

REVIEW

'They said it was bronchiolitis; is it going to turn into asthma doctor?'

DIMOS GIDARIS,¹ DON URQUHART² AND MICHAEL B. ANTHRACOPOULOS³

¹1st Paediatric Department, Aristotle University of Thessaloniki, Hippokrateion General Hospital, Thessaloniki and
³Respiratory Unit, Department of Pediatrics, University of Patras, Patras, Greece, and ²Royal Hospital for Sick Children, Edinburgh, UK

ABSTRACT

Acute bronchiolitis is a common paediatric disease of infancy. Its association with subsequent asthma development has puzzled clinicians and epidemiologists for decades. This article reviews the current state of knowledge regarding the role of acute bronchiolitis in the inception of asthma. There is little doubt that acute bronchiolitis is associated with an increased risk of recurrent wheezing throughout the primary school years although the direction of causality—i.e. whether bronchiolitis in infancy leads to asthma or it merely represents the first clinical presentation of predisposition to asthma—is uncertain. Existing evidence suggests that both host factors (e.g. prematurity, atopic predisposition) and acute viral infection characteristics (e.g. type of virus, severity) are operating in this relationship, perhaps with variable involvement in different individuals. Further clarification of these issues will help paediatricians provide evidence-based information regarding the long-term prognosis of this common disease to the families, and at the same time, it will facilitate prophylactic approaches and therapeutic strategies.

Key words: asthma, bronchiolitis, children, respiratory syncytial virus, rhinovirus.

Abbreviations: COAST, The Childhood Origins of Asthma; hMP, human metapneumovirus; hRV, human rhinoviruses; RSV, respiratory syncytial virus.

INTRODUCTION

Acute bronchiolitis is a common paediatric disease causing significant morbidity and mortality in infancy.^{1,2} On the other hand, asthma has been recognized since late 80s as the most common chronic

disease of childhood.³ Paediatricians and general practitioners announcing a diagnosis of 'bronchiolitis' to the parents are frequently faced with the question: 'Is it going to turn into asthma, doctor?'.⁴ It should be stressed right from the beginning that the answer to this straightforward question is hampered by the poor definitions of both diseases. The complexity of the involvement of host and post-infectious factors perplex the issue even further; thus, uncertainty prevails. The aim of this article is to revisit this long-standing hot debate^{5–13} and to help the practicing physician appraise the conflicting evidence with respect to whether this association is causal or incidental and come up with a common sense, realistic answer. Such an answer is not just a remedy for parental curiosity, but it may also facilitate environmental alterations (i.e. avoidance of well-known triggering factors) as well as guide decisions regarding therapeutic approaches.¹⁴

DEFINING ACUTE BRONCHIOLITIS AND PRESCHOOL ASTHMA

Despite the fact that acute bronchiolitis is the most common reason for hospital admission in infancy, heterogeneous definitions are used in clinical practice and academic description.^{1,15,16} The clinical syndrome of bronchiolitis is characterized by coryza (i.e. stuffy nose and secretions), which is followed by respiratory distress of variable severity. Physicians from North America include wheezing among the major auscultatory findings, whereas doctors from the United Kingdom and most of continental Europe focus on the presence of fine end-inspiratory crackles.^{1,17,18} Additionally, while most physicians accept that this clinical diagnosis is relevant up to the age of 12 months,^{18,19} many studies have recruited children up to the age of 2 or even 3 years.^{20,21} Most frequently, the term 'bronchiolitis' is used to describe the first episode of acute viral infection of terminal and respiratory bronchioli;²² subsequent episodes in preschool years are labelled as 'viral wheeze'.^{23,24} The aforementioned controversies regarding major clinical signs and age range make any effort to draw

Correspondence: Dimos Gidaridis, European Diploma in Paediatric Respiratory Medicine, 1st Paediatric Department—Aristotle University of Thessaloniki—Hippokrateion General Hospital, 9A, Pantazopoulou str, Ampelokipi 56121, Thessaloniki, Greece. Email: dgidaridis@doctors.org.uk

Received 8 February 2014; invited to revise 26 May 2014; revised 13 June 2014; accepted 15 July 2014 (Associate Editor: Claire Wainwright).

conclusions about the long-term prognosis of this common illness fundamentally problematic.^{25–28}

Additionally, the definition of asthma in preschoolers is problematic: the Global Initiative for Asthma guidelines use the term 'asthma' in this age group, whereas the European Respiratory Society has opted to use temporal patterns of wheeze (i.e. episodic vs multiple triggered wheeze), which are also debatable.^{3,23,29}

In conclusion, the definition of acute bronchiolitis varies among guidelines in different parts of the world. In addition, temporal classification of wheezing patterns in preschoolers is often unclear, while epidemiologic phenotypes are of limited value in clinical practice.

AETIOLOGY, RISK FACTORS AND BASIC EPIDEMIOLOGY

Human respiratory syncytial virus (RSV) is the most common cause of acute bronchiolitis in young infants (≤ 12 months).^{15,30} Less frequently, human rhinoviruses (hRV), human metapneumovirus (hMP), human bocavirus, influenza and parainfluenza viruses are implicated.^{31,32} RSV dominates in the first year of life, during winter, while hRV are a commoner cause in older infants; recent advances in molecular diagnostics have strengthened their role as cause of lower respiratory tract infection and acute bronchiolitis.^{33,34} Co-infection by RSV and hRV may increase the severity of bronchiolitis, especially in infants younger than 6 months of age.^{35,36} However, the data regarding different combinations of various viruses and their deleterious consequences are conflicting.³²

The role of allergy in the inception of asthma should not be underestimated.^{37,38} The synergistic interaction between allergy and viruses could be explained by various mechanisms including interferon deficiency, Th2-biased immunity, defective anti-inflammatory response, airway hyperresponsiveness and reduced barrier function.^{34,37} A familial background of atopy could be a unifying explanation for asthma inception and susceptibility to acute bronchiolitis, particularly due to hRV.^{10,39–41}

Risk factors are well recognized; prematurity, age less than 6 weeks, chronic lung, neuromuscular or cardiovascular disease, male gender, low socioeconomic status, Down syndrome, intrauterine tobacco smoke exposure and passive smoking have been frequently 'incriminated'.^{15,17,22,30}

Nair *et al.* have highlighted that RSV bronchiolitis is a global epidemiological problem; they estimated that 66 000 to 199 000 children younger than 5 years died from RSV-associated infections in 2005, with 99% of these deaths occurring in developing countries. Also, they calculated that more than 33 million new cases of RSV infections occurred during the same year in children younger than 5 years of age.² These data, despite the recent observation of a decreasing trend for bronchiolitis hospitalizations in the USA⁴² and bearing in mind the tremendous financial cost,² justify the continuous research interest in bronchiolitis and its long-term outcome.⁴³

In conclusion, bronchiolitis is a viral illness with well-recognized risk factors; it is considered to be a global epidemiological problem.

OTHER METHODOLOGICAL CONCERNS

Apart from the controversies regarding clinical presentation and age, when exploring the outcome of this common disease, one has to bear in mind the several design discrepancies in the studies examined.⁵ Therefore, the variation in the definition of asthma as a long-term outcome of bronchiolitis becomes quite relevant.^{3,23} The severity of the infection also needs to be taken into account; that is, hospitalized patients versus patients treated in the community.⁴⁴ The family history of the children in the cohorts is also a crucial factor; patients with a background of atopy⁴⁵ are quite different from a cohort selected from the general population.²⁰ To complicate matters even further, the viral aetiology of bronchiolitis (especially RSV vs hRV), which is not always known when the patient is treated in the community, may be decisive for long-term prognosis.⁴⁶

In conclusion, discrepancies between different studies regarding selection of patients and definitions of bronchiolitis and long-term outcomes render comparisons and conclusions problematic.

THE ASSOCIATION BETWEEN BRONCHIOLITIS AND ASTHMA

Respiratory syncytial virus bronchiolitis and asthma

Many retrospective studies have linked RSV acute bronchiolitis with asthma.^{47,48} The epidemiological association is best founded by prospective studies. The Tucson Children's Respiratory Study of a general population birth cohort showed a strong association of community-treated RSV bronchiolitis before the age of 3 years with both frequent and infrequent wheezing during the first decade of life; this association ceased to be significant by the age of 13 years.²⁰ Additionally, forced expiratory volume in 1 s at 11 years was significantly lower in RSV-infected infants compared with controls; these children also had significant bronchodilator reversibility at the age of 11 years, suggesting an alteration in their airway tone. Sigurs followed prospectively 47 children hospitalized for bronchiolitis during their first year of life and compared them with contemporaneously matched controls (two controls for each case of the same gender, born on the same date, in the same area—93 controls in total).⁴⁹ This well-designed Swedish study reported an association of RSV bronchiolitis with asthma, as well as aeroallergen sensitization and allergic disease, which persisted into adulthood.⁵⁰ More specifically, asthma and recurrent wheeze was found in 39% of the index cases versus 9% of age- and gender-matched controls, and spirometric indices were reduced in RSV-infected children irrespective of current asthma status.⁵⁰ Because these results are rather unique, it

may be worth commenting on the fact that the inclusion criterion of bronchiolitic infants in the study was 'wheeze' (and not 'crackles') and that the study was performed in the era before hRV identification by polymerase chain reaction was available; in addition, the frequency of asthma in the control group was much lower than the reported prevalence for asthma in Sweden in the same period. The authors emphasize that their results cannot distinguish whether these differences in pulmonary function can be attributed to pre-existing poor lung function or are a consequence of the RSV infection *per se*. Data from a large prenatally recruited cohort from Southwest UK showed that hospitalization for RSV bronchiolitis in infancy led to a 2.5 times increase of physician-diagnosed asthma at the age of 91 months and a 3.5 times increase of reported wheezing at the age of 69–81 months.⁴⁵ A research group from the Netherlands has made interesting contributions after following prospectively 140 infants hospitalized for RSV; they showed that airway morbidity post-RSV bronchiolitis follows a seasonal pattern. Specifically, they reported increased wheezing during all three winter study years, a finding that strongly supports the viral aetiology of post-RSV wheezing over allergic triggers. Additionally, in this prospective study, a clinical picture of airflow limitation during a RSV lower respiratory tract infection was significantly associated with subsequent wheezing episodes; this finding emphasizes the importance of the definition of acute bronchiolitis in determining its long-term prognosis.²⁸ The same group reported a sharp decrease by over 50% during the first year after hospital admission.²⁸ RSV infection is of even more grave consequence in preterm infants, even in those who do not require hospitalization. In a combined hospital and community follow-up study of 126 infants born before 32 weeks of gestational age, RSV bronchiolitis was associated with increased health-care utilization and respiratory symptoms (cough and wheeze).⁵¹ Prematurity and laboratory-confirmed and medically attended RSV infection were recently shown to be independently associated with recurrent wheezing at the age of 5 years in a large retrospective study from North Carolina, which included more than 72 000 children.⁵²

Human rhinoviruses bronchiolitis and asthma

In recent years, hRV have gained increasing respect from clinicians and epidemiologists since it became evident that, apart from being the most common cause of common cold, they can replicate in the lower airways and cause acute exacerbations of asthma.^{33,34,37,53} The recognition of their paramount importance is a consequence of the development of more sensitive and specific molecular techniques.³⁸ The association of hRV bronchiolitis and asthma development is supported by an increasing number of papers. The Childhood Origins of Asthma (COAST) Study prospectively explored the relationship between specific viral illnesses and early asthma in children of asthmatic parents or parents with respiratory allergies.^{12,39} They found that hRV wheezing

illnesses during the first 3 years of life were associated with an impressive—nearly 10-fold—increase in asthma at the age of 6 years; this increase did not change much by mixed RSV and hRV aetiology, hRV wheezing in this study was a much stronger predictor than RSV wheezing for the development of asthma.¹² In the same study, the timing of hRV wheezing illness was found to be of independent predictive value regarding the subsequent development of asthma; hRV wheezing in the first year of life nearly tripled the risk of having asthma at 6 years of age, while the odds ratio for asthma at the same age when a child had hRV wheezing at the age of 3 years was 32.¹² The same group explored the developmental sequence between allergic sensitization and viral-induced wheezing in asthma inception using multistate Markov models. They concluded that 'allergic sensitization precedes rhinovirus wheeze, but the converse is not true'.⁴⁰ A similar high-risk cohort study from Australia has provided similar results regarding hRV wheezing in the first year of life and asthma at the age of 5; in this study, the increased risk of asthma at age 5 was confined to those children that were sensitized to aeroallergens by age 2 years.⁴¹ In a recent Finnish study, self-reported asthma was more common as post-hRV than post-RSV bronchiolitis at the age of 15–18 years.⁵⁴ Guilbert *et al.* followed prospectively 238 children from the COAST birth cohort. They found that children with RV wheezing—and not RSV wheezing—had decreased pulmonary function (as measured by spirometry and impulse oscillometry) up to the age of 8 years.²¹ Midulla *et al.* in a well-designed study examined children with acute bronchiolitis younger than 12 months and found that hRV infection actually is an even more important risk factor in asthma than a positive family history for the disease regarding the development of recurrent wheezing in the following year.¹⁸

Human metapneumovirus bronchiolitis and asthma

Hospitalization for hMP bronchiolitis has been shown to increase preschool asthma. Specifically, a group from Spain found that asthma was five times more common in children hospitalized for hMP bronchiolitis compared with controls; they also showed that this association was at least as strong as the one observed with RSV infections.¹³ Longer-term follow-up studies for the relatively newly found agents that cause bronchiolitis are lacking for the moment.

In conclusion, asthma is much more common in children with a history of RSV, or hMP bronchiolitis, and particularly in those with hRV bronchiolitis and an allergic background.

SEVERITY OF BRONCHIOLITIS AND SUBSEQUENT RISK OF ASTHMA

Carroll *et al.* explored the correlation of bronchiolitis severity and subsequent development of asthma. They found a dose–response relationship between the

severity of infantile bronchiolitis and early childhood asthma. In their study, children hospitalized for bronchiolitis had an odds ratio of 2.82 for asthma at the age of 4–5.5 years relative to controls; children seen in the emergency department with bronchiolitis had an odds ratio of 2.41 and children seen in outpatients had an even lower odds ratio of 1.86. Children with maternal history of asthma showed a similar severity gradient.⁴⁴ A recent large retrospective cohort study, which included children born at gestational age ≥ 32 weeks, confirmed these findings by showing that prolonged hospitalization for RSV had a 2.59 odds ratio for recurrent wheezing at the age of 5 years, whereas an outpatient encounter for RSV infection had an odds ratio of only 1.38.⁵²

In conclusion, severity of bronchiolitis is correlated with subsequent asthma development.

MECHANISMS

For decades the core question regarding the association between acute bronchiolitis and subsequent development of asthma^{7,8,14,55} has been whether predisposed infants (congenitally narrow airways, immune impairment) present earlier with symptomatic airway obstruction as acute bronchiolitis or whether bronchiolitis in infancy *per se* causes asthma.^{8,9,15,55,56} Of course, the detrimental effect of bronchiolitis on predisposed individuals is also quite possible.

Wu *et al.* have provided indirect evidence in support of the notion that bronchiolitis indeed causes asthma by showing that timing of birth with respect to the annual peak of the winter virus season strongly and independently predicts future development of asthma.^{57,58} In this study, children aged approximately 4 months at the time of the winter virus peak had an additional 29% risk of developing asthma in the future. The fact that this association persisted throughout all study years despite the shifting of the viral peak from year to year strongly points towards causality.⁵⁷

Should bronchiolitis cause asthma, its prevention would be expected to result in a reduction of the burden of asthma. Simoes *et al.* in a prospective multicenter, matched, double cohort study showed that RSV prophylaxis with palivizumab in preterm infants with non-atopic background decreased the risk of subsequent doctor-diagnosed recurrent wheezing by 68–80% in the preschool years. In the same study, palivizumab prophylaxis did not have a favourable outcome in children with a positive family history for atopy.^{59,60} A far better designed (double-blind, placebo controlled) recent study from the Netherlands showed that palivizumab prophylaxis led to a relative reduction of 61% in the total number of wheezing days reported by parents during the first year of life regardless of family history of atopic predisposition.⁶¹ Although these results are technically valid only in the case of late preterm infants and, for obvious reasons, cannot be reproduced in previously healthy-term newborns they do ‘proof of concept’ of the direction of causality from RSV bronchiolitis to

postbronchiolitic wheeze in predisposed infants. Should this data be confirmed in longer-term follow-up, a causal role of bronchiolitis in the inception of asthma will be greatly strengthened.

An alternative or, even more likely, additional explanation of the bronchiolitis–asthma association could be that premorbid lung function (and not bronchiolitis *per se*) is responsible for subsequent respiratory morbidity. Along these lines, Turner *et al.* showed in a longitudinal birth cohort study that a reduction in lung function existed at 1 month of age (before bronchiolitis) as well as at the age of 11 years and gave a pessimistic message that everything starts too early for any intervention to be successful.⁶² Similarly, a group from Copenhagen recently reported that bronchial hyperresponsiveness pre-exists in children who later develop severe bronchiolitis.⁶³ The same group suggested that 40% of the spirometric deficit of school-aged asthmatic children was present at birth, long before any interaction with environmental risk factors.⁶⁴ These data support the hypothesis that pulmonary function at birth dictates, at least to a substantial degree, what happens to respiratory health in later life;⁶⁵ of course, subsequent deleterious interaction with environmental factors, such as viruses or, for that matter, direct causation by acute bronchiolitis *per se* cannot be excluded by any means.

An interesting ‘double-hit’ hypothesis linking age-related changes and adaptive immune responses to RSV infection has been proposed.⁶⁶ According to this, Th2-polarized immunity post-exposure to aeroallergens and bronchiolitis act synergistically towards the development of subsequent asthma and respiratory morbidity.^{66–69} The virus–allergen deleterious combination can involve both synergistic damage to the integrity of the respiratory epithelium as well as immunologic interactions.³⁴ This ‘double-hit’ (i.e. atopy plus viral infection) hypothesis could actually evolve into a ‘multiple-hit’ hypothesis since other, perhaps less important, risk factors such as pre- or antenatal and active smoking,^{70–72} pollution and occupational hazards may also contribute to the wheezing disorder and/or pulmonary function deficit in later life.⁷³

Alternatively, bronchiolitis and subsequent development of wheezing may share a common genetic predisposition. Goetghebuer *et al.* showed, in a questionnaire-based study of 164 Caucasian children, that the haplotype IL8-251A occurred in excess in families of children who went on to develop post-bronchiolitic wheeze compared with those who did not.⁷⁴ Koponen *et al.* in a recent study showed that children who are not carriers of IL10rs1800896 allele G are at increased risk for development of preschool asthma following bronchiolitis during the first 6 months of life.⁷⁵ The same group found an association between the non-wild variant mannose-binding lectin genotype and asthma at 6.4 years post-bronchiolitis, but not earlier.⁷⁶ Bont *et al.* concluded that monocyte IL-10 response during RSV bronchiolitis has a predictive value for asthma development.⁷⁷ A group from South China showed that a RANTES (regulated on activation normal T cell expressed and secreted activity) gene promoter poly-

morphism that increases serum RANTES levels is associated with post-bronchiolitic wheeze.⁷⁸ However, although intense research is ongoing in the field of genetic predisposition, no definitive answers are available as yet.^{9,57,79,80}

Other investigators have highlighted interferon deficiencies, often related to atopy, which could explain increased susceptibility to viral infections, secondary to problematic antiviral immunity in asthmatics.^{68,69,81} Stern *et al.* concluded that obstructive episodes of the airways can be anticipated based on the characteristics of the immune system during the first year of life; specifically, this group showed that children with low interferon γ levels at the age of 9 months had increased risk of wheezing between 2 and 13 years of age.⁸² A novel mechanism that has been proposed to explain post-bronchiolitis development of asthma suggests that RSV induces angiogenesis through increased production of vascular endothelial growth factor, which in turn leads to escalation of the inflammatory response.⁶⁹ A more detailed review of the evidence regarding potential inflammatory mechanisms via which acute bronchiolitis, perhaps in concert with a predisposed immune system, may lead to the inception of asthma is beyond the scope of this review.

In conclusion, the plausible mechanisms underlying the association between bronchiolitis and subsequent asthma development most likely involve both directions of causality between these two obstructive respiratory diseases; the relative contribution of each direction of causality may well be determined by the specific characteristics of each individual.

CONCLUSIONS

There is no doubt that acute bronchiolitis of infancy and subsequent development of asthma are strongly associated. Current evidence is inadequate to conclude on the direction of causality between acute bronchiolitis and development of post-bronchiolitic wheeze and much remains to be learned. Given the current state of research, it is quite likely that both host and post-infectious factors of varying significance are involved in this relationship; although the contribution of each may vary based on the individual's characteristics (for example prematurity, predisposition to atopy) and the specific infection (RSV, rhinovirus, etc.). Still, it is probably wise to have a high index of suspicion for future asthma in children who have suffered from bronchiolitis; this could lead to an earlier diagnosis of this all too common chronic disease of childhood.

Truthfully speaking, there is no straightforward answer to the parental question of the title of this review. For the time being, firm advice regarding avoidance of well-known aggravating factors such as parental smoking may be all that we have to offer to the concerned parents of a child that recovers from bronchiolitis; avoidance of allergens and viruses remains problematic.^{83,84} Last but not least, the development of better asthma-predictive indices is urgently needed since the available tools are not

sensitive and specific enough to be useful in daily clinical practice.⁸⁵

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