Nonrespiratory symptoms before loss of asthma control in children

Lisanne Palomar Newton, MD[a], Yvette Osei-Akosa, BA[b], Robert C. Strunk, MD[b], Melissa Krauss, MPH[c], Leonard B. Bacharier, MD[b], Jane M. Garbutt, MD[b], and Katherine Rivera-Spoljaric, MD[b]

Clinical Implications

- Parents of children with persistent asthma identify nonrespiratory signs and symptoms present before periods of uncontrolled asthma.
- Clinicians should be aware of these nonrespiratory symptoms when eliciting early signs of worsening asthma in patients.

TO THE EDITOR:

National Asthma Education and Prevention Program guidelines recommend early treatment of asthma exacerbations through recognition of early signs of worsening asthma.[1] Some asthma management plans include cold symptoms[2,3] as early signs, but most parents focus on lower respiratory tract (LR) symptoms.[4,5] We have previously shown that caregivers perceive multiple nonrespiratory (NR) and upper respiratory (UR) signs and symptoms that occur early in a respiratory tract illness.[6] In the present study, using a daily monitoring system, we aimed to determine how these parent-identified signs and symptoms relate to loss of asthma control.

Caregivers of children aged 2 to 11 years with a diagnosis of asthma completed diary cards daily for 16 weeks during cold and flu season. They documented the presence of 41 (divided into 26 NR, 5 UR, and 10 LR) signs and symptoms (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org) with the use of a Likert scale from 1 to 5 (3 represented baseline or usual; 1 or 2, less than usual; and 4 or 5, more than usual). Parents recorded visits for urgent care and oral corticosteroid use weekly.

Data were analyzed for the 5 days before an episode of loss of asthma control (LOC), defined as ≥2 consecutive days of increased LR symptoms (excluding mild cough), consistent with the American Thoracic Society's moderate asthma exacerbation definition (mild exacerbations include symptoms just outside the normal range of variation, moderate exacerbations include deterioration in symptoms that last ≥2 days and require change in treatment without systemic corticosteroids or hospitalization, and severe exacerbations include treatment with systemic corticosteroids or hospitalization).[7] Controlled periods were defined as the days that excluded those comprising the LOC episode, the 5 days before, and the 2 days after the episode. Logistic regression models were used to determine the odds of other than usual NR or UR symptom day (5 days before and during an episode) with controlled periods as the reference. Generalized estimating equations with an autoregressive correlation structure were used to allow for correlation of observations within individual children over time. Final models were adjusted for child's age, asthma severity, and parental education. For all analyses, a P value $<.05$ was considered significant. SAS version 9.2 (SAS Institute, Inc, Cary, NC) was used for analyses.

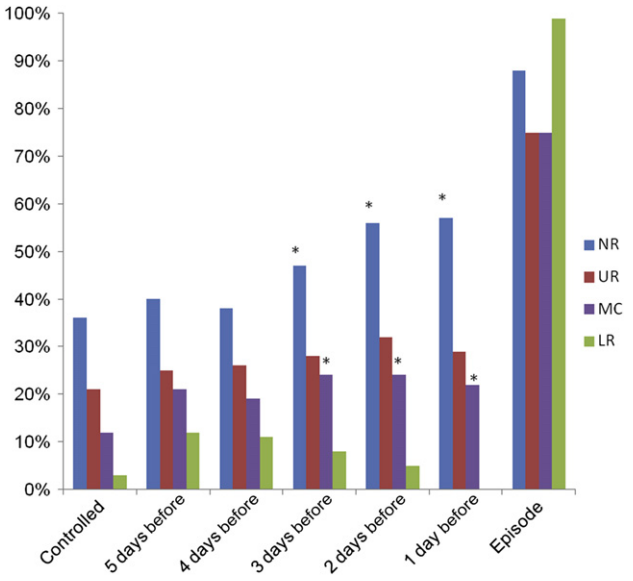

FIGURE 1. Percentage of days with a nonusual symptom before and during a LOC episode (≥2 consecutive days with LR symptoms). Unadjusted results indicated increased reporting of NR symptoms and mild cough in the 3 days before episodes compared with the controlled period (*$P \leq .05$). Note that LR symptoms are not present the day before as an artifact of our episode definition.

We enrolled 27 caregivers who filled out diary cards 82% of days (2467/3024). Most were mothers, employed, and white (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). The average child's age was 7 years, and most were boys. Twenty-one children (78%) experienced 73 episodes of LOC (6 children had 1 episode, 3 had 2 episodes, 1 had 3 episodes, 4 had 4 episodes, 4 had 5 episodes, 2 had 7 episodes, and 1 had 8 episodes). Among these children, 52% were prescribed ≥1 course of oral corticosteroids, 29% reported ≥1 emergency department/hospital visit, and 52% reported ≥1 unscheduled medical provider visit. The median duration of an episode was 5 days (interquartile range, 3-12 days). Approximately 23% (17/73) of the episodes coincided with oral corticosteroid use.

Unadjusted results (Figure 1) indicate increased reporting of NR symptoms in the 3 days before episodes compared with the controlled period and increased mild cough in the 3 days before episodes. After adjusting for age, asthma severity, and parental education, overall a trend was observed for increased likelihood of reporting NR symptoms in the 3 days before episodes, including changes in behavior, mood, and appearance (Table I). Several specific NR symptoms, such as paleness, irritability, anxiety, tension, tiredness, and sleeping problems, among others, showed significant increases in likelihood within the 5 days before an episode compared with a controlled period (Table I). Some NR symptoms were consistently increased over the 3 to

TABLE I. Odds ratios for a day with unusual symptom levels during 5 days before episode, during episode, and during 2 days following episode versus controlled periods

Symptom type	5 Days before episode vs control	4 Days before episode vs control	3 Days before episode vs control	2 Days before episode vs control	1 Day before episode vs control	Days during episode vs control
Nonrespiratory	0.9 (0.7-1.3)	0.9 (0.6-1.4)	1.6 (0.97-2.6)	2.0 (1.00-4.2)*	2.3 (0.98-5.5)	6.6 (3.9-11.0)
Crying	2.3 (1.1-4.6)*	2.3 (1.1-4.8)*	2.9 (1.1-7.4)*	2.2 (0.6-7.4)	2.4 (0.7-8.2)	3.7 (1.8-7.6)*
Paleness	1.7 (1.1-2.7)*	1.6 (0.5-4.9)	3.3 (1.3-8.4)*	4.4 (1.5-12.9)*	4.2 (1.6-11.5)*	9.1 (3.8-22.0)*
Irritability	2.0 (0.98-4.2)	2.1 (1.02-4.4)*	2.0 (1.03-3.8)*	3.2 (1.9-5.6)*	3.6 (1.4-9.2)*	6.0 (3.1-11.7)*
Tension	1.0 (0.5-1.9)	3.4 (1.6-7.2)*	3.1 (1.7-5.7)*	5.6 (3.0-10.4)*	2.8 (1.6-4.9)*	3.6 (1.9-6.8)*
Anxiety	—†	0.7 (0.5-1.1)	2.9 (1.2-7.3)*	3.6 (1.4-9.3)*	2.4 (1.1-5.3)*	3.9 (1.8-8.7)*
Moody	1.3 (0.5-3.3)	1.5 (0.6-3.7)	3.0 (1.5-6.3)*	2.9 (1.4-6.2)*	0.7 (0.1-5.7)	4.9 (2.3-10.1)*
Eye swelling	—†	—†	3.9 (1.2-12.8)*	7.7 (2.0-29.8)*	—†	9.5 (2.5-36.4)*
Tiredness	1.2 (0.2-9.0)	1.0 (0.4-2.8)	2.3 (1.01-5.2)*	1.9 (0.8-4.8)	6.4 (3.2-12.6)*	10.4 (5.3-20.3)*
Dry skin	1.2 (0.9-1.6)	0.9 (0.7-1.3)	1.5 (1.1-2.1)*	1.3 (0.9-1.9)	1.3 (0.8-2.2)	2.4 (1.4-4.0)*
Emotional	1.3 (0.5-3.6)	1.7 (0.8-3.8)	1.8 (0.8-3.8)	2.3 (1.03-5.2)*	1.9 (0.5-6.5)	4.6 (2.4-8.7)*
Talking	1.2 (0.5-3.2)	0.7 (0.1-5.3)	1.7 (0.8-3.8)	2.7 (1.2-6.4)*	2.7 (1.3-5.8)	5.0 (3.0-8.3)*
Sleepiness	0.9 (0.1-9.0)	0.3 (0.1-1.8)	1.4 (0.5-3.7)	1.5 (0.6-3.7)	4.1 (1.9-8.9)*	8.2 (4.3-15.9)*
Sleeping problems	1.3 (0.4-3.7)	0.4 (0.04-4.0)	2.1 (0.9-5.3)	2.4 (0.6-8.9)	3.8 (1.4-10.7)*	7.2 (2.4-21.4)*
Energy	0.2 (0.01-5.8)	0.6 (0.2-1.8)	1.3 (0.5-3.3)	1.8 (0.4-7.0)	3.5 (1.2-10.0)*	6.8 (3.1-14.7)*
Activity	0.6 (0.1-3.0)	0.8 (0.4-1.7)	2.1 (0.7-6.6)	2.7 (0.8-9.7)	3.5 (1.1-10.8)*	6.5 (2.2-19.2)*
Sunken eyes	1.1 (0.6-2.0)	1.2 (0.4-3.4)	1.2 (0.6-2.7)	2.2 (0.8-6.4)	2.4 (1.1-5.3)*	5.4 (2.5-11.6)*
Upper respiratory	0.9 (0.5-1.5)	0.9 (0.4-2.0)	1.1 (0.6-2.1)	1.3 (0.7-2.4)	1.1 (0.6-2.0)	5.5 (3.4-8.7)*
Itchy throat	1.3 (0.8-2.0)	1.6 (0.8-3.5)	2.7 (1.2-5.8)*	3.9 (1.7-9.3)*	2.2 (0.7-6.7)	7.1 (3.3-15.4)*
Runny nose	1.3 (0.98-1.8)	0.6 (0.2-1.8)	1.1 (0.4-3.1)	0.8 (0.3-1.8)	1.7 (0.97-3.0)	8.1 (4.1-16.1)*
Lower respiratory (not included in definition of an episode)						
Mild cough	1.7 (0.9-3.0)	1.6 (0.8-3.5)	2.4 (1.4-4.1)*	2.2 (1.04-4.6)*	2.0 (1.1-3.8)*	12.0 (6.5-22.2)*

Values are odds ratio (95% CI). Controlled period excludes 5 days before episode. All models were adjusted for child's age and asthma classification and parent's education level.

*Lower limit of 95% CI $\geq$ 1.

†Odds ratio cannot be estimated because of no occurrences of unusual symptom level on specified day.

4 days before an episode, with others increased only the day before an episode of LOC. Overall, UR symptoms were not increased during the days before an episode compared with the controlled periods; however, itchy throat was significantly more common 2 or 3 days before an episode than the controlled period. Mild cough was significantly more common in the 3 days before an episode. All symptoms studied were significantly more common during an episode than during controlled periods. The general pattern of some increased NR symptoms before an episode and little indication of increased UR symptoms before an episode remained even when examining only the 17 episodes with steroid use compared with controlled periods, although not as many symptoms were significant because of loss of statistical power.

As a control for the possibility of random variation of NR and UR symptoms, we studied a separate cohort of 19 children with asthma for 4 weeks and used the same methodology during the summer, when asthma symptoms would be expected to be less than during peak cold and flu season. During this well-controlled period, little symptom variability was observed across all symptom categories (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org).

In this study we showed that parents of children with persistent asthma can prospectively identify NR signs and symptoms present before periods of uncontrolled asthma. UR signs and symptoms were not consistently increased before LOC (except for itchy throat), consistent with the recent findings of McMahon et al[8] that parents did not perceive an upper airway prodrome before virus-induced asthma symptoms.

Our study has limitations to consider. First, we have a small sample size and few preschool-aged subjects. A larger sample size with more preschool-aged subjects would give us a better understanding on the commonality of these symptoms across age groups and whether preschool children behave differently as a group. Second, it relies on parental perception of signs and symptoms. Third, there may have been increased vigilance of symptoms in a research setting. Finally, we were unable to confirm that diary cards were completed to accurately reflect the signs and symptoms that were present.

In conclusion, clinicians should be aware of these nonrespiratory symptoms when eliciting early signs of worsening asthma in individual patients. Further investigation is needed to explore whether using NR signs and symptoms could guide augmentation of therapy to prevent LOC and asthma exacerbations.

[a]Department of Allergy and Immunology; Cleveland Clinic Foundation, Cleveland, Ohio

[b]Department of Pediatric Allergy and Pulmonary, Washington University School of Medicine, St. Louis, Mo

[c]Department of Biostatistics, Washington University School of Medicine, St. Louis, Mo

No funding was received for this work.

Conflicts of interest: L. P. Newton has received travel support from the AAAAI FIT Travel Grant. M. Krauss has received research support from the Washington University Institute of Clinical and Translational Sciences. L. B. Bacharier has received consultancy fees from Aerocrine, GlaxoSmithKline, Genentech/Novartis,

Merck, Schering, Cephalon, and DBV and has received lecture fees from Aerocrine, AstraZeneca, Genentech, GlaxoSmithKline, Merck, and Schering. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication July 24, 2012; revised January 17, 2013; accepted for publication January 23, 2013.

Available online March 4, 2013.

Cite this article as: Newton LP, Osei-Akosa Y, Strunk RC, Krauss M, Bacharier LB, Garbutt JM, et al. Nonrespiratory symptoms before loss of asthma control in children. J Allergy Clin Immunol: In Practice 2013;1:304-6. http://dx.doi.org/10.1016/j.jaip.2013.01.012.

Corresponding author: Lisanne Palomar Newton, MD, 9500 Euclid Ave/A90, Cleveland, OH 44195. E-mail: newtonl@ccf.org.

2213-2198/$36.00

© 2013 American Academy of Allergy, Asthma & Immunology

http://dx.doi.org/10.1016/j.jaip.2013.01.012

REFERENCES

1. National Heart, Lung, 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. Available from: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed September 1, 2012.
2. Zemek RL, Bhogal SK, Ducharme FM. Systematic review of randomized controlled trials examining written action plans in children: what is the plan? Arch Pediatr Adolesc Med 2008;162:157-63.
3. Bhogal S, Zemek R, Ducharme FM. Written action plans for asthma in children. Cochrane Database Syst Rev 2006;(3):CD005306.
4. Rivera-Spoljaric K, Bacharier L. Early signs and symptoms as antecedents of wheezing in children with severe intermittent wheezing. J Pediatr 2009;154:877-81.e4.
5. Garbutt J, Highstein G, Nelson K, Rivera-Spoljaric K, Strunk R. Detection and home management of worsening asthma symptoms. Ann Allergy Asthma Immunol 2009;103:469-73.
6. Rivera-Spoljaric K, Jaenicke M, Sridhar S, Krauss MJ, Garbutt JM, Bacharier LB, et al. Caregivers report a wide variety of early signs and symptoms of impending asthma exacerbations that are not different between pre-school versus school-age children. J Allergy Clin Immunol 2011;128:1109-11.e1-5.
7. Reddel H, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations standardizing endpoints for clinical asthma trials and clinical practice. Am J Resp Crit Care Med 2009;180:59-99.
8. McMahon DF, Rajamanickam V, Salazar L, Gangnon R, Gern JE. Do asthma symptoms lag behind cold symptoms in a viral illness? J Allergy Clin Immunol 2012;130:990-1.

ACcESS Variability Study - Diary Card

Instructions: Please enter the appropriate number for each of the symptoms below every day

Key: 1 Less than usual 2 3 Usual 4 5 More than usual

Symptom	**Day:**	**Day:**	**Day:**	**Day:**	**Day:**	**Day:**	**Day:**
Drinking							
Appetite							
Anxiety							
Complaining							
Moody							
Emotional							
Crying							
Talking							
Irritability							
Activity							
Tiredness							
Sleepiness							
Tension							
Energy							
Sleepwalking							
Sleeeping problems							
Paleness							
Rash							
Dry skin							
Itchy skin							
Hives							
Eye redness							
Eye swelling							
Sunken eyes							
Rubbing eyes							
Watery eyes							
Itchy throat							
Clearing of the throat							
Runny nose							
Sneezing							
Nose congestion							
Mild cough							
Deep cough							
Ribs or neck sinking in when breathing							
Breathing fast							
Breathing heavy							
Breathing funny							
Chest tightness							
Coughing during sleep							
Chest pain							
Wheezing							

FIGURE E1. Diary card.

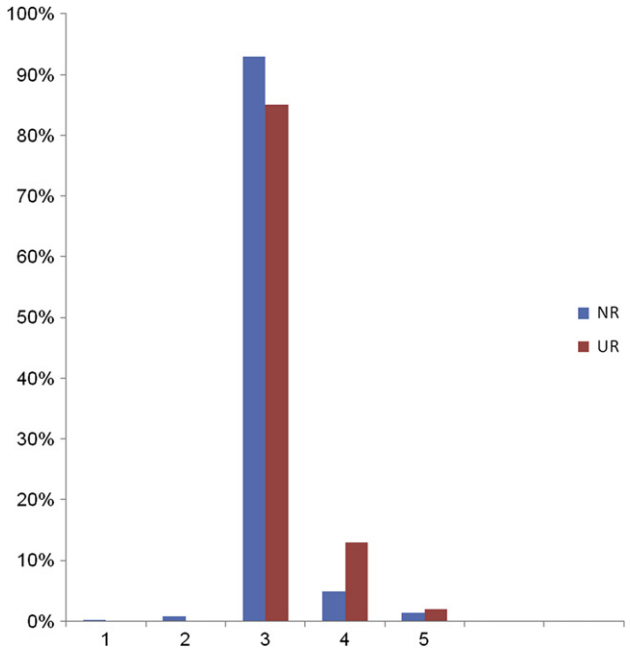

FIGURE E2. Histogram shows percentage of times during well-controlled asthma day (ACQ < 1.5) on which symptoms were 1 to 2 (less than usual), 3 (usual), and 4 to 5 (more than usual) for NR and UR symptoms during a 4-week summer diary card study (n = 19).

TABLE E1. Baseline Demographic Characteristics

	n = 27
Caregiver	
Age (y), mean (range)	38 (29-61)
Gender: female	89%
Education: college or above	48%
Ethnicity: non-Hispanic	100%
Race: Caucasian	67%
Employment: full or part-time	74%
Household income >$50,000	56%
Child	
Age (y), mean (range)	7 (2-11)
Gender: male	67%
Ethnicity: non-Hispanic	100%
Race: Caucasian	59%
Health insurance	
Insured	100%
Medicaid	41%
Asthma classification	
Mild persistent	44%
Moderate persistent	56%
Atopic, parental report of allergic rhinitis and/or eczema	63%