RESPIRATORY INFECTION

Seasonality of long term wheezing following respiratory syncytial virus lower respiratory tract infection

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Background: It is well known that respiratory syncytial virus (RSV) lower respiratory tract infection (LRTI) is associated with subsequent wheezing episodes, but the precise natural course of wheezing following RSV LRTI is not known. This study aimed to determine the continuous development of wheezing following RSV LRTI in children up to the age of 3 years.
Methods: A prospective cohort study was performed in 140 hospitalised infants with RSV LRTI. Continuous follow up data were obtained with a unique log in which parents noted daily respiratory symptoms.
Results: A marked decrease in wheezing was seen during the first year of follow up. The burden of wheezing following RSV LRTI was observed during the winter season. Signs of airflow limitation during RSV LRTI were strongly associated with wheezing during the follow up period. Total and specific serum immunoglobulin E levels, patient eczema, and parental history of atopy were not associated with wheezing.
Conclusions: Airway morbidity following RSV LRTI has a seasonal pattern, which suggests that viral upper respiratory tract infections are the predominant trigger for wheezing following RSV LRTI. There is a significant decrease in airway symptoms during the first 12 months after admission to hospital. Simple clinical variables, but not allergic risk factors, can predict the development of wheezing following RSV LRTI.

Recurrent episodes of wheezing in early childhood following respiratory syncytial virus (RSV) bronchiolitis have well been documented and occur in 42–71% of cases.[1] It is thought that these wheezing episodes are triggered by viral upper respiratory tract infections (URTI).[2] Wheezing following RSV lower respiratory tract infections (LRTI) appears to be independent of atopy,[3] although an association has been found with allergy.[2 4–8] Follow up studies have shown bronchial hyperresponsiveness 4–8 years after admission to hospital with RSV bronchiolitis.[2 8 9] Although it is clear that RSV LRTI is associated with subsequent wheezing, no continuous data on respiratory symptoms and long term airway morbidity following RSV LRTI are available. Infants who go on to have wheezing episodes do so within 12–24 months after the first episode of RSV LRTI.[2] Data in the literature show that wheezing following RSV LRTI is transient.[3 8] The Tucson birth cohort study shows that wheezing at age 6 years is no longer associated with a history of RSV LRTI before the age of 3 years.[8] More precise information on the development of wheezing following RSV LRTI is, however, unavailable.

Questionnaires have been used to estimate the relation between RSV LRTI and subsequent wheezing.[3 5 6 8 10] It is difficult to assess how accurate a questionnaire is in providing data on airway symptoms following RSV LRTI. In particular, recall bias by parents might interfere with accuracy. In addition, lung function measurements have been performed to address pulmonary function following RSV LRTI,[2 8 11 12] but it is not known how well lung function relates to respiratory symptoms.[13] Moreover, lung function is measured from the age of 6 years while airway symptoms have already substantially decreased by that time.

To overcome the limitations of currently used follow up methods, we performed a prospective long term log based study to demonstrate the continuous development over time of airway morbidity following RSV LRTI. We hypothesised that the severity of wheezing following RSV LRTI decreases over 3 years after admission to hospital. In addition, we hypothesised that wheezing following RSV LRTI has a seasonal pattern.

METHODS

Study population

One hundred and forty children at six hospitals in the Netherlands were prospectively studied during two winter epidemics. Two hospitals had a paediatric intensive care unit. Inclusion criteria were hospital admission, lower respiratory tract symptoms, age <13 months, and positive immunofluorescence for RSV in epithelial cells from nasopharyngeal secretions. There were no standard criteria used for admission to hospital. Symptoms of LRTI[8] were severe chest cough, wheezing, hoarseness, stridor, shortness of breath, cyanosis and apnoea. Infants with wheezing respiration before RSV infection were excluded. A history of premature birth and the presence of physical sounds of airflow limitation on admission (expiratory wheeze or prolonged expiration) were recorded during hospitalisation. The medical ethical committee approved the study in all participating centres. Parents of subjects gave written informed consent.

Log

Starting 3 weeks after discharge from hospital, parents recorded respiratory symptoms, airway medication, and doctors' visits on a daily basis in a log until the age of 3 years (fig 1). Parents were instructed how to use the log by one of the investigators (LB). Daily respiratory symptoms recorded included ''runny nose'', ''coughing'', and ''wheezing''. The absence of respiratory symptoms was also noted. To improve compliance, telephone contact was maintained every 3 months during the entire follow up period. The completed log was returned to the investigators by mail every 3 months. Respiratory symptoms were analysed per quarter. Since infants were not all hospitalised on the same date, the

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number of wheezing days for the first quarter was corrected according to the number of missing days during the first quarter. To quantify respiratory symptoms following RSV LRTI, the numbers of days of wheezing were counted and classified as 0, 1–5, or >5 wheezing days/quarter. The main outcome variable was the percentage of children with >5 wheezing days/quarter. In addition, the number of wheezing episodes experienced by each child was counted.[14] A disease episode was defined as the presence of respiratory symptoms for two or more consecutive days. Children were considered lost to follow up if more than two logs (two quarters) were not returned.

Questionnaire

At the end of the follow up period (age 3 years) an extended Dutch version of the standardised questionnaire of the British Medical Council and the Dutch version of the European Community Respiratory Health Survey questionnaire were used to obtain data on respiratory symptoms, allergy, parental smoking habits, medication, and allergy symptoms among first degree family members.[15 16] Parental history of atopy was defined as the presence of asthma, eczema, or hay fever in at least one parent.

Serum immunoglobulin E

At the end of the follow up period (age 3 years) total IgE and specific IgE against a panel of common inhalation (house dust mite *Dermatophagoides farinae*, cat dander, dog dander, mixed grass pollen) and food allergens (cow's milk, egg white, soya bean, wheat, peanut) were measured in serum by CAP system FEIA (Pharmacia Diagnostics, Uppsala, Sweden). The geometric mean (SD) of a large normal control population measured at our laboratory at age 3 years is 8.0 (32) kU/l.

Statistical analysis

The numbers of days and episodes of wheezing are expressed as median values. Serum IgE is expressed as geometric mean. Because there is no gold standard for atopic status, four atopic parameters were distinguished: patient eczema, parental history of atopy, total serum IgE, and allergen specific IgE. Differences in sex, prematurity, requirement of mechanical ventilation, parental history of atopy between infants with and without signs of airflow limitation during the initial RSV LRTI were analysed using a χ^2 test. Differences in age, number of episodes of wheezing or coughing, and number of days of coughing or wheezing between infants with and without signs of airflow limitation during the initial RSV LRTI were analysed using the Mann-Whitney U test.

Imputation of data for missing logs was performed to allow for statistical analysis of incomplete data. Missing values were replaced with the mean of the previous and subsequent values. When values at the end of the third follow up year were missing, these missing values were replaced by the mean of the previous value and the value of the same quarter during the previous year. Thus, missing values were replaced by values that were completely dependent from observations of the same child. To estimate the potential effect of imputation on the model, we compared our model with the

1999
Fourth quarter
WEEK 40
(Sept 27 - Oct 3)

When your child had no respiratory symptoms at all during this week, then this is noted at the bottom of the page.

When symptoms have been observed, then symptom scores for every day of the week have to be completed.

0 = not
1 = mild
2 = moderate
3 = severe

	Runny nose (0-3)	Cough (0-3)	Wheeze (0-3)	Short of breath (0-3)	Doctor's visit (y/n)
Monday					
Tuesday					
Wednesday					
Thursday					
Friday					
Saturday					
Sunday					

☐ There were no airway symptoms this week (mark here)

Medication use
Note dose and frequency

Figure 1 Example of a log page (English translation). One log page is used to note daily respiratory symptoms during 1 week. The presence or absence of ''runny nose'', ''cough'', and ''wheeze'' were noted. Severity of symptoms and presence or absence of respiratory distress were not analysed.

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model that would result from an alternative approach for imputation. Using this alternative imputation strategy, missing values were imputed by the mean of non-missing values of other children during the same quarter of the same follow up year. Thus, with the alternative approach missing values were replaced by values that were completely independent of observations from the same child. Following imputation, analysis of log derived follow up data was performed using general linear model (GLM) repeated measures analysis. We analysed the simple predictive value of relevant parameters for recurrent wheezing, as well as the predictive value in complex models with more than one predictor. Post hoc Bonferroni correction was performed. All statistics was performed with Statistical Package for the Social Sciences (SPSS), version 10.0. Significance was defined by a two sided α level of 0.05.

RESULTS

Subject characteristics

One hundred and forty children (77 boys) of median age 2 months with RSV LRTI were enrolled (table 1). Forty one patients (29%) were born prematurely (median 34 weeks, range 25–36 weeks). Twenty nine subjects (21%) needed mechanical ventilation. Four patients (3%) had cardiac disease and two (2%) had chronic lung disease. Signs of airflow limitation were noted in 84 (60%). None of the patients received ribavirin or systemic corticosteroids during their initial RSV LRTI. All patients survived RSV LRTI.

Wheezing following RSV LRTI

Complete follow up data were available for 106 children; a single log was missing from 19 children, two logs were missing from seven children, and eight children were lost during the follow up period, of whom one had died 3 months after RSV LRTI from meningococcal disease. Wheezing days and episodes per quarter are shown in figs 2 and 3. The results were compared using two different imputation models. Differences between both models were limited and therefore we conclude that imputation of missing values had little effect on our results.

Wheezing following RSV LRTI was characterised by two novel findings. Firstly, a sharp decrease of >50% in wheezing was observed during the first year of follow up ($p<0.001$). In particular, the percentage of children with severe wheezing (>5 days/quarter) decreased. Secondly, an increase in respiratory wheeze occurred during the winter periods in all three study years ($p<0.001$).

The clinical follow up data in the logs and questionnaires were compared (table 2). An underestimation of "ever wheeze" was found in the questionnaires compared with the log registrations, particularly for children who only wheezed during the first year of follow up. Another major finding which was not anticipated was the overestimation of respiratory wheeze by parents during the previous 12 months in the questionnaires compared with the log registrations.

Table 1 Clinical characteristics of infants admitted to hospital with RSV LRTI aged <13 months (n = 140)

Variable	
Boys	77 (55%)
Premature	41 (29%)
Median (range) age (weeks)	7 (0–52)
Exclusively breast fed during infancy	42 (30%)
On mechanical ventilation during RSV	29 (21%)
Signs of airflow limitation during RSV LRTI	84 (60%)
Parental history of atopy	62 (44%)
Smoke exposure before or after RSV LRTI	29 (21%)

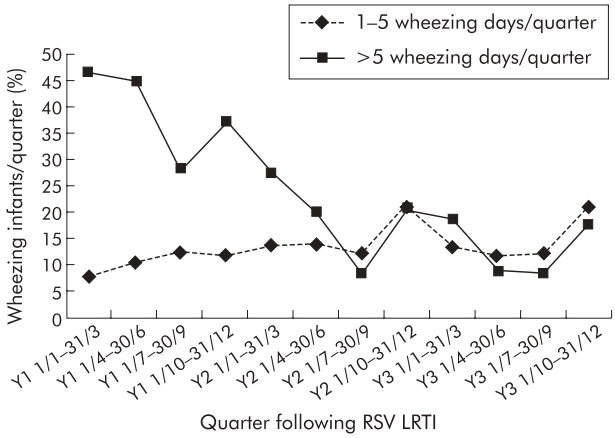


Figure 2 Number of days with respiratory wheeze per quarter following RSV LRTI. Parents recorded daily respiratory symptoms which were analysed per quarter. Infrequent wheeze (1–5 days/quarter) and frequent wheeze (>5 days/quarter) are distinguished.

We analysed the predictive value of relevant clinical parameters for wheezing following RSV LRTI. Sex, age at onset of RSV LRTI, mechanical ventilation, or neonatal breast feeding were not related to wheezing during the follow up period. In addition, we did not find a relation between environmental tobacco smoke exposure before or after inclusion in the study and wheezing during follow up. Signs of airflow limitation during RSV LRTI (expiratory wheeze or prolonged expiration) were significantly associated with wheezing during the follow up period ($p<0.001$, fig 4). Baseline characteristics of infants with and without signs of airflow limitation during RSV LRTI were similar (data not shown).

Atopic parameters in relation to wheeze during follow up

We analysed the association between patient eczema or parental history of atopy and wheezing during the follow up period. No significant association was found between eczema or parental history of atopy and the total number of episodes/days of wheezing during the whole follow up period and for

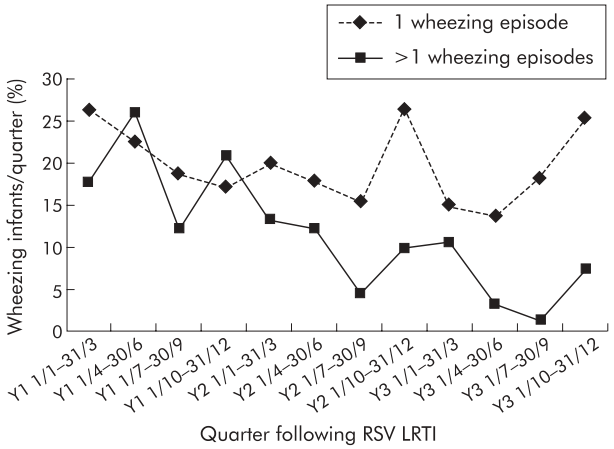


Figure 3 Number of episodes of respiratory wheeze per quarter following RSV LRTI. An episode is defined as respiratory symptoms for more than 1 day. Infants with 1 and >1 wheezing episodes per quarter are distinguished.

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Table 2 Comparison between log derived and questionnaire derived follow up data

			Discordance	
	Questionnaire	Log	Quest+/log−	Quest−/log+
Ever wheezing	79 (60%)	110 (83%)	1 (1%)	32 (24%)
Wheezing in previous 12 months	56 (42%)	47 (36%)	23 (17%)	14 (11%)

Log derived data were provided by parents who recorded daily respiratory symptoms in a log. These were compared with results from a standardised questionnaire taken at age 3 years (n = 132). Comparisons were made between logs and questionnaires for ''ever wheezing following RSV LRTI'' and ''wheezing during the past 12 months''. Data are shown as number (%).

each follow up year separately (not shown). Serum IgE was determined in the 126 infants who completed the study. In six infants no blood was obtained. Mean serum IgE was 11 (95% CI 9–15) kU/l. Infants were defined as having high IgE (>25 kU/l, highest quarter) or low IgE (⩽25 kU/l). The association between total or allergen specific IgE and wheezing during the follow up period was analysed (not shown). No significant association was found between total or allergen specific IgE and the total number of episodes/days of wheezing during the whole follow up period or for each follow up year separately. We tested whether atopic parameters were predictive of wheezing during follow up when analysed together in one GLM, but no significant relation was found.

To evaluate whether serum IgE or parental history were appropriate indicators of atopic status we analysed the association between total and allergen specific serum IgE, parental history of atopy, and eczema. Patient eczema was associated with parental history of atopy ($p<0.01$) but not with total or allergen specific serum IgE. Parental history of atopy appeared to be an appropriate indicator of atopy in infants but was not related to airway morbidity following RSV LRTI.

DISCUSSION

To our knowledge, this is the first long term log based longitudinal study in a large cohort of infants admitted to hospital with RSV LRTI. Recurrent wheezing markedly decreased during the first 3 years following hospitalisation with RSV LRTI. An increase in wheezing during the winter season has not previously been reported. Signs of airflow limitation during RSV LRTI were predictive of recurrent wheeze during follow up. Atopic characteristics such as parental history of atopy, specific IgE, or patient eczema were not related to recurrent wheeze following RSV LRTI.

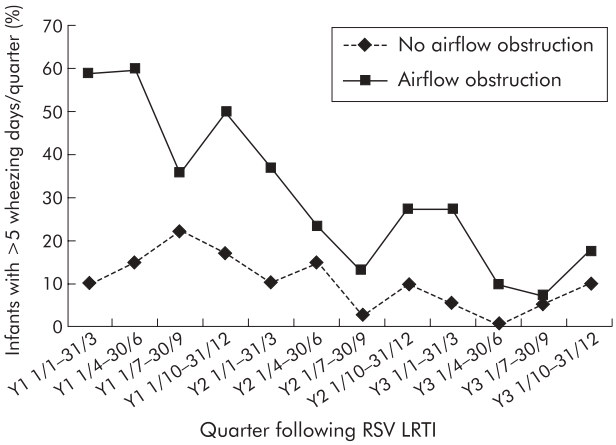


Figure 4 Days of respiratory wheeze following RSV LRTI in relation to airflow obstruction during RSV LRTI. Parents recorded daily respiratory symptoms which were analysed per quarter. The proportion of infants with frequent wheeze (>5 days/quarter) are shown. Patients with and without signs of airflow limitation are distinguished ($p<0.001$).

Previous studies have shown that wheezing following RSV LRTI is transient.[2 3 5 8] It has been reported that wheezing following RSV LRTI usually subsides by the age of 4–6 years. The rapid fall in the number of wheezing days during the first year of follow up in this study has not previously been reported. It is unlikely that this decrease in airway symptoms reflects decreased adherence to the log for two reasons: firstly, fig 1 shows that parents were instructed to fill out the log even when there were no symptoms, and secondly, the seasonal increase in reported symptoms suggests adequate adherence. Previous studies have used repeated questionnaires to measure airway morbidity following RSV LRTI. In these studies questionnaires are used for the first time 1–3 years after the RSV LRTI. These studies have therefore been unable to demonstrate a strong continuous decrease in wheezing during the first year of follow up.

The seasonal pattern of wheezing following RSV LRTI may provide a clue to triggers of wheezing episodes. Wheezing episodes following RSV LRTI are thought to be the result of increased exposure to respiratory viruses during the autumn and winter seasons.[2] This would be in agreement with a community based longitudinal study (not focusing on RSV) which found that viral URTI occur during wheezing episodes in asthmatic school children.[17] The seasonal increase in the prevalence of viral infections in autumn and winter coincides with the seasonal increase in house dust mite exposure[18] and, consequently, bronchial hyperresponsiveness. We cannot therefore exclude the possibility that differences in allergen exposure contribute to the seasonality of wheezing following RSV LRTI.[19]

The results of this study may be of direct clinical use. Although indications for admission to hospital may not be uniform throughout the world, infants admitted with RSV LRTI form a recognisable group of patients for paediatricians. To date, it is difficult to estimate expected long term airway morbidity following RSV LRTI for individual infants. An increased risk of recurrent wheeze exists until school age, which is probably independent of atopic factors.[2 8] This study provides three additional clinically useful tools to estimate more precisely long term airway morbidity following RSV LRTI—the marked decrease in wheezing during the first year of follow up following RSV LRTI, the seasonal pattern, and the predictive value of signs of airflow limitation during RSV LRTI for subsequent wheeze.

The relationship between RSV LRTI and the development of allergy is intriguing. Sigurs *et al* showed an increased risk for allergy in hospitalised patients with RSV at ages 3 and 7 years compared with matched controls,[4 20] but other studies have not been in agreement with these findings.[2 3 7 10 12 21] Most convincingly, Stein and colleagues showed in a birth cohort study that RSV LRTI before the age of 4 years is not associated with subsequent allergic sensitisation, irrespective of disease severity.[8] Our study was not designed to analyse

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the association between RSV LRTI and allergy. However, our data indicate a limited role for atopy in the pathogenesis of wheezing following RSV LRTI. The absence of a relationship between a family history of atopy, patient eczema, or serum IgE at age 3 years on the one hand and wheezing following RSV LRTI on the other hand shows that (the larger part of) wheezing following RSV LRTI cannot be explained by atopy. Thus, in line with previous studies, we conclude that wheezing following RSV LRTI is not caused by allergy induction.[3]

We compared the respiratory symptoms derived from questionnaires with log derived data and found a discrepancy in reported wheezing. As expected, some parents noted wheezing in the log but did not confirm this in the questionnaire. This could be explained by parents forgetting symptoms (recall bias). We had not anticipated that a substantial proportion of parents would mention in the questionnaire that their child had had wheezing during the past 12 months but would not note this in the log. This too could be explained by recall bias, with parents forgetting that the last episode of wheezing occurred more than 12 months ago. We did not attempt to validate log data. However, in the absence of a gold standard, log derived data may provide an accurate tool for analysing airway morbidity following RSV LRTI.

This log based longitudinal study is the first report on long term daily respiratory symptoms in infants admitted to hospital with RSV LRTI. The results show that airway morbidity following RSV LRTI markedly decreases during the first year after hospitalisation. The seasonal pattern of wheezing following RSV LRTI is not only of direct clinical use, but also suggests that viral URTI are the predominant trigger for wheezing following RSV LRTI. No relationship was found between wheezing following RSV LRTI and atopy. Clinical variables during RSV LRTI such as signs of airflow limitation can be used to predict subsequent wheezing.

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