

BRIEF REPORT

Respiratory outcome of infants with or without documented wheezing during bronchiolitis

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ABSTRACT

The presence of wheezing during bronchiolitis may be associated with recurrent episodes of wheezing and asthma.

The objectives were to assess the inter-observer agreement of wheezing recorded by a digital stethoscope during a bronchiolitis and to assess whether the identification of wheezing was associated with an increased incidence of recurrent wheezing at three years and asthma at six years.

Two hundred and seventy infants (<2 years) with bronchiolitis were included, while follow-up data at 3 and 6 years were available for 144 (33 had definite wheezing during bronchiolitis: 23%) and 112 (28 had definite wheezing during their bronchiolitis: 25%) children, respectively.

The overall agreement percentage between the two raters for wheezing (249 infants were available for the two raters) was 71%, with a free-marginal kappa of 0.42 (95% CI [0.31, 0.53]), which is a moderate agreement. The prevalence of definite (two observers) wheezing was 58/270 (21%) that was associated with tobacco exposure and, at 3 years of age, with more respiratory episodes and asthma medications while it was not associated with asthma at 6 years.

In conclusion, the agreement over wheezing during bronchiolitis is moderate, but it ought to be diagnosed since it is associated with recurrent respiratory episodes (wheezing).

IMPACT STATEMENT

The formal identification of wheezing during a bronchiolitis episode is associated with recurrent episodes of respiratory episodes.

INTRODUCTION

Acute viral bronchiolitis is one of the leading causes of lower respiratory tract infection and hospitalization in the first 12-24 months of life (1, 2). Studies report that 17-60% of children with bronchiolitis might develop recurrent wheezing in the years following their initial admission to hospital (2). Severe bronchiolitis (*i.e.*, bronchiolitis requiring hospital admission) has been associated with an increased risk of asthma, with 30%-50% developing asthma by 5 years of age (3).

Four phenotypes of bronchiolitis have been identified in a multicenter study (4). Overall, in this study 64% of the infants exhibited wheezing, and the presence or absence of wheezing was a variable that allowed for the differentiation of the

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KEY WORDS

Wheezing; bronchiolitis; asthma; interobserver agreement; auscultation.

phenotypes (4). In another multicenter study, wheezing was associated with the use of albuterol among infants hospitalized for bronchiolitis (5).

Thus, the formal identification of wheezing during bronchiolitis may have both immediate and long-term consequences, and one may wonder whether the presence of wheezing may increase the risk of recurrent wheezing within the first 3 years of life and the risk of asthma at 6 years.

This issue deserves to be evaluated because the identification of wheezing requires auscultation skills, which not all non-physician providers may have (6, 7).

The objectives of our study were to assess the inter-observer agreement of respiratory sounds recorded by a digital stethoscope and to assess whether the identification of wheezing was associated with an increased incidence of recurrent wheezing at three years of age and asthma at six years of age.

METHODS

This trial (WheezOut: ClinicalTrials.gov Identifier: NCT04811248) is the follow-up study of the WheezSmart trial (ClinicalTrials.gov Identifier: NCT02897960) devoted to recording respiratory sounds in infants with acute respiratory symptoms (using both a smartphone and a digital stethoscope). For the WheezOut study, only children from one center (Robert Debré hospital) were followed up. The study complied with STROBE statement for observational studies.

Ethical approval was obtained from the Comité de Protection des Personnes SUD-EST IV (ID-RCB: 2020 – A01482-37). The parents were informed of the collection of prospective data for research purposes, and they could request that their child be exempted in accordance with French law (observational non-interventional study). All infants (younger than 2 years) referred to the emergency department for acute respiratory symptoms and diagnosed by the attending physician as having bronchiolitis (as defined by the American Academy of Pediatrics (8)) were enrolled during one bronchiolitis season (10/26/2016 to 04/28/2017) and were followed up by telephone.

In the emergency room, the following data were recorded by the physician: sex, age, pulsed saturation in the room air, and presence of wheezing upon auscultation. The physician also recorded respiratory sounds using a digital

stethoscope (Littman™ 3200 Digital Electronic Stethoscope) that has been demonstrated to be more sensitive than clinician auscultation in detecting wheezing (9). Since these data were acquired at the initial evaluation of the infant, the need for hospitalization was not recorded. All recordings obtained with the stethoscope were classified by two physicians (PB and CD) who identified instances of wheezing, rhonchus and coarse crackles. These two physicians assessed their skills using the Reference Database of Respiratory Sounds (<https://www.ers-education.org/e-learning/reference-database-of-respiratory-sounds/wheezes/>).

Telephone interviews at 3 and 6 years of age

The questions that were recorded when the child was three years of age are described in **Table 1**. The eight questions from the wheezing module for 6-7-year-olds from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire were recorded when the child was six years of age (10) and are described in **Table 2**.

Statistical analysis

Results were expressed as a mean $\pm$ SD or median [25th; 75th percentile] depending on the distribution of the variable or as a proportion, with a 95% confidence interval (CI) for the main results. Categorical variables were compared using Fisher's exact test and continuous variables using the Mann Whitney test. A p value < 0.05 was deemed significant. All statistical analyses were performed with StatView 5.0 software (SAS Institute, Cary, NC, United States). To evaluate the inter-observer agreement, Randolph's free-marginal multirater kappa with 95% CIs was calculated (11). The kappa values were interpreted as follows: 0-0.20 slight, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 substantial, and 0.80-1.0 almost perfect agreement (12).

RESULTS

Two hundred-and-seventy infants with bronchiolitis were included in the winter sample of 2016-2017. When they were three years of age, 144 families responded to the telephone interview; at 6 years of age, 113 families responded. In total, data at 3 and 6 years of age were available for 112 children (one family responded only when their child was 6 years of age, no data at three years of age).

Table 1. Characteristics at three years of age.

Characteristic	Wheezing at inclusion, n = 33 (23%)	No wheezing at inclusion, n = 111 (77%)	P value
Gestational age, weeks	39 [38; 40]	40 [38; 40]	0.325
Pregnancy smoking, n (%)	6 (18)	8 (7)	0.089
Sex: female, n (%)	12 (36)	43 (39)	0.841
SpO ₂ at inclusion, %	98 [96; 99]	98 [96; 99]	0.967
Respiratory episodes # before 3 years of age			
Number	3 [2; 4]	1 [1; 3]	<0.001
Hospitalized, n	0 [0; 1]	0 [0; 1]	0.349
Respiratory episodes (≥3) before 3 years of age, n	18 (55)	46 (41)	0.167
Asthma treatment*, n	23 (70)	47 (42)	0.009
Wheezing at cold, n	18 (55)	54 (49)	0.692
Wheezing at laughing/crying, n	5 (15)	12 (11)	0.541
Wheezing at exercise, n	2 (6)	12 (11)	0.523
Night awaking, n	7 (21)	33 (30)	0.384
Family asthma, n	13 (39)	42 (38)	>0.999
Maternal asthma, n	5 (15)	18 (16)	>0.999
Family allergy, n	9 (27)	43 (39)	0.303
Passive smoking, n	22 (67)	47 (42)	0.014

#: these respiratory episodes were either diagnosed as bronchiolitis by a doctor or associated with possible wheezing necessitating hospitalization and/or nebulized treatment and/or respiratory therapist intervention.

*: fluticasone; budesonide; beclomethasone; salbutamol.

Table 2. Core questionnaire according to wheezing at six years of age in the 112 children who were also assessed at three years of age.

Characteristic	Whole population n = 112	Wheezing at inclusion n = 28 (25%)	No wheezing n = 84 (75%)	P value
Ever wheezing, n (%)	67 (60)	18 (64)	49 (58)	0.659
Wheezing in last year, n (%)	17 (15)	2 (7)	15 (18)	0.126
wheezing attacks: none/1-3/4-12/>12, n	51/13/3/0	16/1/1/0	35/12/2/0	0.220
sleep awaking: never/<1/≥1 per week, n	62/1/4	18/0/0	44/1/4	0.371
speech limitation, n	3	0	3	0.558
Ever asthma, n (%)	40 (36)	11 (39)	29 (35)	0.655
Wheezing at exercise last year, n (%)	6 (5)	0 (0)	6 (7)	0.334
Cough at night last year, n (%)	37 (33)	8 (29)	29 (35)	0.647
Characteristics at three years of age				
recurrent respiratory episodes, n	49 (44)			
asthma treatment, n	56 (50)			
wheezing at exercise, n	11 (10)			
family allergy, n	42 (37)			

When comparing the characteristics of these 112 infants at the time of inclusion as compared to the 158 infants whose families did not respond to a telephone interview, the presence of definite (see below) wheezing at the time of inclusion (28/112 vs. 30/158) and the proportion of infants who already had repeated respiratory episodes (25/112 vs. 34/158) were not significantly different ($p = 0.236$ and $p = 0.875$, respectively).

Interrater agreement for respiratory sounds

The overall agreement percentage between the two raters for wheezing (249 infants were available for the two raters) was 71.08%, with a free-marginal kappa of 0.42 (95% CI [0.31, 0.53]), which is a moderate agreement. The prevalence of definite (two observers) wheezing was 58/270 (21%), and the prevalence of possible wheezing (at least one observer) was 151/270 (56%).

The overall agreement percentage between the two raters for rhonchus (241 infants were available for the two raters) was 71.78%, with a free-marginal kappa of 0.44 (95% CI [0.32, 0.55]), which is a moderate agreement. Finally, the overall agreement percentage between the two raters for coarse crackles (254 infants were available for the two raters) was 84.65%, with a free-marginal kappa of 0.69 (95% CI [0.60, 0.78]), which is substantial. The prevalence of possible crackles was 58/271 (21%).

Interview at three years of age

Table 1 shows the results of the interview according to the presence of definite wheezing at the time of inclusion. Children with wheezing at the time of inclusion, as compared to those without wheezing, were more frequently exposed to tobacco smoke (22/33 vs. 47/111, $p = 0.014$), had more respiratory episodes during infancy (3 episodes [2; 4] vs. 1 [1; 3], $p < 0.001$), and received asthma medication more frequently (23/33 versus 47/111, $p = 0.009$).

Interview at six years of age (core questionnaire wheezing module for 6-7-year-olds)

The results of the eight questions are provided in **Table 2**. Overall, 67/112 (60%, 95% CI [50, 69]) of the children who had at least one case of bronchiolitis experienced wheezing or whistling in the chest in the past. Cases of wheezing were logically associated with asthma diagnoses: 34/40 vs. 33/72 ($p < 0.001$).

An asthma diagnosis (ever asthma in **Table 2**, $n = 40/112$, 36%, 95% CI [27, 45]) was mainly related to the recurrent wheezing phenotype: 31/49 versus 9/63 ($p < 0.001$). Asthma at 6 years of age (wheezing in the last year, **Table 2**: 17/112, 15%, 95% CI [9, 23]) was associated with wheezing during exercise at 3 years of age (4/11 versus 7/101, $p = 0.002$) and with a family history of allergies (21/42 vs. 21/70, $p = 0.044$) but not with the early wheezing criteria (either recurrent respiratory episodes: 10/17 vs. 39/95, or asthma treatment before 3 years of age: 12/17 vs. 44/95, $p = 0.174$ and $p = 0.065$; respectively).

Asthma at 6 years of age was not associated with the presence of wheezing at the initial auscultation (**Table 2**).

DISCUSSION

This prospective study, which included infants referred to the emergency department, demonstrates that the identification of wheezing at auscultation during a bron-

chiolitis episode was associated with tobacco exposure, recurrent wheezing, and asthma treatment at three years of age, but not with asthma at six years of age.

The first important issue is whether our population is representative of infants with bronchiolitis. The observed rate of infants with bronchiolitis and subsequent recurrent wheezing in the first three years of age (64/144, 44%) is within the expected range (2). The rate of 6-year-old children with wheezing during the last year (17/112, 15%; 95% CI: 9 to 23%) is consistent with the rate of 12.5% of recurrent wheezing in the fifth year of life among infants hospitalized for respiratory syncytial virus (13). To the best of our knowledge, no previous study has evaluated the benefit of the identification of wheezing during bronchiolitis. Since the presence of wheezing may help to define bronchiolitis phenotypes (4), it was important to assess inter-observer agreement. Elphick et al. investigated the validity and reliability of computerized acoustic analysis in the detection of abnormal respiratory noises in 102 infants and showed that the level of agreement between observers concerning the presence of wheezing was poor for both examinations with a stethoscope and acoustic analysis (14). Our results are consistent with those of Liu *et al.*, who found a weighted kappa of 0.43 for the auscultation of children with asthma or bronchiolitis (7). Overall, these results support the argument for the use of auscultation by digital stethoscopes or digital wheeze detectors, which are more sensitive in detecting wheezes (9, 15), and even artificial intelligence in order to diagnose respiratory sounds (16).

Our main result is the demonstration that definite wheezing upon auscultation is associated with respiratory prognoses, namely repeated respiratory episodes and asthma treatment at 3 years of age. The fact that wheezing was associated with exposure to parents' tobacco use is consistent with the demonstrated risk of the increased incidence of wheezing due to this exposure (17).

Our study has limitations due to its design. Only half of the families were available for a telephone interview when their child was three years of age, and this percentage decreased to ~40% at six years of age. Recurrence of respiratory episodes (necessitating hospitalization and/or nebulized treatment and/or respiratory therapist intervention), a more stringent criterion than recurrent wheezing, was retrospectively recorded (at three

years of age: telephone interview) and a recall bias cannot be eliminated. Furthermore, rhinovirus-induced bronchiolitis has more strongly been associated with the risk of developing wheeze and childhood asthma than respiratory syncytial virus (18), which was not recorded. Finally, no assessment of lung function was obtained, which is also a limitation, even if lung function parameters obtained from impulse oscillometry and asthma probability are belonging to independent dimensions of the wheezing disease (19), confirming that there is a paucity of evidence to guide clinicians in selecting diagnostic tests for recurrent or persistent wheezing (20). In conclusion, the identification of wheezing during bronchiolitis is associated with recurrent respiratory episodes (wheezing) at three years. This result supports a plea for the use of digital stethoscopes with artificial intelligence in order to detect pathologic pediatric breath sounds.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have declared no conflict of interests.

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Ethical approval

Human studies and subjects

Ethical approval was obtained from the Comité de Protection des Personnes SUD-EST IV (ID-RCB: 2020 – A01482-37). The parents were informed of the collection of prospective data for research purposes, and they could request that their child be exempted in accordance with French law (observational non-interventional study).

Data sharing and data accessibility

The respiratory sound database is available for researchers upon request to the Corresponding Author.

Publication ethics

Plagiarism

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

All the data corresponds to the real.

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