Published in final edited form as:

J Pediatr. 2009 June ; 154(6): 877–81.e4. doi:10.1016/j.jpeds.2008.12.029.

Signs and Symptoms that Precede Wheezing in Children with a Pattern of Moderate-to-Severe Intermittent Wheezing

Katherine Rivera-Spoljaric, MD, MSCI¹, Vernon M. Chinchilli, PhD², Lindsay J. Camera, BS², Robert S. Zeiger, MD, PhD³, Ian M. Paul, MD, MSc², Brenda R. Phillips, MS², Lynn M. Taussig, MD⁴, Robert C. Strunk, MD¹, and Leonard B. Bacharier, MD¹ for the Childhood Asthma Research and Education (CARE) Network

¹ Washington University School of Medicine, St. Louis, MO

² Penn State College of Medicine, Hershey, PA

³ Kaiser Permanente, San Diego, CA

⁴ National Jewish Medical and Research Center, Denver, CO

Abstract

Objectives—To examine parent-observed signs and symptoms as antecedents of wheezing in preschool children with prior moderate to severe wheezing episodes, as well as to determine the predictive capacity of these symptom patterns for wheezing events.

Study Design—Parents (n = 238) of children 12–59 months of age with moderate-to-severe intermittent wheezing enrolled in a year-long clinical trial completed surveys that captured signs and symptoms at the start of respiratory tract illnesses. Sensitivity, specificity, negative predictive value, and positive predictive values for each symptom leading to wheezing during that respiratory tract illness were calculated.

Results—The most commonly reported first symptom categories during the first respiratory tract illness were “nose symptoms” (41%), “significant cough” (29%), and “insignificant cough” (13%). The most reliable predictor of subsequent wheezing was “significant cough”, which had specificity of 78% and positive predictive value of 74% for predicting wheezing.

Conclusions—“Significant cough” is the most reliable antecedent of wheezing during a respiratory tract illness. It may be useful to consider individualized symptom patterns as a component of management plans intended to minimize wheezing episodes.

INTRODUCTION

Many preschool children experience a pattern of moderate to severe recurrent intermittent wheezing with acute respiratory tract illnesses, and these episodes are associated with significant morbidity[1] [2]. To minimize symptom burden and systemic corticosteroid use, as well as frequent visits to the physician’s office and/or the emergency department, parents frequently seek advice on when to initiate therapy to prevent the subsequent development of wheezing associated with respiratory tract illnesses. The National Asthma Education and Prevention Program (NAEPP) Guidelines suggest that to effectively manage a wheezing illness at home, parents and patients need to recognize early signs and symptoms of an asthma exacerbation [3]. However, the Guidelines do not discuss what these signs or

Corresponding Author: Katherine Rivera-Spoljaric, MD, MSCI, Washington University School of Medicine, Department of Pediatrics, Campus Box 8116-NWT, St. Louis, MO 63110-1077, Phone: 314-454-2694, Fax: 314-454-2515, rivera_k@kids.wustl.edu.

Potential Conflicts of Interest: None

symptoms might be or how they likely vary between patients. Furthermore, the current literature does not help clinicians understand how to best approach this issue which is often difficult to assess since clinicians, anecdotally, recognize significant interpersonal variability amongst young children with recurrent wheezing. In addition, in the preschool population, symptom recognition and reporting relies heavily on parental perception, the accuracy of which has been subject to controversy in previous studies [4–10]. Nevertheless, the majority of treatment decisions are made at home based upon parental experience and intuition regarding the severity of illness, supplemented by a given set of clinical guidelines. The aim of this study is to analyze the signs and symptoms reported prospectively by a group of parents of children with moderate-to-severe intermittent wheezing at the onset of a respiratory tract illness (RTI) in order to identify symptom patterns during the conduct of an interventional clinical trial. Our hypothesis was that these parents will identify symptoms of a respiratory tract illness that reproducibly precede the development of an exacerbation of wheezing.

STUDY DESIGN

Two-hundred and thirty-eight children 12–59 months of age were randomized in the Acute Intervention Management Strategies (AIMS) trial, a multicenter, double-blind, placebo-controlled study performed by the National Health Lung and Blood Institute (NHLBI) sponsored Childhood Asthma Research and Education (CARE) Network. The inclusion criteria for the trial were aimed at identifying children who experienced moderate-severe wheezing episodes (≥ 2) in the preceding year in the context of an upper respiratory tract infection but who remained well between episodes and did not demonstrate features of “persistent asthma”. Participants randomly received inhaled corticosteroid (budesonide), leukotriene receptor antagonist (montelukast), or placebo for 7 days at the onset of each RTI for a period of 1 year. All participants received study medication plus albuterol inhalation treatments four times daily while awake (plus as needed) for the first 48 hours of the onset of an illness followed by albuterol by inhalation on an as needed basis. Additional rescue albuterol treatments could be administered on an as needed basis. Parents were instructed to begin study medications when the child-specific symptom(s) were detected. This trial was approved by each center’s Institutional Review Board and parents signed informed consents. [1]

Initial surveys were completed by the parents at randomization with clinical coordinator supervision. Identical surveys were subsequently completed at home at the onset of each subsequent RTI during the trial with responses reviewed over the phone with the clinical coordinators within 48–72 hours of initiation of study medication to discuss the scenario that prompted study medication use as well as to describe the course of the illness. These surveys determined the signs and symptoms which preceded the eventual development of wheezing (Table 1a). The surveys detailed a variety of symptom categories as well as specific symptoms within each category (Table 1b). Parents chose the very first symptom they noticed as part of a RTI likely to include wheezing, the most important symptom that made them certain of the subsequent development of extensive wheezing, and the symptom that led them to initiate treatment (study medications). The survey was developed and refined based on a pilot study of 28 parents of children with the same inclusion criteria as described above which completed prior to the clinical trial at each clinical center. Parents were also provided with a diary card to record respiratory symptoms on a twice daily basis which supplemented the data provided by the parent on the illness survey.

Statistical analysis

Frequency distributions were determined for each of the responses. We then calculated sensitivity, specificity, negative predictive value, and positive predictive values for each

symptom category, based on the subsequent development of wheezing during that RTI from diary card entries. These were calculated along with an analysis of concordance of responses during subsequent RTI. Trend tests also were applied to assess whether the reporting of a symptom category changed in frequency over time. P values <0.05 were considered statistically significant.

An additional analysis was performed on the subset of 64 children who experienced at least one respiratory tract illness during which prednisolone was administered (RTI + P) and at least one respiratory tract infection during which prednisolone was not administered (RTI – P). A score between 0 and 1 was constructed for each child, in which 0 reflects total disagreement with respect to a specific symptom category between RTI + P and RTI – P episodes and 1 reflects total agreement. Then a 95% confidence interval was constructed for the mean score with respect to each symptom category.

RESULTS

Parental and Patient Characteristics

Two hundred and thirty eight children were randomized between March and November of 2004. 215 children experienced at least one RTI, of which 176 experienced two (or more) RTIs during the 12-month trial. All parents completed the survey at randomization and were asked to complete the survey at the onset of each subsequent RTI. Parents completed surveys for 194 (90%) of the first RTI and for 148 (84%) of the second RTI.

Over one half of participating parents had at least some college education and the majority had a household income of \$50,000 or more (Table E1, online only). The survey was completed predominantly by mothers (96%). The majority of the children were male (64.7%), white (55.9%), and more than 70% experienced at least 4 wheezing episodes over the preceding 12 months and did not experience active symptoms during the month preceding enrollment and during a 2 week prospective run-in period (1). Additional characteristics of the children randomized into the trial have been detailed elsewhere (1).

Symptoms

“Nose symptoms” and “significant cough” (cough that is concerning, constant, interrupts activity, interrupts sleep, repetitive, or what parents call “The asthma cough”) were the very first symptoms of a RTI reported most often at randomization and at the onset of the first two RTIs (Figure 1a). As participants experienced increasing numbers of RTIs during the trial, “nose symptoms” remained the most prevalent very first symptom, but the frequency with which “significant cough” was reported as the very first symptom increased significantly (Figure 1a, $p=0.03$ for trend). There was no significant change in the frequencies of the four other major symptom categories (“insignificant cough”, “noisy chest”, “breathing problems”, and “behavior changes”) over the first two RTIs.

The most commonly reported response in the most important symptom category at randomization and during the first RTI and second RTI was “significant cough” (40%, 50%, and 53% of participants, respectively) (Figure 1b). While the frequency of “significant cough” as the most important symptom increased numerically between randomization and the second RTI, this change was not statistically significant. Similarly, there was no significant change in the frequencies of the five other major symptom categories for most important symptom.

The symptom for which parents initiated study medication at randomization, first RTI, and second RTI was most commonly “significant cough” (42%, 46%, and 51% of participants, respectively) (Figure 1c). There was a numerical increase in the proportion of parents who

initiated treatment for “nose symptoms” as the number of RTIs increased, along with numerical decreases in initiation of study medication due to “noisy chest” or “breathing problems”; however, trend analysis found that these differences were not statistically significant.

There were no differences in symptom reporting patterns between the three study treatment groups across RTIs for the very first symptom ($p=0.65$), most important symptom ($p=0.57$), or symptom used to initiate treatment ($p=0.53$). Early symptom patterns did not influence episode severity, as reflected by oral corticosteroid use, as the early symptom patterns during RTI episodes which led to oral corticosteroid use did not differ from RTIs that did not require oral corticosteroid use ($p=0.88$).

Sixty-nine percent of participants developed wheezing during the first RTI as reported on diary cards. The performance characteristics of individual symptoms reported as very first, most important, and reason for initiation of treatment in the first RTI are shown in Table 2. For the very first symptom, parental identification of “significant cough” was highly specific (78%) and was associated with a positive predictive value of 74% in predicting wheezing during the RTI. When reported as the most important symptom, “noisy chest” was associated with very high specificity (97%) and positive predictive value (90%) for the development of wheezing, but this finding is confounded by wheezing as a specific symptom within the “noisy chest” category and although noisy chest is very specific it has low sensitivity. “Significant cough” had the highest sensitivity (47%) and positive predictive value (62%) when identified as the most important symptom. When identified as the symptom used for initiation of treatment, “significant cough” had a sensitivity of 48% and a PPV of 68% for predicting subsequent wheezing, in contrast to “insignificant cough” which had a very low sensitivity of 8%, but a high PPV of 71%. Treatment group did not influence the performance characteristics described above, as there were no significant differences in sensitivities or specificities by treatment group (all $p>0.05$).

Consistency of Responses between RTIs

“Significant cough” was the symptom most likely to be identified consistently between RTIs. If “Significant cough” was reported as the most important symptom during the first RTI, 62% of parents reported this category as most important during the second RTI (Table 3). Other symptom categories had lower concordance rates between the first two RTIs. This pattern was similar to that observed between the symptom category identified based upon prior history (at randomization) and the symptom category reported during the first RTI (Table E2, online only).

DISCUSSION

Recognition of the variability in patterns of symptom development between patients is imperative for appropriate management strategies for children with moderate-to-severe intermittent wheezing. Thus, clinicians must understand these symptom patterns and assist parents of children in this population to recognize such patterns in order to provide timely and effective treatment. This is complicated by imperfect parental identification of wheezing, as clinicians depend heavily on reported parental impressions and perceptions[4, 5]. Among preschool children with a history of moderate to severe intermittent wheezing enrolled in the AIMS trial, “nose symptoms” were the most commonly recognized first symptom at the onset of a RTI that parents suspected would eventually include wheezing. However, “nose symptoms” had low sensitivity and positive predictive value for subsequent wheeze. While reported less frequently than “nose symptoms” as the very first symptom of RTI, “significant cough” was identified most often as the most important symptom that predicted wheezing, although with relatively low sensitivity but fair PPV for predicting

wheezing. These results suggest that parental perceptions of the development of particular respiratory symptoms at the onset of a RTI, particularly “significant cough”, have acceptable positive predictive values and specificities for predicting subsequent wheezing following the onset of a RTI, and may serve as indicators for escalation of therapy in an attempt to minimize subsequent wheezing. In other words, waiting for the appearance of wheezing to initiate therapy is too late. Clinicians should discuss the specific characteristics of the cough, with their patient’s parents during asthma management planning. Also these findings suggest that, even though “significant cough” was the symptom category most predictive of subsequent wheezing, all children need to be treated individually since not all parents identified “significant cough” as the most important symptom or symptom leading to treatment, implying that all children are not alike and that intrapersonal and interpersonal variability will play a role as well in individual management.

These data may be of critical importance when conducting clinical trials involving management of RTIs in children with an aim to prevent wheezing and associated morbidities. In the past two decades there have been multiple clinical trials in children targeting this aim[11–20]. These trials have used a variety of different approaches to trigger initiation of study intervention such as “first sign of an attack”[11]; “onset of upper respiratory tract symptoms which typically precipitated asthma attacks”[12]; “first sign of upper respiratory tract infection”[16]; and “increased in symptom scores by one point in a symptom scale”[19]. It may be that lack of attention to the clinical features in our papers led to sub-maximal responses in these trials. We propose that by having a better understanding of the early changes that occur prior to a wheezing illness in each particular patient, we may be able to educate parents of children on when to initiate a specific intervention, which may lead to improved clinical outcomes.

There are some limitations to consider associated with this study. First, since parents completed the survey during the course of a clinical trial under close monitoring, their responses may be the result of increased vigilance and not generalizable to the usual clinical setting in which supervision is less intense. The majority of parents identified significant symptoms instead of trivial or controversial signs of RTI. It is our impression that the majority of parents of children with moderate to severe recurrent wheezing are very attentive to their children during RTIs and therefore would be expected to provide accurate responses to similar questions. Also, the parents were well-educated and it is not clear how these results would translate in a less educated group. There could be a parental learning effect as the number of RTIs progressed, such that ongoing guided observation may lead to a shift between symptom categories. Nevertheless, as described above, the consistency between responses for significant cough between RTIs was 43% for first symptom and 62% for most important symptom. This suggests that even though some parents recognized different symptom patterns with subsequent RTIs, the majority recorded similar symptom observations across RTIs when reporting significant cough. Our definition of noisy chest included wheezing, which likely accounts for the very high specificity and positive predictive value. Also, it is likely that study treatment(s) had an effect on the appearance of wheezing, however our study was not designed to approach this question. This analysis is based on parental reporting and perception of symptoms with the aid of a coordinator and or physician assistance to decide RTI management. However, these children were not examined by a physician with each RTI; therefore wheezing was not objectively documented. Despite this, it is common in clinical practice to provide an “action plan” for parents to initiate home based treatment as well as telephonic assistance for wheezing treatment without physician examination.

Conclusion

In summary, the presence of “significant cough” as an early sign of RTI is a frequently reported and reliable predictor of subsequent lower RTI associated wheezing in preschool children with a history of severe intermittent wheezing. However, “one size does not fit all,” as several symptom categories were also frequently identified as antecedents of wheezing episodes. This suggests a need for further investigation of individualized management strategies that will be maximally effective for each child, since inter- and intrasubject variability in early symptom recognition patterns among the preschool wheezing population exist.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Source: Grants 5U10HL064287, 5U10HL064288, 5U10HL064295, 5U10HL064307, 5U10HL064305, 5U10HL064313 from the National Heart, Lung, and Blood Institute; General Clinical Research Centers at Washington University School of Medicine (M01 RR00036) and National Jewish Medical and Research Center (M01 RR00051)

ABBREVIATIONS

RTI Respiratory tract illness

References

1. Bacharier LB, Phillips BR, Bloomberg GR, Zeiger RS, Paul IM, Krawiec M, et al. Severe intermittent wheezing in preschool children: a distinct phenotype. *J Allergy Clin Immunol*. 2007 Mar.119:604–10. [PubMed: 17336610]
2. Elizur A, Bacharier LB, Strunk RC. Pediatric asthma admissions: chronic severity and acute exacerbations. *J Asthma*. 2007 May.44:285–9. [PubMed: 17530527]
3. National Heart L, and Blood Institute and the National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR 3): Guidelines for the Diagnosis and Management of Asthma. 2007. [cited; Available from: <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm>]
4. Cane RS, Ranganathan SC, McKenzie SA. What do parents of wheezy children understand by “wheeze”? *Archives of disease in childhood*. 2000 Apr.82:327–32. [PubMed: 10735844]
5. Cane RS, McKenzie SA. Parents’ interpretations of children’s respiratory symptoms on video. *Archives of disease in childhood*. 2001 Jan.84:31–4. [PubMed: 11124780]
6. Young B, Fitch GE, Dixon-Woods M, Lambert PC, Brooke AM. Parents’ accounts of wheeze and asthma related symptoms: a qualitative study. *Archives of disease in childhood*. 2002 Aug.87:131–4. [PubMed: 12138062]
7. Yoos HL, Kitzman H, McMullen A, Sidora K. Symptom perception in childhood asthma: how accurate are children and their parents? *J Asthma*. 2003 Feb.40:27–39. [PubMed: 12699209]
8. Halterman JS, Yoos HL, Kitzman H, Anson E, Sidora-Arcoleo K, McMullen A. Symptom reporting in childhood asthma: a comparison of assessment methods. *Archives of disease in childhood*. 2006 Sep.91:766–70. [PubMed: 16705016]
9. Cunha SS, Newcombe PJ. Parental understanding of wheeze and its impact on asthma prevalence estimates. *Eur Respir J*. 2007 May 29.:1069–70. author reply 70. [PubMed: 17470630]
10. Michel G, Silverman M, Strippoli MP, Zwahlen M, Brooke AM, Grigg J, et al. Parental understanding of wheeze and its impact on asthma prevalence estimates. *Eur Respir J*. 2006 Dec. 28:1124–30. [PubMed: 16870670]

11. Wilson NM, Silverman M. Treatment of acute, episodic asthma in preschool children using intermittent high dose inhaled steroids at home. *Archives of disease in childhood*. 1990 Apr. 65:407–10. [PubMed: 2189367]
12. Connett G, Lenney W. Prevention of viral induced asthma attacks using inhaled budesonide. *Archives of disease in childhood*. 1993 Jan.68:85–7. [PubMed: 8435016]
13. Connett GJ, Warde C, Wooler E, Lenney W. Use of budesonide in severe asthmatics aged 1–3 years. *Archives of disease in childhood*. 1993 Sep.69:351–5. [PubMed: 8215545]
14. Garrett J, Williams S, Wong C, Holdaway D. Treatment of acute asthmatic exacerbations with an increased dose of inhaled steroid. *Archives of disease in childhood*. 1998 Jul.79:12–7. [PubMed: 9771245]
15. Volovitz B, Bentur L, Finkelstein Y, Mansour Y, Shalitin S, Nussinovitch M, et al. Effectiveness and safety of inhaled corticosteroids in controlling acute asthma attacks in children who were treated in the emergency department: a controlled comparative study with oral prednisolone. *The Journal of allergy and clinical immunology*. 1998 Oct.102:605–9. [PubMed: 9802368]
16. Svedmyr J, Nyberg E, Thunqvist P, Asbrink-Nilsson E, Hedlin G. Prophylactic intermittent treatment with inhaled corticosteroids of asthma exacerbations due to airway infections in toddlers. *Acta Paediatr*. 1999 Jan.88:42–7. [PubMed: 10090546]
17. Volovitz B, Nussinovitch M, Finkelstein Y, Harel L, Varsano I. Effectiveness of inhaled corticosteroids in controlling acute asthma exacerbations in children at home. *Clinical pediatrics*. 2001 Feb.40:79–86. [PubMed: 11261454]
18. FitzGerald JM, Becker A, Sears MR, Mink S, Chung K, Lee J. Doubling the dose of budesonide versus maintenance treatment in asthma exacerbations. *Thorax*. 2004 Jul.59:550–6. [PubMed: 15223858]
19. Harrison TW, Osborne J, Newton S, Tattersfield AE. Doubling the dose of inhaled corticosteroid to prevent asthma exacerbations: randomised controlled trial. *Lancet*. 2004 Jan.24:271–5. [PubMed: 14751699]
20. Volovitz B. Inhaled budesonide in the management of acute worsenings and exacerbations of asthma: a review of the evidence. *Respiratory medicine*. 2007 Apr.101:685–95. [PubMed: 17125984]

Figure 1.
A,B,C. Histograms representing the frequencies of symptoms reported by parents as the very first symptom (1A), most important symptom (1B), and symptom to initiate study medication (1C) of a respiratory tract illness (RTI)
1A First symptom of a respiratory tract illness (RTI)
1B Most important symptom of a respiratory tract illness (RTI)
1C Symptom to initiate study medication during a respiratory tract illness (RTI)

Table 1

Respiratory tract illness (RTI) survey and symptoms included in the survey

A. Questions	
1	What is usually the very first symptom you notice that leads you to believe your child is starting a breathing illness?
2	What is usually the most important symptom you notice that makes you feel very certain that the illness will lead to significant breathing problems?
3	What two symptoms are usually present when you first give medications intended to lessen the symptoms of your child's breathing illness?

B. Symptoms included in the survey	
General Symptom Category	Specific Signs and Symptoms
Appearance changes	Dark circles under the eyes, glassy eyes, watery eyes
Appetite changes	Eating less/won't eat, spitting up/vomiting
Behavior problems	Bedwetting, fussy/ cranky/ irritable, hyperactive, less active (won't play)
Breathing problems	Breathing worse, can't breathe, nasal flaring, not breathing well, pulling if ribs/neck, rapid breathing, short of breath, color change, turning blue
Changes in sleep patterns	Awakening, sleepy during the day/lethargic
Insignificant cough	Infrequent, mild, not concerning
Significant cough	Concerning, constant, interrupts activity, interrupts sleep, repetitive, "The asthma cough"
Fever	Any fever, high fever, skin feels warm/hot to touch
Noisy breathing	Hoarse voice, snoring
Noisy chest	Gurgling, rattling, wheezing
Nose symptoms	Congested/stuffy, runny, sneezing

Table 2
Performance characteristics of symptom categories in predicting wheezing during first respiratory tract illness (RTI)

Predictors of wheezing during first RTI		Sensitivity	Specificity	PPV	NPV
Very first symptom	Significant Cough	33%	78%	74%	37%
	Insignificant Cough	13%	88%	67%	34%
	Nose	37%	50%	59%	29%
	Noisy Chest	3%	100%	100%	35%
Most important symptom	Significant Cough	47%	45%	62%	31%
	Nose	11%	81%	54%	32%
	Noisy Chest	15%	97%	90%	37%
	Significant Cough	48%	56%	68%	36%
Symptom to treatment	Insignificant Cough	8%	94%	71%	34%
	Nose	24%	66%	57%	31%
	Noisy Chest	9%	100%	100%	36%

Table 3

Concordance between survey responses during respiratory tract illness (RTI)

Symptom		Rate of Concordance First RTI to Second RTI		
1 st RTI	2 nd RTI	Very first symptom	Most important symptom	Symptom to treatment
Nose	Nose	47%	9%	42%
Significant Cough	Significant Cough	43%	62%	64%
Insignificant Cough	Insignificant Cough	--	8%	9%
Insignificant Cough	Significant Cough	38%	25%	36%
Significant Cough	Insignificant Cough	10%	8%	4%
Noisy Chest	Noisy Chest	--	23%	--
Behavior Change	Behavior Change	33%	20%	--