

**PERSPECTIVE**

# Is age during bronchiolitis the most important predictor of post-bronchiolitis outcome?

## 1 | INTRODUCTION

The risk of asthma is increased in children who have suffered from bronchiolitis in infancy and/or from wheezing associated with lower respiratory tract infection (LRTI) in early childhood. Asthma in mothers seems to be the most consistent risk factor for later asthma in children. Long-term follow-ups have suggested that the increased post-bronchiolitis asthma risk continues until adulthood. Bronchiolitis has usually been defined as the first episode of LRTI with expiratory difficulty. However, bronchiolitis may present with or without wheezing, and so, the border between bronchiolitis and infection-associated early-childhood wheezing is blurred with much overlapping in symptoms and signs between these two clinical entities. An essential information, such as the presence or absence of previous wheezing that is needed for diagnostic definitions, is mainly based on medical histories received from parents. This means a challenge to the reliability of the clinical definitions. Eventually, the age of the child on admission in childhood may be the only indisputable criterion for classification of various LRTIs with respiratory distress when their outcomes are studied.

## 2 | INFLUENCE OF AGE ON CLINICAL PICTURE OF BRONCHIOLITIS

Age of infants is associated with clinical findings of bronchiolitis. Most of severe cases needing for example intensive care occur in infants younger than three months. Younger age is associated with higher respiratory rate, more chest retractions and less wheezing, more crackles on auscultation, more feeding problems and more infiltrations in chest radiographs. In young infants, the clinical picture of bronchiolitis resembles that of viral pneumonia, often called as pneumonitis.

Likewise, age of infants is associated with viral aetiology of bronchiolitis. All respiratory viruses can cause bronchiolitis, but respiratory syncytial virus (RSV) predominates in infants under 6 months of age, and rhinovirus in children over 12 months of age.<sup>1</sup> The causative viruses, no doubt, are partly but not exclusively responsible for the clinical findings of bronchiolitis.

The connection of allergy, atopy and eosinophilia with bronchiolitis remains unresolved. There is an evidence that bronchiolitis in

young infants is not associated with atopy, or when such association has been revealed, it has presented as sensitisation to food allergens. Sensitisation to inhaled allergens starts to take place during the second or third year of life, and when present, the risk of post-bronchiolitis asthma is increased. A normal response to viral infection is eosinopaenia, and so, normal eosinophils when studied during bronchiolitis, may mean an accelerated eosinophil response.

Tobacco smoke exposure in early life seems to be associated with severity of bronchiolitis, further with the need for hospitalisation and intensive care, and finally with poorer post-bronchiolitis outcomes through different mechanisms for smoking by mothers and fathers. Maternal smoking, especially if happened during pregnancy, can cause permanent changes in children's airways, whereas paternal smoking increases the probability of active later smoking, and further and an increased risk of asthma and chronic obstructive disorders.<sup>2</sup>

The outcomes are different after RSV and rhinovirus bronchiolitis. Rhinovirus bronchiolitis is associated more often than RSV bronchiolitis with subsequent childhood asthma.<sup>1</sup> RSV bronchiolitis, instead, seems to be associated with lung function deficiency, including the development of irreversible lung function deficiency from the age of 11–13 years onwards.<sup>3</sup>

## 3 | LONG-TERM POST-BRONCHIOLITIS FOLLOW-UPS

Four prospective cohort studies consisting of patients hospitalised for infection associated wheezing in early childhood, including bronchiolitis in infancy, were started in Finland and Sweden in the 1980's and 1990's. Follow-ups of the post-bronchiolitis cohorts have continued beyond puberty, as summarised recently in this journal.<sup>4</sup> In adolescence, doctor-diagnosed (or allergy-related) asthma was present in 30% of cases in three studies, compared to 1%–5% of controls. Self-reported (or symptom-based) asthma was present in 39%–64% of cases, compared to 9%–15% of controls.

Three of these research groups have published the results on clinical outcomes assessed at 24–29 years of age.<sup>4</sup> Doctor-diagnosed asthma was present in 31%–37% of cases in two studies and in 10% of cases in one study, compared with 5%–11% of controls, respectively.

**Abbreviations:** LRTI, lower respiratory tract infection; RSV, respiratory syncytial virus.

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Self-reported symptom-based asthma was present in 35%–36% of cases, compared with 11%–15% of controls. Thus, about a third of the former patients hospitalised for infection-associated wheezing in early childhood presented with asthma in young adulthood.

#### 4 | INFLUENCE OF AGE ON OUTCOME OF BRONCHIOLITIS

In total, 32 original articles with 292,844 participants were included in a meta-analysis on asthma after bronchiolitis in infancy.<sup>5</sup> Bronchiolitis was defined as the first wheezing episode before 24 months of age. Bronchiolitis increased the risk of subsequent asthma on average to 2.46-fold (95% confidence interval (CI) 2.14–2.82,  $p < 0.001$ ). After categorising the studies into different groups based on age at the end of follow-up (<10 years, >10 years), by geographical region (Europe, North America, South America, Asia) and by study quality (moderate, high), the associations between bronchiolitis and childhood asthma remained significant in all subgroup analyses. Analyses were not done in relation to age of the patients on admission. There was only one study, performed in Tampere, Finland, which included only infants admitted at the age under six months alone, and in this study, the risk of subsequent asthma was not increased at 11–13 years of age (relative risk 1.22 (95% CI 0.66–2.43).

#### 5 | INFLUENCE OF VIRAL AETIOLOGY ON OUTCOME OF BRONCHIOLITIS

The role of early-life rhinovirus-induced wheezing has been highlighted in the development of asthma later in childhood. This was also seen in the previous questionnaire-based and follow-up studies of the Finnish cohort of originally 100 children hospitalised for their first episode of wheezing under 24 months of age. Within the cohort, self-reported asthma was more common after wheezing induced by rhinoviruses than after wheezing induced by RSV at the median ages of 7.2 years (70.0% vs. 10.0%)<sup>1</sup> and at the median age of 18.5 years (64.3% vs. 42.9%).<sup>4</sup>

#### 6 | CONCLUSION

In the future studies on the risk of asthma, the study group should be limited to those admitted at younger than 12 months of age, or even at younger than six months of age. Wheezing cases at 12 months to 23 months of age form a heterogeneous group consisting of patients with first wheezing, repeated wheezing or even asthma, and they should be studied as an own category separately from bronchiolitis. Especially important this separation is in meta-analyses, which are often due to differences in designs of original studies containing the data with substantial heterogeneity.

The first wheezing episode diagnosed by a doctor, often used as a criterion of bronchiolitis, does not mean that mild self-improved

asthma-presumptive symptoms have not occurred. Since most severe bronchiolitis cases demanding for example intensive care occur mainly in infants younger than three months of age, the outcomes might be needed to be analysed separately for 0–3 months, 3–6 months and 6–11 months age groups. In optimal studies, the cases can be analysed also in relation to RSV versus rhinovirus aetiology, presence versus absence of asthma in parents, especially in mothers, and presence versus absence of exposure to tobacco smoke prenatally and/or postnatally in infancy.

#### CONFLICT OF INTEREST

Nothing to declare.

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