing, but the odds risk fell to insignificant by age 13. These same 8-yr-olds had an “asthma” diagnosis more commonly at age 8, but not age 13.

Several reports are available looking at BHR and young children with wheezing. Unfortunately, two of the reports provide no specific evidence that the children had RSV prior to the onset of wheezing. The report of Clarke et al. (28) found enhanced BHR in both

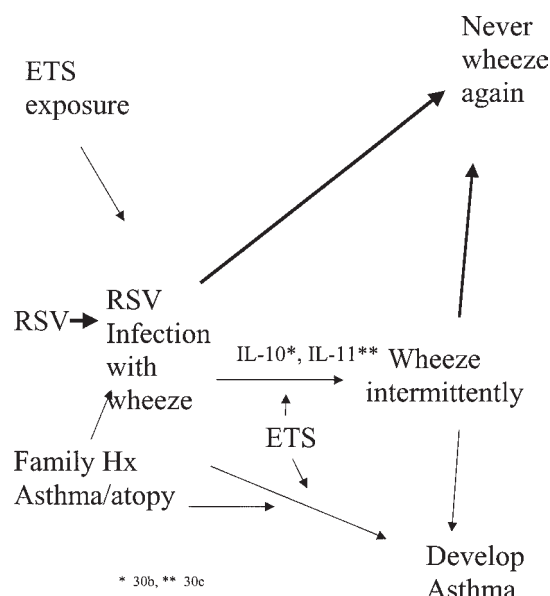


Fig. 2. Proposed scenario for clinical consequences of RSV bronchiolitis.

control and wheezing infants, 6–8 mo of age. The wheezing infants had at least one atopic parent. The $V_{\max}$ FRC was significantly lower in the wheezing infants. Stick et al. (29) reported a difference in BHR between wheezing and controls at 12 mo.

A report by Tepper et al. (30) of infants (enrolled at 2.3–5.5 mo) with documented RSV and BHR measures showed lower measures of $V_{\max}$ FRC at 4 mo, and enhanced BHR at 4 mo and 10 mo post-RSV in infants as compared to control (no RSV infections).

In summary, a quote by the former Ohio St. football coach Woody Hayes applies to RSV, wheezing, and “asthma”/BHR: “There are three things that happen with every forward pass, and two of them are bad.” This is summarized in Fig. 2.

Suggested Studies

1. Infants enrolled prior to RSV season, but without previous wheezing symptoms. BHR measured at baseline, and after RSV infection (documented). Repeated measures of BHR, with stratification into never wheeze again, or recurrent wheezing.

Small Airways and BHR

A single study (10) examined $V_{\max}$ FRC and BHR in infants, and failed to find a correlation. Smoke exposure *in utero* is likely a large determinant of small airway diameter, which may be the prime factor responsible for BHR. However, this requires further study. Recent reports have suggested that very low-birthweight children are subject to wheezing/asthma-like conditions (31,32).

Unclassified Wheezing and BHR

An increasing body of epidemiologic data has revealed a broader range of clinical entities that are associated with recurrent wheezing other than infantile asthma. For example, it may be conceivable that carefully performed future studies might reveal that young children with chronic sinusitis or post-parainfluenza viral infection are more prone to recurrent wheezing. Would chronic sinusitis lead to increases in BHR?

A study from Japan (33) using an interesting method of determining BHR—the deflection of the transcutaneous pO₂ level during a methacholine challenge—evaluated BHR in young children four groups: Controls, bronchiolitis, wheezy bronchitis, and asthma. The bronchiolitis group was studied 1 mo after their “bronchiolitis” episode (RSV done in 8 with 5+), and the wheezy bronchitis group had recurrent wheezing. The asthmatics were all atopic. The children had a broad age range. The bronchiolitis mean age was 7 mo, and the asthmatics mean age was 4.6 yr of age. The order of methacholine responsiveness was asthma > bronchiolitis > wheezy bronchitis = controls. The authors also separated bronchiolitis and wheezy bronchitis into those children who did or did not eventually develop asthma.

Studies of this type show the limitation of research that does not use well-defined clinical diagnoses. For instance, “wheezy bronchitis” is not a term utilized in American medicine, and is mostly descriptive, akin to “reactive airway disease.”

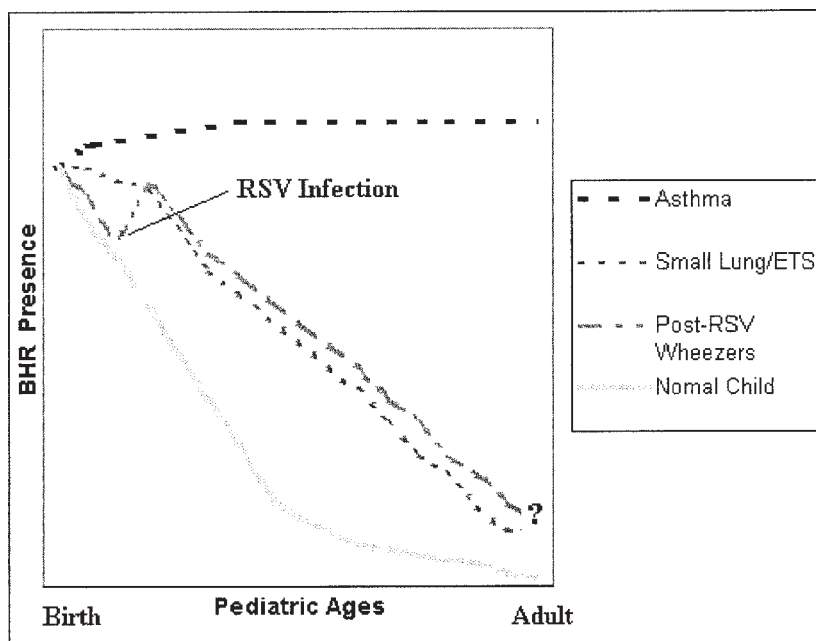


Fig. 3. Available evidence suggests that all infants have BHR at birth. Those children who *will* develop asthma likely maintain their BHR until “asthma” happens, and BHR persists. Non-asthmatic infants may start to lose BHR until their RSV illness, at which time some infants (*post-RSV wheezers*) have a slower BHR loss. Infants with *small lungs/ETS* probably lose BHR more slowly than normals. It is possible that adolescents with *small lungs/ETS* or *post-RSV* wheezers have more BHR than normals, although it is not well-understood (?).

Overlapping Wheezing Phenotypes and BHR

When “wheezing” is used as an entry criteria for inclusion into a study of BHR in infants, the results often do not provide enough differentiation of the subgroups included. An early report on the BHR in wheezy infants (34), using histamine inhalation and a whole-body plethysmograph serves to illustrate the principle of “unclassified wheezing.” In this report, 11 infants (3–13 mo of age) were challenged. Nine infants had atopic family histories, five had eczema, and seven had smoking parents. It was no surprise that 9 of the 11 infants responded to histamine by the last dose (8 g/L); and on repeat challenge only the original non-responders failed to respond again. The limited numbers do not allow sub-group analysis, and no attempt was made to separate infants by history or confounding histories, or for degree of BHR.

Summary

Our understanding of wheezing infants and children has become much clearer in the past 5 yr. Yet further studies are needed, and until cytokine markers are readily available that might further separate wheezing phenotypes, controversy remains. Until well-segregated wheezing phenotypes exist, the presence of BHR, the severity of BHR, and the duration of BHR will remain an inexact science. Based on current knowledge, we propose a possible scenario relating the epidemiologically recognized wheezing phenotypes and BHR, as shown in Fig. 3.

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