

Bronchiolitis

Age and Previous Wheezing Episodes Are Linked to Viral Etiology and Atopic Characteristics

Tuomas Jartti, MD,* Pasi Lehtinen, MD,* Tytti Vuorinen, MD,† and Olli Ruuskanen, MD*

Background: Diagnostic criteria for bronchiolitis are variable.**Objective:** To study how the risk factors for recurrent wheezing and asthma vary by different definitions of bronchiolitis.**Methods:** Viral etiology and atopic characteristics were studied in 259 hospitalized wheezing children (median age, 14 months; range, 0–36 months). The data were analyzed according to age (<6, <12, <24 and <36 months) and whether they had a history or no history of a previous wheezing episode. Sixteen viruses were detected by conventional and molecular methods. Atopic characteristics included the presence of eczema, specific and total IgE responses, blood eosinophil count, and modified asthma predictive index.**Results:** Evidence of respiratory virus infection was found in 93% of the cases and allergic sensitization in 26% of the cases. Rhinovirus infections and atopic characteristics (sensitization, blood eosinophil count, and modified asthma predictive index) increased by age and were significantly more common in children with recurrent wheezing episodes than in first-time wheezers in age categories of <24 and <36 months ($P < 0.05$ for all).**Conclusions:** In children with bronchiolitis, 2 clinical factors, age and number of previous wheezing episodes, are linked to inflammatory (atopy-related factors) and virologic risk factors of asthma (rhinovirus-associated disease). According to current US and UK guidelines, bronchiolitis includes wheezing children <24 months of age. Our observations suggest that the clinical definition should include only children with their first episode of wheezing.**Key Words:** bronchiolitis, definition, age, virus, atopy

(Pediatr Infect Dis J 2009;28: 000–000)

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text; simply type the URL address into any Web browser to access this content. Clickable links to the material are provided in the HTML text and PDF of this article on the Journal's Web site (www.pidj.com).

Bronchiolitis is a clinical diagnosis.^{1–7} It has usually been defined as an acute seasonal illness characterized by rhinitis, dry wheezy cough, tachypnea, and hypoxia in young children. Typical pulmonary findings on auscultation include fine inspiratory crackles and a high-pitched expiratory wheeze. Because of the clinical nature of the diagnosis, the definitions and the treatment

practices of bronchiolitis have been variable.^{8,9} In the 22 trials during the last 3 years, the upper age limit ranged from 3 to 24 months; 50% of the studies focused solely on the first episode of wheezing and 41% solely on respiratory syncytial virus (RSV) infection (see Table 1, Supplemental Digital Content, <http://links.lww.com/A751>).

The diagnosis of bronchiolitis is likely to include different disease entities with different immunopathogenesis according to viral etiology, wheezing phenotype, and preceding inflammatory state (atopy or no atopy).^{10–21} These factors might affect the response to treatment and might confound clinical trials. The long-term prognosis of bronchiolitis varies greatly.^{14,15,17,18,22,23} Previous studies have not broken down the definition of bronchiolitis into the risk factor profile of recurrent wheezing, or later, asthma, by upper age limit of the definition and number of previous wheezing episodes.^{12–25} Therefore, our objective was to define detailed viral etiology and atopic characteristics by different clinical definitions of bronchiolitis.

METHODS

Subjects

The study was carried out in the Department of Pediatrics, Turku University Hospital (Turku, Finland) between September 2000 and May 2002 (study breaks were June–July 2001 and Christmas week 2001). Children aged 3 months to 16 years took part in a clinical trial (VINKU-study) evaluating the efficacy of systemic corticosteroids for the treatment of virus-induced wheezing, which was the primary goal of the study.^{16,17} The viral etiology of the illnesses was studied extensively, as previously described.^{10,11} The predefined inclusion criterion was acute wheezing necessitating hospitalization. The study was commenced only after obtaining written informed consent from the parents. The study population for the current secondary analysis was completed retrospectively by including also <3-month-old hospitalized infants from the same time period (Fig. 1). Their predefined inclusion criteria were presence of wheezing and hospitalization for bronchiolitis. Predefined exclusion criteria included systemic corticosteroid treatment in the preceding 4 weeks, chronic disease (other than atopy-related disease), intensive care unit treatment, or previous participation in this study. The study protocol was approved by the Ethics Committee of the Turku University Hospital.

Definitions

Atopy was defined as positive immunoglobulin (Ig) E antibodies to any of the common allergens (cut-off level 0.35 kU/L for codfish, cow's milk, egg, peanut, soybean, wheat, cat, dog, horse, birch, mugwort, timothy, *Cladosporium herbarum*, and *Dermatophagoides pteronyssinus*; fluoroenzyme immunoassay [CAP FEIA, Phadiatop Combi Phadia, Uppsala, Sweden]).^{16,17} Aeroallergen sensitization was defined as positive IgE antibodies to any of the latter 8 allergens. Perennial aeroallergen sensitization was defined as positive IgE antibodies to the dog, cat, or *D. pteronyssinus*. Birch, mugwort, timothy, and *C. herbarum* were considered

Accepted for publication September 23, 2008.

From the Departments of *Pediatrics and †Virology, Turku University Hospital, Turku, Finland.

Supported by the Academy of Finland, the Finnish Cultural Foundation, the Turku University Foundation, the Foundation for Pediatric Research, and the Paulo Foundation.

Address for correspondence: Tuomas Jartti, MD, Department of Pediatrics, Turku University Hospital, P.O. Box 52, FIN-20520 Turku, Finland. E-mail: tuomas.jartti@utu.fi.

Copyright © 2009 by Lippincott Williams & Wilkins

ISSN: 0891-3668/09/2804-0001

DOI: 10.1097/INF.0b013e31818ee0c1

as seasonal aeroallergens. We slightly modified the asthma predictive index (API), according to the criteria for initiating daily long-term control therapy for asthma in children aged 0 to 4 years, as suggested by the Heart, Lung and Blood Institute of USA; ie, ≥ 4 wheezing episodes within the past year of which at least 1 confirmed by a physician, or prolonged symptoms lasting ≥ 6 weeks and requiring symptomatic treatment > 2 times per week, and ≥ 1 major risk factors (physician-diagnosed atopic eczema or parental asthma) and ≥ 2 minor risk factors (allergic rhinitis, wheezing apart from colds or blood eosinophil count $\geq 0.40 \times 10^9/L$) originally introduced by Castro-Rodriguez et al.^{19,20}

Sample Collection and Analysis

On admission, a nasopharyngeal aspirate sample was obtained using a standardized procedure, as described elsewhere.¹⁰ Virus antigen detection and virus culture were carried out immediately, and the samples obtained for polymerase chain reaction (PCR) assays were stored in tubes at -70°C before processing. In the 219 children aged 3 to 35 months, complete virus diagnostic evaluation of nasopharyngeal aspirate specimens included the following: PCR for 16 viruses (enteroviruses, rhinoviruses, RSV, coronaviruses [229E, OC43, NL63, and HKU1], metapneumovirus [hMPV], human bocavirus, influenza A and B viruses, adenovirus, and parainfluenza virus [PIV] type 1-type 4); virus culture for 10 viruses (adenovirus, influenza A and B viruses, PIV type 1-type 3, RSV, enteroviruses, rhinovirus, and hMPV); antigen detection for 7 viruses (adenovirus, influenza A and B viruses, PIV 1-PIV 3, and RSV); IgG serologic testing of acute and convalescent phase serum samples for 7 viruses (adenovirus, enteroviruses, influenza A and B viruses, PIV type 1/type 3, and RSV); and IgM serology for enteroviruses in 193 children (88%).^{10,11} Of the 33 children aged < 3 months, RSV antigen detection was carried out in 26 (79%) infants and RSV and rhinovirus PCR in 21 (64%) infants (21 of 26 [81%] were RSV positive and 6 of 21 [29%] were rhinovirus positive). All rhino-enterovirus PCR-positive samples could not be typed by hybridization. Twelve such samples, which were available for sequence analysis, showed rhinoviruses. On the basis of this finding, all 35 nontypable rhino-enteroviruses were classified as rhinoviruses.

Blood samples for eosinophil analyses were collected at study entry. The samples were analyzed according to the standard clinical routine in the Central Laboratory, Turku University Hospital, Turku, Finland.

Statistics

The normality of data distribution was tested using the Kolmogorov-Smirnov test. Mann-Whitney U test was used for continuous data. χ^2 test or Fisher exact test (when counts < 5) were used for dichotomous data. Univariate associations between age and dichotomous dependent variables were studied using simple logistic regression. Then age, previous episodes (yes or no), and interaction between age and previous episodes were used as

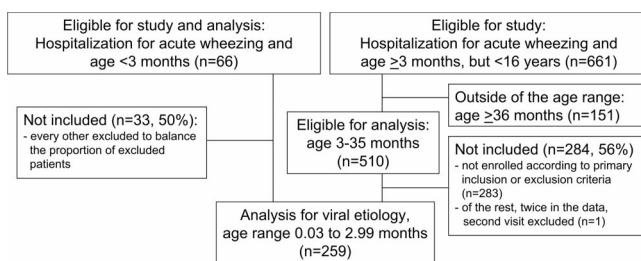


FIGURE 1. Study flow chart.

TABLE 2. Viral Etiology According to Different Definitions of Bronchiolitis

Virus*	<6 Months			<12 Months			<24 Months			<36 Months		
	1st Episode	≥ 2 nd Episode	Any Episode	1st Episode	≥ 2 nd Episode	Any Episode	1st Episode	≥ 2 nd Episode	Any Episode	1st Episode	≥ 2 nd Episode	Any Episode
RSV	41/52 (79%)	3 (75%)	45/57 (79%)	53/83 (64%)	9 (53%)	63/102 (62%)	69/137 (50%)	14 (25%)	84/200 (42%)	75/160 (47%)	20 (23%)	96/253 (38%)*
Rhinovirus	12/47 (25%)	1 (25%)	14/52 (27%)	22/78 (28%)	6 (35%)	29/97 (30%)	39/132 (30%)	27 (47%)	68/195 (35%)	48/155 (31%)	42 (48%)	93/248 (38%)
Enteroviruses	2/47 (4%)	0 (0%)	2/52 (4%)	6/78 (8%)	1 (6%)	8/97 (8%)	19/132 (14%)	14 (25%)	34/195 (17%)	26/155 (17%)	22 (25%)	49/248 (20%)
hBoV	2/20 (10%)	0 (0%)	2/24 (8%)	7/48 (15%)	3/16 (19%)	10/65 (15%)	24/98 (25%)	8/53 (15%)	33/157 (21%)	27/117 (23%)	13/78 (17%)	41/201 (20%)
Adenovirus	2/25 (8%)	0 (0%)	2/30 (7%)	2/56 (4%)	1 (6%)	4/75 (5%)	7/110 (6%)	7 (12%)	16/167 (10%)	7/133 (5%)	14 (16%)	23/226 (10%)
PIV types 1-4	1/25 (4%)	0 (0%)	1/30 (3%)	4/56 (7%)	0 (0%)	5/75 (7%)	7/110 (6%)	3 (5%)	13/167 (8%)	8/133 (6%)	6/86 (7%)	17/225 (8%)
hMPV	2/25 (8%)	1 (25%)	3/30 (10%)	7/56 (13%)	2 (12%)	9/75 (12%)	7/110 (6%)	2 (4%)	10/167 (6%)	9/133 (7%)	2 (2%)	12/226 (5%)
Coronavirus	2/25 (8%)	1 (25%)	3/30 (10%)	3/56 (5%)	1 (6%)	4/75 (5%)	4/110 (4%)	1 (2%)	5/167 (3%)	4/132 (3%)	2 (2%)	6/225 (3%)
Flu A or B	0/25 (0%)	0 (0%)	0/30 (0%)	1/56 (2%)	0 (0%)	2/75 (3%)	2/110 (2%)	1 (2%)	4/167 (2%)	2/133 (2%)	3 (3%)	6/226 (3%)
≥ 2 viruses	11/52 (21%)	2 (50%)	15/57 (26%)	18/56 (32%)	6 (35%)	26/75 (35%)	42/137 (31%)	19 (33%)	65/200 (33%)	48/160 (30%)	34 (39%)	86/253 (34%)
≥ 1 viruses	49/52 (94%)	4 (100%)	54/57 (95%)	52/56 (94%)	16 (94%)	70/75 (93%)	127/137 (93%)	54 (95%)	187/200 (94%)	148/160 (93%)	81 (93%)	235/253 (93%)

Data expressed as positive findings (%) in subjects undergoing any viral detection method.

*Of all 259 study children aged < 3 years, the number of previous episodes was available in 253.

χ^2 test or Fisher exact test between 1st versus ≥ 2 nd episode groups in each age category: $P < 0.001$; $^{\dagger} P < 0.05$; $^{\ddagger} P < 0.01$.

Flu indicates Influenza virus; hBoV, human bocavirus; PIV, parainfluenza virus; RSV, respiratory syncytial virus.

predictors of outcome variables (viral etiology or atopic characteristics) in the logistic regression analyses. Because the interaction was not significant in any analysis, the interaction term was dropped from the final analysis. Results of logistic regression analyses are expressed as odds ratios (OR) with 95% confidence intervals (CI) and predicted probabilities. Total serum IgE level and blood eosinophil count were analyzed using generalized linear model with negative binomial distribution. The analysis procedure of these 2 variables was similar to dichotomous outcomes (first only age was used as predictor, then age, previous episode and interaction between them, and finally age and previous episodes), and their results are expressed as relative risk. The statistical analyses were carried out using SAS/STAT(r) software, Version 9.1.3 SP4 of the SAS System for Windows, SAS Institute Inc., Cary, NC.

RESULTS

Study Subjects

The formation of the data set for the analysis of viral etiology is shown in Figure 1. The median age of the 259 children

in the study was 1 year 2 months (range, 0–36 months). Atopic characteristics were available in 227 children. The median age of these children was 1 year 3 months (range, 3–36 months). About half of all eligible hospitalized children throughout the study period were included in the analysis (see Fig. 2, Supplemental Digital Content, <http://links.lww.com/A754>). Four children in the first-time wheezing group and 15 children in the recurrent wheezing group had inhaled corticosteroid medication on arrival.

Viral Etiology According to the Definition of Bronchiolitis

One or more viruses were found in 235 of 253 (93%) children. The etiology of bronchiolitis according to different clinical definitions (<6, <12, <24, and <36 months) is shown in Table 2. RSV was the most common viral agent in children aged <12 months, but rhinovirus was prominent in the age categories of <24 months or older. Viral etiology was also analyzed with consideration to whether children had a history or no history of a previous wheezing episode (Table 2). No differences were found in children aged <12 months. In children aged <24 months, rhinovirus was a more common causative agent of bronchiolitis in

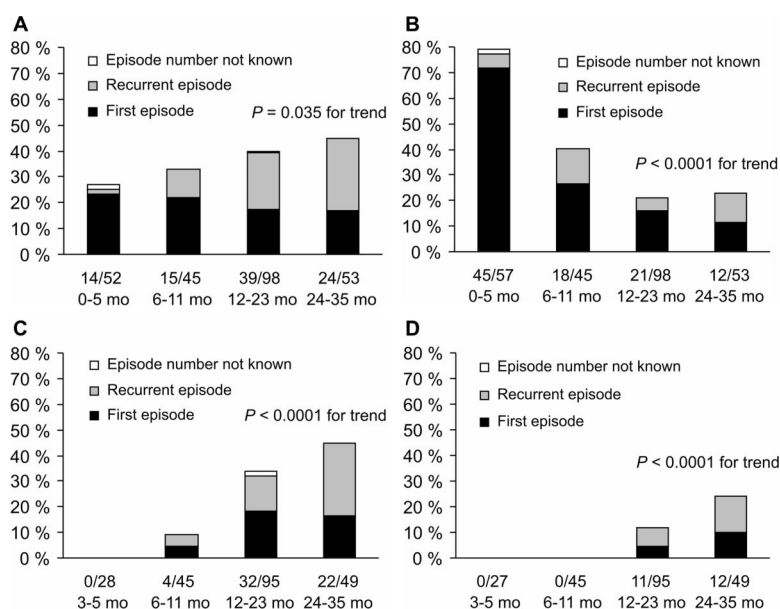


FIGURE 3. The percentage of children with rhinovirus infection (A) respiratory syncytial virus infection (B) any sensitization (C) and aeroallergen sensitization (D) of all tested children in each age category. P values for overall trends are presented. See Table 2 for more statistics.

TABLE 3. The Associations Between Viral and Atopic Characteristics and Age

Factor	Detection Rates With Increasing Age Years			
	Without Adjustments		Adjusted to Previous Wheezing Episode	
	OR or RR (95% CI)	P	OR or RR (95% CI)	P
Rhinovirus	1.43 (1.03–2.00)	0.035	1.26 (0.88–1.81)	0.20
Enterovirus	2.54 (1.65–3.90)	<0.0001	2.52 (1.61–3.94)	<0.0001
Respiratory syncytial virus	0.30 (0.20–0.46)	0.0001	0.34 (0.22–0.52)	<0.0001
Metapneumovirus	0.24 (0.076–0.78)	0.018	0.28 (0.084–0.91)	0.035
Any sensitization	3.34 (2.08–5.36)	<0.0001	3.22 (1.98–5.23)	<0.0001
Food sensitization	2.47 (1.56–3.90)	0.0001	2.44 (1.52–3.92)	0.0002
Aeroallergen sensitization	4.65 (2.32–9.31)	<0.0001	4.38 (2.15–8.91)	<0.0001
Atopic eczema	2.35 (1.33–4.16)	0.0034	2.30 (1.27–4.16)	0.0057
Positive modified API	3.65 (2.00–6.68)	<0.0001	3.11 (1.62–5.97)	0.0006
B-Eos, $\times 10^9/L$	1.70 (1.26–2.29)	0.0004	1.67 (1.23–2.27)	0.0011
Total IgE level, kU/L	4.97 (3.62–6.81)	<0.0001	4.17 (3.06–5.70)	<0.0001

Analyzed using regression analysis. RR used only for B-Eos and total IgE level. B-Eos indicates blood eosinophil count.

those with recurrent wheezing than in those experiencing their first episode (47% vs. 30%, $P = 0.018$). In children aged <24 months, RSV was less common in recurrent wheezers than in first-time wheezers (25% vs. 50%, $P = 0.0009$). Similar findings were also seen in the <36-month-old age group.

The associations between virus infection, age, and previous wheezing episode were studied further using regression analysis. Rhinovirus ($P = 0.035$, Fig. 3A) and enterovirus ($P < 0.0001$) detection rates increased and RSV ($P < 0.0001$, Fig. 3B) and hMPV ($P = 0.018$) detection rates decreased with increasing age (years) in univariable models (Table 3; data according to age categories of 0–5, 6–11, 12–23, and 24–35 months are shown in Table 4, Supplemental Digital Content, <http://links.lww.com/A752>). No associations were found between age and total or mixed virus detection rates. Previous wheezing episode had a stronger influence for encountering rhinovirus than age (in the model including the occurrence of previous wheezing episode and age, respectively, OR: 1.83; 95% CI: 1.03–3.25; $P = 0.040$; and OR: 1.26; 95% CI: 0.88–1.81; $P = 0.20$). Otherwise, the adjustment to previous wheezing episode did not modify viral detection rates (Table 3). No interaction was found between age and the occurrence of previous wheezing episode. Thus, children with bronchiolitis had higher risk for rhinovirus infection regardless of age if they had at least 1 previous wheezing episode. The predicted probabilities for rhinovirus infection at ages 6, 12, 24, and 36 months are shown in Table 5 (eg, it was 0.50 for a 24-month-old child with at least 1 previous wheezing episode).

Atopic Characteristics According to the Definition of Bronchiolitis

Atopic characteristics according to different clinical definitions of bronchiolitis are shown in Table 6. Eczema emerged first, followed by food and aeroallergen sensitizations and increased blood eosinophil count. Overall, 59% of children had parental allergies and 22% had parental asthma. Atopic characteristics were also analyzed with consideration of whether children had a history or no history of a previous wheezing episode. In children aged <12 months, the total serum IgE value was higher in recurrent wheezers than in first-time wheezers ($P = 0.016$). In children <24 months of age, many atopic characteristics were more pronounced

in recurrent wheezers than in first-time wheezers as seen in aeroallergen sensitization (13% vs. 4%, $P = 0.050$), positive modified API (14% vs. 4%, $P = 0.035$), blood eosinophil count (medians, 0.3 vs. $0.1 \times 10^9/L$, $P = 0.044$), and in total IgE (medians, 23 vs. 9.0 kU/L, $P = 0.0016$). Similar findings were also seen in the age category of <36 months (Table 6).

The associations between atopic characteristics, age, and previous wheezing episode were studied further using regression analysis. The prevalence of many atopic characteristics increased with increasing age years: any sensitization ($P < 0.0001$, Fig. 3C), food sensitization ($P = 0.0001$), aeroallergen sensitization ($P < 0.0001$, Fig. 3D), atopic eczema ($P = 0.0034$), positive modified API ($P < 0.0001$), blood eosinophil count ($\times 10^9/L$, $P = 0.0004$), and total IgE (kU/L, $P < 0.0001$) in univariable models (Table 3, data according to age categories of 0–5, 6–11, 12–23, and 24–35 months are shown in Table 7, Supplemental Digital Content, <http://links.lww.com/A753>). These associations persisted after adjusting to the occurrence of previous wheezing episode (Table 3). No interaction was found between age and the occurrence of previous wheezing episode. The risk of atopy increased by age in children with bronchiolitis, regardless of previous wheezing episodes. The predicted probabilities for various atopic characteristics at ages 6, 12, 24, and 36 months are shown in Table 5 (eg, the predicted probability for any sensitization was 0.42 for a 24-month-old child with at least 1 previous wheezing episode).

Recurrent wheezers tended to have more often parental asthma than first-time wheezers in the univariable model (OR: 1.88; 95% CI: 0.98–3.61; $P = 0.057$). This tendency did not persist when adjusted for child's age ($P = 0.12$). Similarly, parental allergy tended to be associated with child's previous wheezing status in the univariable model (OR: 1.64; 95% CI: 0.93–2.87; $P = 0.087$). This tendency persisted when adjusted for child's age (OR: 1.64; 95% CI: 0.91–2.95; $P = 0.098$).

DISCUSSION

About half of the recent clinical trials have used 12 months and half have used 24 months as an upper age limit of bronchiolitis, and half of the studies have focused on the first episode of wheezing. We show here that the viral etiology and the atopic

TABLE 5. The Predicted Probabilities For Viral And Atopic Characteristics In Children Suspected For Bronchiolitis At Exact Ages 6, 12, 24, and 36 Months

Factor	Wheezing Episode	Predicted Probabilities at Different Ages			
		6 Months	12 Months	24 Months	36 Months
Rhinovirus	1st	0.28	0.30	0.36	0.41
	≥2nd	0.42	0.44	0.50	0.56
Respiratory syncytial virus	1st	0.50	0.47	0.23	0.09
	≥2nd	0.47	0.34	0.15	0.06
Any sensitization	1st	0.09	0.15	0.37	0.65
	≥2nd	0.11	0.18	0.42	0.70
Food sensitization	1st	0.11	0.16	0.32	0.53
	≥2nd	0.12	0.17	0.33	0.55
Aeroallergen sensitization	1st	0.02	0.03	0.13	0.40
	≥2nd	0.03	0.05	0.19	0.51
Eczema	1st	0.35	0.38	0.43	0.48
	≥2nd	0.32	0.34	0.39	0.45
Atopic eczema	1st	0.05	0.08	0.16	0.31
	≥2nd	0.06	0.09	0.18	0.34
Positive modified API	1st	0.01	0.03	0.08	0.20
	≥2nd	0.07	0.12	0.31	0.58
B-Eos $\geq 0.40 \times 10^9/L$	1st	0.18	0.27	0.49	0.72
	≥2nd	0.14	0.21	0.42	0.65

Analyzed using logistic regression analysis.

TABLE 6. Atopic Characteristics According to Different Definitions of Bronchiolitis

Factor	<6 Months*				<12 Months				<24 Months				<36 Months			
	1st Episode		≥2nd Episode		1st Episode		≥2nd Episode		1st Episode		≥2nd Episode		1st Episode		≥2nd Episode	
	n = 25	n = 4	n = 30	n = 56	n = 17	n = 110	n = 75	n = 57	n = 173	n = 133	n = 87	n = 226 [†]				
Sensitization	0/24 (0%)	0 (0%)	0/29 (0%)	2/54 (4%)	2 (12%)	19/106 (18%)	4/74 (6%)	15/56 (27%)	36/170 (21%)	27/126 (21%)	29/85 (34%) [‡]	58/219 (26%)				
Food	0/24 (0%)	0 (0%)	0/29 (0%)	2/54 (4%)	2 (12%)	19/106 (18%)	4/74 (6%)	14/56 (25%)	35/170 (21%)	26/126 (21%)	24/85 (28%) [‡]	52/219 (24%)				
Aeroallergen	0/23 (0%)	0 (0%)	0/28 (0%)	0/54 (0%)	0 (0%)	4/105 (4%)	0/73 (0%)	7/56 (13%) [‡]	11/169 (7%)	9/125 (7%)	14/85 (16%) [‡]	23/218 (11%)				
Seasonal	0/23 (0%)	0 (0%)	0/28 (0%)	0/54 (0%)	0 (0%)	4/105 (4%)	0/73 (0%)	7/56 (13%) [‡]	11/169 (7%)	9/125 (7%)	14/85 (16%) [‡]	23/218 (11%)				
Perennial	0/24 (0%)	0 (0%)	0/29 (0%)	0/54 (0%)	0 (0%)	4/105 (4%)	0/74 (0%)	7/56 (13%) [‡]	11/170 (6%)	8/126 (6%)	10/85 (12%)	18/219 (8%)				
Eczema	8/26 (31%)	1 (25%)	9 (30%)	17 (30%)	6 (35%)	38/111 (34%)	24 (32%)	21/56 (38%)	61 (35%)	47/132 (36%)	35/85 (41%)	85/225 (38%)				
AE	0/24 (0%)	0 (0%)	0 (0%)	2/54 (4%)	1 (6%)	10/105 (10%)	3/74 (4%)	7/55 (13%)	18/168 (11%)	13/125 (10%)	13/84 (15%)	27/217 (12%)				
Par. allergy	13 (52%)	2 (50%)	15 (50%)	28 (49%)	12 (71%)	59 (54%)	41/75 (55%)	38/56 (68%)	101/171 (59%)	72 (54%)	56/85 (66%)	132/223 (59%)				
Par. asthma	4 (16%)	0 (0%)	4 (13%)	9 (16%)	4 (24%)	18 (16%)	14/75 (19%)	15/56 (27%)	23/171 (13%)	23 (17%)	24/85 (28%) [‡]	48/223 (22%)				
mAPI	0 (0%)	0 (0%)	0 (0%)	1 (2%) ^{***}	0 (0%)	5 (4%) ^{***}	2 (3%)	8/56 (14%) [‡]	15 (9%)	6 (4%) ^{***}	22/86 (26%) [‡]	30 (13%)				
B-Eos, × 10 ⁹ /L ^{††}	0.1 (0.0–0.2)	0.1 (0.1–0.1)	0.1 (0.0–0.2)	0.1 (0.0–0.2)	0.1 (0.0–0.2)	0.1 (0.0–0.3)	0.1 (0.0–0.2)	0.3 (0.1–0.4) [‡]	0.2 (0.0–0.4)	0.2 (0.0–0.4)	0.3 (0.1–0.5) [‡]	0.2 (0.1–0.4)				
S-IgE kU/L ^{‡‡}	3.0 (2.0–5.5)	4.0 (1.5–5.2)	3.0 (2.0–6.0)	6.0 (2.0–14)	20 (6.0–46) [‡]	9.0 (3.0–22)	7.0 (3.0–19)	23 (8.0–62) [‡]	12 (5.0–33)	12 (4.0–42)	25 (11–105) [‡]	18 (6.0–56)				

Data expressed as number of cases (%) or medians (interquartile range).

[‡]In the 33 children aged <3 months, no atopic characteristics were available.[†]Of all 227 children aged 3–35 months, the number of previous episodes was available in 220.[‡]χ² test, Fisher exact test, or Mann-Whitney U test between 1st versus ≥2nd episode groups in each age category: [‡]P < 0.05; [†]P < 0.01; [‡]P < 0.0001.^{***}Children with prolonged wheezing symptoms.^{††}Data available: aged 3–5 months (n = 30); 3–11 months (n = 74); 3–23 months (n = 172); 3–35 months (n = 223).^{‡‡}Data available: age 3–5 months (n = 29); 3–11 months (n = 72); 3–23 months (n = 165); 3–35 months (n = 212).

AE indicates atopic eczema; Par., parental; API, modified asthma predictive index; mAPI, positive modified API; B-Eos, blood eosinophil count; IgE, immunoglobulin E; S-IgE, total IgE.

characteristics are highly affected by the definition of bronchiolitis used. Upper age limits of 12 and 24 months differentiated whether RSV dominated, or whether its prevalence was comparable to that of rhinovirus. Together with the increased occurrence of rhinovirus, the prevalence of many atopic characteristics increased with age. Importantly, a history of previous wheezing influenced the emergence of virus and of atopy-related risk factor profiles for recurrent wheezing and asthma in the age categories of <24 months or older.

Early atopic sensitization, especially to perennial/aeroallergens, is a well-documented risk factor for asthma, and the persistent form of childhood asthma is mainly atopic.^{15,18,19,22,23} The rate at which the infant immune system attains adult-equivalent competence and capability to clear viral infections seem to be inversely related to the risk of atopy.^{18,26} Depending on the age cut-off for bronchiolitis, the overall prevalence of any sensitization ranged between 0% and 26%, that of aeroallergen sensitization ranged between 0% and 11%, and that of atopic eczema ranged between 0% and 12%. Thus, the proportion of atopic, asthma-prone children was dependent on the age criterion used. These atopic characteristics were also slightly more pronounced in children with at least 1 previous wheezing episode. Similar changes were seen in other atopy-related factors such as blood eosinophil count (predictor of reactive airway disease) and in modified API (effective predictor of school-age asthma).^{19,20,27,28} Noteworthy, revised algorithms to define young asthma prone children have also been suggested.^{29,30} We think that the diagnosis of bronchiolitis should include as homogenous patient population as possible (ie, without any preexisting inflammatory state). Atopic inflammation in cases of bronchiolitis is likely to influence responses to treatment and long-term prognosis, and thereby confound clinical trials.

Long-term prospective studies have linked bronchiolitis to development of physician-diagnosed asthma/abnormal pulmonary function in children up to 19 years of age.^{14,18,31–33} RSV-induced bronchiolitis has been associated with current asthma in children up to 13 years of age.^{31,32} Kotaniemi-Syrjänen et al were the first to recognize rhinovirus-associated early wheezing as a risk factor for school-age asthma.¹⁴ Three subsequent studies have confirmed rhinovirus as an important risk factor for recurrent wheezing among young wheezing children,^{15,17,18} and the risk seems to be higher than the risk associated with RSV infection.^{14,15,17} Although children susceptible to rhinovirus-associated early wheezing have had pronounced atopic characteristics,¹⁶ they have been recognized as an independent risk group.^{14,15,17,18} In contrast to RSV,^{34–36} initial data suggest that rhinovirus may be a potential determinant for response to prednisolone treatment in young wheezing children.^{16,17} These findings emphasize the importance of searching for rhinovirus in addition to RSV as a potential etiologic agent of bronchiolitis. The predictive role of other respiratory viruses, including recently found human metapneumovirus and human bocavirus, has not yet been assessed.

The US and UK guidelines suggest that the diagnosis of bronchiolitis in infants <24 months of age is a clinical diagnosis and does not require diagnostic testing.^{6,7} The definition does not include viral etiology, number of previous wheezing episodes, or atopic status. For example, in young wheezing children, the risk for asthma or recurrent wheezing is increased 4- to 26-fold by rhinovirus infection (5-fold compared with RSV), 4-fold by maternal asthma, 3- to 4-fold by atopy, and 2- to 3-fold by the presence of eczema.^{14,15,17,22,31,33} Thus, bronchiolitis defined by current guidelines may include several different diseases with common clinical manifestations, but different responses to treatment and different prognoses.^{37,38}

Our data have limitations. We included only hospitalized children. In infants <3 months of age (33 children), the data on atopic characteristics were not systematically collected and viral diagnostics focused only on RSV and rhinovirus, but allergies, especially those to aeroallergens, and other viruses than RSV and rhinovirus are very rare in this age group. Viral infections other than RSV may be slightly underestimated. We studied only half of the wheezing patients during the study period, but children were steadily recruited over the study period, arguing against a selection bias (see Fig. 2, Supplemental Digital Content, <http://links.lww.com/A754>).

We conclude that 2 clinical factors, age and the number of previous wheezing episodes, are linked to inflammatory (atopy-related factors) and virologic risk factors of asthma (rhinovirus-associated disease) within a group of children suspected of having bronchiolitis. Inclusion of asthma-prone children in bronchiolitis is likely to confound clinical practice and trials. The clinical definition should include only children <24 months of age with the first episode of wheezing. This definition characterizes bronchiolitis better as a disease induced by respiratory viral infection without prominent asthma-like airway inflammation. Another option would be to limit the clinical definition of bronchiolitis to the first year of life (without previous episodes), where rhinovirus-associated wheezing, atopy, and asthma are less likely. These definitions (or stricter definitions; eg, excluding those with atopic eczema or food allergy) should be put to the test of prospective follow-up to determine the predictive value of identifying children who have a low risk for developing asthma. The challenge for clinical trials, however, is to identify young children with high risk for asthma early and provide them with effective treatment. To accomplish this, a subgroup of young wheezing children, even of first-time wheezers, needs probably to be defined by viral etiology (namely, rhinovirus) and/or atopic status.

ACKNOWLEDGMENT

The authors thank Tarja Ikävalko for assistance.

REFERENCES

1. Hazinski TA. Infectious bronchiolitis. In: Rudolph CD, Rudolph AM, eds. *Rudolph's Pediatrics*. New York, NY: McGraw-Hill; 2003:1984–1985.
2. Goodman D. Bronchiolitis. In: Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson Textbook of Pediatrics*. 17th ed. Philadelphia, PA: W.B. Saunders Company; 2004:1415–1417.
3. Hall CB, McBride JT. Bronchiolitis. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases*. 6th ed. Philadelphia, PA: Elsevier Churchill Livingstone; 2005:812–818.
4. Wohl ME. Bronchiolitis. In: Chernick V, Boat TF, Wilmott RW, et al, eds. *Kendig's Disorders of the Respiratory Tract in Children*. 7th ed. Philadelphia, PA: Saunders Elsevier; 2006:423–432.
5. Smyth RL, Openshaw PJ. Bronchiolitis. *Lancet*. 2006;368:312–322.
6. American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis. Diagnosis and management of bronchiolitis. *Pediatrics*. 2006;118:1774–1793.
7. Scottish Intercollegiate Guidelines Network. Bronchiolitis in children. A national clinical guideline. November 2006. Available at: <http://www.sign.ac.uk/pdf/sign91.pdf>.
8. Christakis DA, Cowan CA, Garrison MM, et al. Variation in inpatient diagnostic testing and management of bronchiolitis. *Pediatrics*. 2005;115:878–884.
9. Bordley WC, Viswanathan M, King VJ, et al. Diagnosis and testing in bronchiolitis: a systematic review. *Arch Pediatr Adolesc Med*. 2004;158:119–126.
10. Jartti T, Lehtinen P, Vuorinen T, et al. Respiratory picornaviruses and respiratory syncytial virus as causative agents of acute expiratory wheezing in children. *Emerg Infect Dis*. 2004;10:1095–1101.
11. Allander T, Jartti T, Gupta S, et al. Human bocavirus and acute wheezing in children. *Clin Infect Dis*. 2007;44:904–910.

12. Rakes GP, Arruda E, Ingram JM, et al. Rhinovirus and respiratory syncytial virus in wheezing children requiring emergency care. IgE and eosinophil analyses. *Am J Respir Crit Care Med*. 1999;159:785–790.
13. Papadopoulos NG, Moustaki M, Tsolia M, et al. Association of rhinovirus infection with increased disease severity in acute bronchiolitis. *Am J Respir Crit Care Med*. 2002;165:1285–1289.
14. Kotaniemi-Syrjänen A, Vainionpää R, Reijonen TM, et al. Rhinovirus-induced wheezing in infancy—the first sign of childhood asthma? *J Allergy Clin Immunol*. 2003;111:66–71.
15. Jackson DJ, Gangnon RE, Evans MD, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med*. 2008;178:667–672.
16. Jartti T, Lehtinen P, Vanto T, et al. Evaluation of the efficacy of prednisolone in early wheezing induced by rhinovirus or respiratory syncytial virus. *Pediatr Infect Dis J*. 2006;25:482–488.
17. Lehtinen P, Ruohola A, Vanto T, et al. Prednisolone reduces recurrent wheezing after a first wheezing episode associated with rhinovirus infection or eczema. *J Allergy Clin Immunol*. 2007;119:570–575.
18. Kusel MM, de Klerk NH, Keadze T, et al. Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. *J Allergy Clin Immunol*. 2007;119:1105–1111.
19. Castro-Rodriguez JA, Holberg CJ, Wright AL, et al. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med*. 2000;162:1403–1406.
20. National Heart, Lung and Blood Institute. National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Full Report 2007. Available at: <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf>.
21. Mansbach JM, McAdam AJ, Clark S, et al. Prospective multicenter study of the viral etiology of bronchiolitis in the emergency department. *Acad Emerg Med*. 2008;15:111–118.
22. Martinez FD, Wright AL, Taussig LM, et al. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med*. 1995;332:133–138.
23. Illi S, von Mutius E, Lau S, et al. Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. *Lancet*. 2006;368:763–770.
24. Heymann PW, Carper HT, Murphy DD, et al. Viral infections in relation to age, atopy, and season of admission among children hospitalized for wheezing. *J Allergy Clin Immunol*. 2004;114:239–247.
25. Murray CS, Poletti G, Keadze T, et al. A Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. *Thorax*. 2006;61:376–382.
26. Copenhaver CC, Gern JE, Li Z, et al. Cytokine response patterns, exposure to viruses, and respiratory infections in the first year of life. *Am J Respir Crit Care Med*. 2004;170:175–180.
27. Ehlenfeld DR, Cameron K, Welliver RC. Eosinophilia at the time of respiratory syncytial virus bronchiolitis predicts childhood reactive airway disease. *Pediatrics*. 2000;105:79–83.
28. Karakoc F, Remes ST, Martinez FD, et al. The association between persistent eosinophilia and asthma in childhood is independent of atopic status. *Clin Exp Allergy*. 2002;32:51–56.
29. Guilbert TW, Morgan WJ, Zeiger RS, et al. Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. *J Allergy Clin Immunol*. 2004;114:1282–1287.
30. Piippo-Savolainen E, Korppi M. Wheezy babies—wheezy adults? Review on long-term outcome until adulthood after early childhood wheezing. *Acta Paediatr*. 2008;97:5–11.
31. Stein RT, Sherrill D, Morgan WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet*. 1999;354:541–545.
32. Piippo-Savolainen E, Remes S, Kannisto S, et al. Asthma and lung function 20 years after wheezing in infancy: results from a prospective follow-up study. *Arch Pediatr Adolesc Med*. 2004;158:1070–1076.
33. Sigurs N, Gustafsson PM, Bjarnason R, et al. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med*. 2005;171:137–141.
34. Roosevelt G, Sheehan K, Grupp Phelan J, et al. Dexamethasone in bronchiolitis: a randomised controlled trial. *Lancet*. 1996;348:292–295.
35. De Boeck K, van der Aa N, Van Lierde S, et al. Respiratory syncytial virus bronchiolitis: a double-blind dexamethasone efficacy study. *J Pediatr*. 1997;131:919–921.
36. Bülow SM, Nir M, Levin E, et al. Prednisolone treatment of respiratory syncytial virus infection: a randomized controlled trial of 147 infants. *Pediatrics*. 1999;104:e77.
37. Everard ML. The relationships between respiratory syncytial virus infections and the development of wheezing and asthma in children. *Curr Opin Allergy Clin Immunol*. 2006;6:56–61.
38. Everard ML. Current pharmacological treatments for bronchiolitis are useless. The case for the pro's. *Paediatr Respir Rev*. 2006;7:598–100.