Severe intermittent wheezing in preschool children: A distinct phenotype

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Background: Young children with wheezing predominantly with respiratory tract illnesses experience severe exacerbations separated by extended periods of wellness and may be described as having "severe intermittent wheezing," a diagnostic category not currently recognized in national guidelines.
Objective: We sought to characterize a cohort of children with recurrent severe wheezing.
Methods: A total of 238 children 12 to 59 months enrolled in the Acute Intervention Management Strategies trial were characterized through comprehensive allergy, asthma, environmental, and quality of life assessments.
Results: Asthma symptoms over the period of the preceding year occurred at frequencies consistent with intermittent asthma, as 94.5% of children experienced activity limitation ≤ 2 times per month. However, frequent severe exacerbations were common, because 71% experienced ≥ 4 wheezing episodes over the period of the preceding year, 95% made at least 1 primary care visit, 52% missed school or daycare, 40% made an emergency department visit, and 8% were hospitalized for wheezing illnesses. Atopic features were common, including eczema (37%), aeroallergen sensitization (46.8%), and positive asthma predictive index (59.7%). Oral corticosteroid use in the previous year (59.7% of the cohort) identified a subgroup with more severe disease documented by a higher incidence of urgent care visits ($P = .0048$), hospitalizations ($P = .0061$), aeroallergen sensitization ($P = .047$), and positive asthma predictive indices ($P = .007$).
Conclusion: Among preschool children enrolled in the Acute Intervention Management Strategies trial, a subgroup was identified with severe intermittent wheezing characterized by atopic features and substantial illness-related symptom burden despite prolonged periods of wellness.
Clinical implications: Preschool children with recurrent severe wheezing episodes experience significant illness-related morbidity and exhibit features of atopic predisposition.
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Key words: *Childhood asthma, wheezing, intermittent asthma*

Recurrent wheezing illnesses early in life are common and result in significant morbidity. Rates for asthma-related emergency department visits[1] and hospitalizations are highest among children younger than 5 years,[1-5] reflecting the severity and acuity of these illnesses along with the difficulty in outpatient management.

Clinical experience and observation reveal that many children with recurrent wheezing primarily in the setting of respiratory tract illnesses (RTIs) lack chronic baseline symptoms consistent with the current description of persistent asthma.[6] According to current national guidelines, mild intermittent asthma in preschool children is characterized by symptoms occurring 2 days or fewer per week, nocturnal symptoms occurring 2 nights or fewer per month, with brief exacerbations of variable intensity.[6] Although the current guidelines recognize only 1 form of

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Abbreviations used
AIMS: Acute Intervention Management Strategies
API: Asthma Predictive Index
CARE: Childhood Asthma Research and Education Network
ICS: Inhaled corticosteroid
LTRA: Leukotriene receptor antagonist
RTI: Respiratory tract illness

intermittent asthma—mild intermittent asthma—many children who wheeze with RTIs often experience severe exacerbations separated by extended periods of wellness. The severity of these episodes appears to contradict the descriptive term of ''mild,'' suggesting a more appropriate descriptor of ''severe intermittent asthma'' for children with intermittent symptoms at baseline who experience severe episodes.

On the basis of the morbidity associated with severe intermittent asthma, coupled with the lack of convincing evidence for the preferred management strategy, the Childhood Asthma Research and Education (CARE) Network developed the Acute Intervention Management Strategies (AIMS) trial to examine whether various treatment approaches using episodic treatment at the early signs of acute respiratory tract illnesses change the course of severe intermittent asthma over a 1-year study period compared with conventional therapy. This report presents a detailed description of the enrolled population to characterize the entity of severe intermittent wheezing.

METHODS

The AIMS trial is a multicenter, double-blind, randomized, placebo-controlled, double-dummy, parallel group comparison of 3 treatment regimens in children 12 to 59 months of age with recurrent episodes of moderate to severe wheezing meeting the eligibility criteria (Table I). Participants received 1 of the following regimens for 7 days at the first sign of respiratory tract illness–associated symptoms: (1) active inhaled corticosteroid (ICS; budesonide [Pulmicort Respules (AstraZeneca, Wilmington, Del) 1.0 mg twice daily and placebo leukotriene receptor antagonist (LTRA) once daily (budesonide group)]), or (2) active LTRA (montelukast [Singulair (Merck & Co., Inc. West Point, Pa) 4 mg once daily] and placebo ICS twice daily [montelukast group]), or (3) placebo ICS twice daily and placebo LTRA once daily (conventional therapy group). All participants received albuterol inhalation treatments (Proventil HFA [Schering-Plough Co., Kenilworth, NJ] or nebulization solution) 4 times daily while awake (plus as needed) for the first 48 hours followed by albuterol by inhalation on an as-needed basis. The trial was reviewed and approved by the CARE/National Heart, Lung, and Blood Institute Protocol Review Committee and the institutional review boards at each CARE center, and written informed consent was obtained from the parent of each participant.

Patients who met all of the selection criteria at the screening visit were followed for 2 weeks, during which time parents completed diary cards twice daily to assure absence of symptoms consistent with persistent asthma (Table I). Each of 5 symptom categories (nocturnal cough, daytime cough, wheezing, difficulty breathing, or symptoms interfering with activities) was scored on a 0 to 5 scale, with 0 representing no symptoms and 5 representing very severe symptoms using the validated Pediatric Asthma Caregiver Diary[7] supplemented by AIMS protocol-specific items. Children were excluded if, during the 2-week run-in period, the response to the questions on albuterol use, wheezing, difficulty breathing, nighttime cough, and asthma symptoms interfering with activities was $\geq$1 or daytime cough was $>$ 2 on an average of 4 or more days per week.

Comprehensive allergy and asthma questionnaires were administered at enrollment. Allergy skin testing to a panel of 8 inhalant (house dust mite mix, cat, dog, tree mix, grass mix, weed mix, mold mix, and cockroach mix) and 3 food allergens (milk, egg, and peanut), serum total IgE level, peripheral blood eosinophil counts, assessments of quality of life (PedsQL[8] and Juniper Pediatric Asthma Caregiver's Quality of Life Questionnaire[9]), an environmental survey, and physical examinations including stadiometer measurements of recumbent length (participants $\leq$2 years of age) and standing height (participants $>$ 2 years of age) were performed at the randomization visit.

In an effort to identify children at highest risk for persistence of asthma symptoms during childhood, each participant was categorized using a modified Asthma Predictive Index (API).[10]

Statistical analyses

Diary symptom score ratings were summarized by using medians and included a nocturnal cough frequency rating (0 = not at all, 1 = very little, 2 = several times, 3 = frequently, 4 = almost all night) and a symptom severity rating (0 = none, 1 = very mild, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe). Continuous variables were summarized by using descriptive statistics including means, medians, and SDs, and groups were compared by using and Kruskal-Wallis tests. Discrete variables were summarized in frequency tables, and groups were compared by using Fisher exact or exact Pearson χ^2 tests. An analysis was performed to examine whether the inclusion criterion of oral corticosteroid use in the preceding year (inclusion criterion 3b, Table I) identified a subgroup of children with more severe disease. All summary statistics and analyses were performed via SAS Version 9.1 statistical software (SAS Institute, Inc, Cary, NC).

RESULTS

Study cohort

Between March and November 2004, 238 children were randomized in the AIMS trial. Baseline demographics of this cohort are presented in Table II. Fifty-eight children were terminated from the study during the run-in phase—46 because of symptom frequencies exceeding the inclusion criteria, 6 because of use of exclusionary medications, and 6 because of inadequate adherence to diary card completion. The children who enrolled in the trial but who were not randomized were comparable to those who were randomized except for greater numbers of emergency department visits in the previous year (1.4 $\pm$ 1.8 vs 1.0 $\pm$ 2.1; P = .009), albuterol use during the run-in period (1.1 $\pm$ 1.8 days/wk vs 0.4 $\pm$ 0.8 days/wk; P = .001), and night awakenings during the run-in period (1.6 $\pm$ 1.9 nights/week vs 0.2 $\pm$ 0.5 nights/week; P $<$ .0001). The majority of randomized participants were male (64.7%), and 44.1% were of a self-reported ethnic minority. Nearly 90% of mothers had completed high school, and 68% of families reported annual household incomes of $30,000 or more.