Severe bronchiolitis profiles and risk of asthma development in Finnish children

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Key messages:

- In a cohort of children (age <2 years) hospitalized for bronchiolitis in Finland, severe bronchiolitis profiles identified by a clustering approach were differentially associated with childhood asthma evaluated both 4 and 7 years later.
- The highest risk of childhood asthma was observed in children with ‘profile A’ bronchiolitis, characterized by history of wheezing and eczema; wheezing during acute illness; and rhinovirus infection.

Capsule summary:

A bronchiolitis profile characterized by history of wheezing and eczema, wheezing during acute illness, and rhinovirus infection had highest risk of childhood asthma.

Key words: Respiratory infections, Cluster Analysis, Respiratory Syncytial Virus, Rhinovirus, Asthma

Abbreviations:

CI: confidence interval

ED: emergency department

LCA: latent class analysis (LCA)

MARC: Multicenter Airway Research Collaboration

OR: odds ratio

RSV: respiratory syncytial virus

ABSTRACT

Background: Recent studies support the existence of several entities under the clinical diagnosis of "bronchiolitis". Among infants with severe bronchiolitis, distinct profiles have been differentially associated with development of recurrent wheezing by age 3 years. However, their associations with actual asthma remain unclear.

Objectives: To study the association between severe bronchiolitis profiles identified by a clustering approach and childhood asthma.

Methods: Among 408 children (age <2 years) hospitalized with bronchiolitis in Finland (2008-2010), latent class analysis identified three severe bronchiolitis profiles: profile A (47%), characterized by history of wheezing/eczema, wheezing during acute illness and rhinovirus infection; profile BC (38%), characterized by severe illness and RSV infection; and profile D (15%), the least severely ill group including mostly children without wheezing and with rhinovirus infection. Children were followed by questionnaire 4 years later (86%, n=348) and through a nationwide social insurance database 7 years later (99%, n=403). Current asthma at 4- and 7-year follow-ups was defined by regular use (parental report and medical records) or purchase (social insurance database) of asthma control medication.

Results: Compared with profile BC, we observed increased risk of current asthma associated with profile A both at 4-year follow-up (age- and sex-adjusted odds ratio, 2.42; 95%CI: 1.23-4.75) and at 7-year follow-up (3.14; 1.33-7.42). No significant difference in asthma risk was observed between profile D and profile BC.

Conclusion: These longitudinal results provide further support for an association between a distinct severe bronchiolitis profile (characterized by history of wheezing/eczema and rhinovirus infection) and risk of developing childhood asthma.

Abstract word count: 250

INTRODUCTION

Severe bronchiolitis, most commonly caused by respiratory syncytial virus (RSV) or rhinovirus, is a leading cause of hospitalization in the first years of life.[1,2] Besides its considerable acute burden, severe bronchiolitis is a risk factor for development of respiratory diseases in childhood such as recurrent wheezing and/or asthma.[2] Studies in various countries have reported that 20% to 30% of infants hospitalized for bronchiolitis (severe bronchiolitis) later develop wheezing or asthma, with higher proportion among those with rhinovirus or non-RSV bronchiolitis.[3–5] However, among children with severe bronchiolitis, those with increased risk of asthma development remain incompletely characterized.

Recent studies support the existence of several entities under the clinical diagnosis of "bronchiolitis", which may be differentially associated with long-term respiratory outcomes.[6–9] Hypothesis-free statistical clustering approaches, such as latent class analysis (LCA), are increasingly used to address phenotypic heterogeneity in respiratory research[10–12] and have been applied recently to characterize distinct clinical profiles of severe bronchiolitis.[7,13–15] In a prospective, multicenter cohort study of 408 children hospitalized with bronchiolitis in Finland (30th Multicenter Airway Research Collaboration [MARC-30] Finland), we previously identified three severe bronchiolitis profiles using LCA.[13] The profiles were labelled 'A', 'BC' and 'D', to match with profiles identified in a similar cohort in the US (MARC-30 US, four profiles identified: 'A', 'B', 'C' and 'D'). Briefly, profile A was characterized by history of wheezing, history of eczema, wheezing at the emergency department (ED) presentation, and rhinovirus infection. Profile BC was characterized by more severe illness (as measured by inadequate oral intake, hospital length of stay ≥3 days) and RSV infection. Profile D was the least severely ill group and included mostly children without wheezing at ED presentation and who tended to have rhinovirus infection.

The viral etiology, an important component of the profiles and strong determinant of risk of developing asthma, differs by geographic region, with a higher prevalence of rhinovirus infection in Finland than in the US.[13,16,17] Despite these differences, similar severe bronchiolitis profiles were identified in the Finnish study and in two multicenter studies of children hospitalized for bronchiolitis in the US (MARC-30 and MARC-35).[7,13] Among US infants, the distinct bronchiolitis profiles were differentially associated with development of recurrent wheezing by age 3 years.[7] However, their associations with actual asthma require further investigation.

In the current study, we investigate for the first time the association between severe bronchiolitis profiles identified by a clustering approach and childhood asthma at 4 and 7 years after bronchiolitis hospitalization.

RESULTS AND DISCUSSION

A total of 408 children younger than 24 months hospitalized with severe bronchiolitis were recruited from three University Hospitals in Finland during the winter seasons 2008 to 2010. The mean age at baseline was 9.3 months (standard deviation [SD]: 6.7) and 38% of the children were female. Four to five years after hospitalization (4-year follow-up), data on asthma medication were collected by questionnaire or interviews in 349 (86%) children (mean age 5.4 years, SD: 0.94), and for those who reported regular use of asthma medication, medical records were reviewed.[3] Seven to nine years after hospitalization (7-year follow-up), data of 403 (99%) children were linked to the Finnish Social Insurance Institution of Finland (Kela) nationwide database,[18] which records asthma-related benefits, including discount from drug purchase. Asthma-related benefits and drug purchase were evaluated at the time of the child's 7th birthday. **Table 1** describes the three severe bronchiolitis profiles at baseline among children with 7-year follow-up data. Profile A was the most prevalent (47%), while 38% of the children were profile

BC and 15% profile D. The distribution of the profiles did not differ between children with and without 4-year follow-up data (p=0.45).

At 4-year follow-up, 38% of profile A children, 14% of profile BC children, and 28% of profile D children had current asthma, defined as the prescription of regular asthma control medication (inhaled corticosteroids or leukotriene receptor antagonists) in the past 12 months. At 7-year follow-up, 24% of profile A children, 6% of profile BC children and 10% of profile D children had current asthma, defined as current asthma benefit recorded in Kela social insurance database with repeated purchase of asthma control medication in the past 12 months.

In age- and sex-adjusted models (**Table 2**), increased risk of current asthma was observed in profile A children compared with profile BC children at 4-year (odds ratio, 2.42; 95%CI: 1.23-4.75) and at 7-year (3.14; 1.33-7.42) follow-up. An association between profile D and current asthma was suggested at 4-year follow-up but was not significant (1.77; 0.79-3.98), and the OR value was lower at 7-year follow-up (1.27; 0.41-3.90). Associations between profile A and current asthma remained strong and significant in analyses with adjustment for five additional factors (number of siblings at home, exposure to environmental tobacco smoke, maternal smoking during pregnancy, gestational age and breastfeeding) and accounting for a potential center effect. In sensitivity analyses restricted, respectively, to children aged <12 months and to children without history of wheezing at baseline (stricter definition of bronchiolitis), results were consistent with a similarly increased risk of current asthma in profile A children compared with profile BC children: the risk was elevated but non-significant at 4-year follow-up (age <12 months: 1.60; 0.70-3.71, n=226, with 22 asthma cases in profile A; without history of wheezing: 2.04, 0.86-4.83, n=221, with 22 cases in profile A) and significant at 7-year follow-up (age <12 months: 3.15; 1.06-9.35, n=261, with 16 asthma cases in profile A; without history of wheezing: 5.51, 1.71-17.8, n=254, with 17 asthma cases in profile A).

Our results confirm and extend previous findings from a similar US cohorts, where multiple profiles were identified[7,13] and the highest risk of recurrent wheezing by age 3 years was observed in a similar group of 'profile A' children.[7] Profile A was characterized by a history of breathing problems and eczema during infancy and non-RSV (mostly rhinovirus) infection. The current study makes an important addition by replicating these results in a different cohort with longer follow-up (4-5 and 7-9 years after hospitalization), providing the opportunity to study actual asthma rather than wheezing phenotypes which may be transient in early childhood.[19] Profile A was the most consistent profile between the US and Finnish cohorts.[7,13] Probably because of differences in the distribution of viral etiology in US and Finland and age distribution of the cohorts, the other profiles were slightly different. Interestingly, in US cohorts, we identified two distinct profiles of children predominantly with RSV infection, labelled 'B' and 'C', which differed in the severity of the acute illness. Profile C, which included the most severely ill children, also had a higher risk of developing recurrent wheezing compared to profile B, although to a lesser extent than profile A. In the current Finnish cohort, only one RSV-predominant profile (BC) was identified. Children in this profile had characteristics of profiles B and/or C identified in the US cohorts, including some indicators of more severe illness (longer hospital stay, inadequate oral intake), although moderate-to-severe retractions were less prevalent than in profile A. It is notable that a more than 2-fold increased risk of childhood asthma was observed in profile A children even when compared to profile BC, suggesting that among children hospitalized with bronchiolitis (i.e., already with a severe disease), profile A characteristics (history of wheezing and eczema, wheezing during acute illness, and rhinovirus infection) are stronger predictors of childhood asthma than further indicators of acute severity. The current study is limited to bronchiolitis cases severe enough to require hospitalization, although profile D children may resemble milder (outpatient) cases. Similar work in different cohorts, including outpatient cases, are needed to determine whether profile A characteristics are also associated with increased asthma risk among children with milder bronchiolitis.

In the current Finnish cohort with high prevalence of rhinovirus infection, two profiles of children predominantly with rhinovirus bronchiolitis were identified (A and D). However, a significantly increased risk of childhood asthma was only observed among profile A children. Profile D was the smallest group of children and had limited statistical power to detect modest associations. Nonetheless, the pattern of associations (>2-fold increased risk in profile A only) suggests that the elevated risk of childhood asthma in profile A is not only driven by rhinovirus etiology, and that other characteristics (history of wheezing and eczema, and wheezing during acute illness) may be important to identify children with higher risk of asthma. Although no IgE or allergen testing was performed in the current study, we have previously showed in a US cohort that profile A infants tended to have greater IgE level and had significantly higher eosinophil counts than other profiles. Evidence exists for an interaction between viral infections – especially rhinovirus – and early-life sensitization to multiple allergens and asthma risk, and this hypothesis needs to be further explored in the context of severe bronchiolitis.[20]

A strength of our study was to observe consistent results when restricting analyses to stricter definitions of bronchiolitis.[9] Results were also similar at 4-year and at 7-year follow-up and with different sources of data to define asthma – i.e., parent questionnaire/interviews combined with review of medical records *vs.* an almost exhaustive linkage to a national social insurance database (Kela). Both definitions were based on regular use of asthma control medication, in order to favor specificity, which is recommended when studying asthma risk factors.[21] Kela benefits can only be applied to children who have had continuous asthma medication for 6 months and need to continue treatment, and thus is a relatively strict criteria to define asthma.[21] However, because different data sources and asthma definitions were used at 4-year and 7-year follow-ups, we could not evaluate asthma/wheezing trajectories in childhood (e.g., transient vs. persistent symptoms), which would deserve further investigation.

Because profile A comprises children with history of wheezing and eczema before the severe bronchiolitis episode and with wheezing during the acute illness, we earlier hypothesized that profile A was composed of children presenting with early signs of asthma during a severe, often rhinovirus-/non-RSV bronchiolitis episode.[13] The current findings provide further support for this hypothesis and suggest that some groups of children may benefit from asthma-related treatments,[22,23] both for short-term and long-term clinical outcomes. The current study focuses on observable characteristics (phenotypes) that may help clinicians identify such patients and did not aim at identifying the mechanisms underlying the observed association. A complementary endotyping work[6,24] with more integrative approaches using simultaneously clinical, biological and -omics data would provide insight on the different pathways linking infant bronchiolitis profiles to childhood asthma.

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Table 1. Description of the children hospitalized for severe bronchiolitis (baseline) according to the profiles (A, BC and D) among children with 7-year follow-up (n=403)

	All (n=403)	Profiles A (47%, n=190)	Profiles BC (38%, n=153)	Profiles D (15%, n=60)
	*Percent (n)**		*Percent**	
Age (months)				
<2	15 (62)	3	30	18
2-5.9	26 (104)	15	42	20
6-11.9	24 (95)	31	14	25
≥12	35 (142)	52	14	37
Age (months), mean	9.3	12.3	5.5	9.5
Girls	38 (155)	32	45	42
Parental history of asthma	24 (97)	25	27	15
History of wheezing	37 (149)	55	16	35
History of eczema	29 (117)	41	18	20
Wheeze at ED presentation	69 (277)	94	62	10
Cough at ED presentation	65 (244)	78	68	14
Inadequate oral intake at ED presentation	21 (82)	10	38	12
Retractions at ED presentation				
None	16 (60)	5	13	54
Mild	41 (152)	30	55	36
Moderate to severe	43 (161)	65	32	10
Hospital length-of-stay ≥3 days	32 (127)	25	45	22
Viral etiology				
RSV	42 (171)	5	100	13
Rhinovirus	32 (129)	54	0	43
Viral etiology (mutually exclusive categories)				
RSV only	35 (141)	1	89	5
Rhinovirus only	23 (92)	39	0	30
RSV and rhinovirus	2 (9)	3	0	5
RSV and other non-rhinovirus	5 (21)	1	11	3
Rhinovirus and other non-RSV	7 (28)	12	0	8
Non-RSV and non-rhinovirus	28 (112)	44	0	48
Number of pathogens				
No pathogen identified	14 (57)	22	0	25
1	70 (284)	60	89	57
2	14 (55)	15	10	18
≥3	2 (7)	3	1	0

*Results are expressed as % (n) or % (observed proportion in the study population [“All”], and probability of individuals presenting the characteristics within profiles A, BC and D), unless otherwise specified. Variables in bold were included in the latent class analysis to identify the profiles.
Abbreviations: ED, emergency department; RSV, respiratory syncytial virus.
Profile A: history of wheezing and eczema, wheezing at ED presentation, more often rhinovirus.
Profile BC: wheezing at ED presentation, more often RSV only, most severe. Profile D: non-wheezing at ED presentation, least severe, more often rhinovirus.

Table 2. Association between severe bronchiolitis profile at baseline and asthma at 4-year and 7-year follow-up

	Current asthma at 4-year follow-up (n=348)				Current asthma at 7-year follow-up (n=403)			
	n total	n current asthma	OR* (95% CI)	OR† (95% CI)	n total	n current asthma	OR* (95%CI)	OR† (95% CI)
Profile A	158	60	**2.42 (1.23-4.75)**	**2.01 (1.01-4.02)**	190	45	**3.14 (1.33-7.42)‡**	**2.93 (1.21-7.11)‡**
Profile BC	136	19	1	1	153	9	1	1
Profile D	54	15	1.77 (0.79-3.98)	1.47 (0.64-3.40)	60	6	1.27 (0.41-3.90)	1.17 (0.37-3.67)

Logistic regression models *adjusted for age at baseline and sex; † with further adjustment for number of siblings at home, exposure to environmental tobacco smoke, maternal smoking during pregnancy, gestational age and breastfeeding, and accounting for a potential center effect (patient clustering at the hospital level), n=338 at 4 years, n=392 at 7 years. ‡ p=0.06 for comparison of profile A vs. profile D. Results in boldface are statistically significant.

Abbreviations: OR, odds ratio; CI, confidence interval.