Demographic and clinical characteristics of children and adolescents with severe or difficult-to-treat asthma

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Background: Young patients with severe or difficult-to-treat asthma are an understudied population.
Objective: To assess age-associated and gender-associated differences in children and adolescents in the observational study, The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens.
Methods: Cross-sectional baseline data for patients greater than or equal to 6 years and less than or equal to 17 years (n = 1261) were stratified by age group (6-8, 9-11, 12-14, and 15-17 years). The χ^2 test for categorical variables and analysis of variance for continuous variables were used to identify differences among age groups, stratified by gender.
Results: Most patients had moderate (55%) or severe (41%) asthma by physician assessment. Of those using greater than or equal to 3 long-term controllers (62%), 53% of children (6-11 years) and 44% of adolescents (12-17 years) reported an oral corticosteroid burst and 25% and 19%, respectively, had an emergency department visit in the previous 3 months; 10% and 15%, respectively, reported past intubation. In females, weight for age ranged between the 67th and 70th percentiles; height for age was between the 42nd and 54th percentiles ($P < .01$ among age groups). Lung function was lower in adolescents than children: prebronchodilator percent predicted forced expiratory volume in 1 second (FEV_1)/forced vital capacity was 0.92 (6-8 years) and 0.83 (15-17 years), P less than .05, in males; and 0.94 (6-8 years) and 0.87 (15-17 years), P less than .05, in females.
Conclusions: Children and adolescents demonstrated high rates of health care use and loss of lung function, despite using multiple long-term controllers.
Clinical implications: Asthma treatments that prevent loss of lung function and reduce health care resource use are needed in young patients with severe or difficult-to-treat asthma. (J Allergy Clin Immunol 2007;119:1156-63.)

Key words: *Asthma, health care use, long-term controllers, lung function, observational, pediatric*

Asthma is one of the most common chronic childhood medical disorders in the United States, which affects more than 9 million children under 18 years of age.[1] The prevalence of asthma symptoms and asthma diagnosis in US children is among the highest in the world.[2] In children aged 5-14 years, the prevalence of self-reported asthma increased from 1.5 million cases in 1980 to 2.3 million cases in 1999.[3] Along with increasing prevalence, asthma severity seems to be on the rise in pediatric and adolescent patients, based on increases in the rates of office visits, hospital admissions, and emergency department (ED) visits. Moreover, the increasing burden of asthma is consistently focused on children and young adolescents. Asthma-attributable mortality nearly doubled between 1980 and 1999 in children aged 5 to 14 years, which was a substantially greater increase than that observed in older adolescents and adults.[3]

Children and adolescents with severe or difficult-to-treat asthma are an understudied population. Most of the economic burden of asthma is related to severe disease,[2] and severe disease is associated with more symptoms, more limitations in daily activities, greater medical resource use, and higher health care costs.[4] Additional

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Abbreviations used
BMI: Body mass index
CAMP: Childhood Asthma Management Program
ED: Emergency department
FVC: Forced vital capacity
HCU: Health care use
IRB: Institutional review board
NHANES: National Health and Nutrition Examination Survey
TENOR: The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens

information is needed about these patients and the treatment patterns and outcomes related to their asthma.

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) is an observational study of a large cohort of patients with severe or difficult-to-treat asthma. This TENOR analysis focuses on cross-sectional baseline data from the children and adolescents enrolled in the study. It provides the opportunity to characterize and better understand the natural history of asthma in these patients in terms of disease severity, lung function, medication use, and health care use (HCU). We hypothesized that children and adolescents with severe or difficult-to-treat asthma would have high rates of HCU and loss of lung function despite being on currently accepted guideline-directed therapy.

METHODS

Study design and participants

The TENOR study was a prospective, observational, 3-year study (2001-2004) conducted in the United States in patients with severe or difficult-to-treat asthma who received care from either an allergist or a pulmonologist. No experimental intervention was involved; participants continued to receive medications and treatments for their asthma as directed by their asthma specialist. The design and protocol of TENOR were approved by a central institutional review board (IRB) and, when necessary, by the IRB at each site; Genentech, Inc, contracted with an independent, external IRB to review and approve the protocol for sites without an IRB. All patients or their parents/guardians supplied written informed consent.

The TENOR study included patients greater than or equal to 6 years of age with severe or difficult-to-treat asthma; patients with mild or moderate asthma were eligible for enrollment if their physician considered their asthma difficult-to-treat and if they met the additional inclusion and exclusion criteria.[5] Patients had to have evidence of either high HCU (2 or more unscheduled care visits for asthma or 2 or more oral corticosteroid bursts) or high medication use (currently requiring $\geq$3 medications to control asthma or long-term daily high doses of inhaled corticosteroids or use of 5 mg/day or more of oral prednisone), or both, in the past year.[5] Patients were excluded if they were heavy smokers ($\geq$30 pack-years) or if they had a diagnosis of cystic fibrosis. Few current or former smokers were included in this cohort; therefore, smoking data were not included in this analysis. Additional detail regarding inclusion/exclusion criteria has been described previously[5] and can be found in this article's Online Repository at www.jacionline.org.

Demographic, clinical, and laboratory assessments

Data presented in this analysis were obtained at study entry and are cross-sectional. In addition to assessing the asthma severity of each participant, physicians reported whether their patient's asthma was considered difficult-to-treat based on specified parameters (that is, complex treatment regimen, multiple drugs required, unable to avoid triggers, frequent exacerbations, severe exacerbations, and/or unresponsive to therapy).[5]

For participants less than 12 years of age, the parent or guardian was present to help answer interview questions and complete questionnaires fully and accurately; if needed, adolescents were permitted to obtain assistance from a parent (or other adult if a parent was not available). Demographic (age, gender, race, height, and weight), clinical data (including HCU and medication use), and laboratory data (total serum IgE, spirometry) were collected by study coordinator interview and evaluation. Overweight was defined as weight-for-age greater than or equal to the 95th percentile based on the US growth charts developed by the Centers for Disease Control.[6]

HCU

Data on asthma-related HCU were based on data collected at study entry by study coordinator interview[5] and included ED visits, overnight hospitalizations, corticosteroid bursts, and unscheduled office visits/contacts with physician during the previous 3 months. Baseline data on intubation was obtained in answer to the question "have you ever been intubated?"

Asthma medications

Information about all current asthma medications, including long-term controller and quick-relief medications, was collected by the study coordinator during an interview in which patients and parents actually brought in their medications for review.

IgE data

Total serum IgE levels (IU/mL) were measured at baseline by each study site using any commercially available assay. All total serum IgE assay tests used in TENOR received 510 (k) Food and Drug Administration approval and were considered substantially equivalent in accuracy and precision.[7] In addition, all total serum IgE assays were calibrated to the World Health Organization's second International Reference Preparation for Human Serum IgE, World Health Organization IRP 75/502.

Spirometry

Spirometry measurements in TENOR were performed according to American Thoracic Society guidelines.[8] All sites were required to have a certified device that was calibrated daily for performing flow spirometry. For this analysis, predicted values for spirometry measures were race-adjusted. Formulas of Wang et al[9] were applied for the predicted values of white and black patients. Because these formulas do not address Hispanics, the formulas of Hsu et al[10] were used for Hispanic patients. About 5% of patients self-described as "other" did not have predicted spirometry values calculated but were included in the overall study.

Data retrieval and monitoring

The TENOR study used a Web-based system for data collection (developed using Quintiles WebCollect services and PhaseForward's InForm application; Quintiles Transnational Corp, Research Triangle Park, NC). Data were entered directly on electronic case report forms and transferred in encrypted form onto a secure server at the data coordinating center. All study coordinators received website and study protocol training.