Comparison of asthma exacerbations in pediatric and adult patients with severe or difficult-to-treat asthma

To the Editor:

Optimally controlled asthma remains elusive in many children, as suggested by the high frequency of exacerbations requiring oral corticosteroid courses in those taking long-term controller medications. Although lower than the rate of 122 per 100 person-years in children taking placebo, children with mild-to-moderate asthma taking inhaled corticosteroids in the Childhood Asthma Management Program study demonstrated an oral corticosteroid–treated exacerbation rate of 70 per 100 person-years.[1]

Studies assessing rates of asthma exacerbations in children with severe or difficult-to-treat asthma are lacking. The goal of the current study was to compare the rates of asthma exacerbations, specifically overnight hospitalizations, emergency department (ED) visits, and oral corticosteroid courses, in children and adolescent or adult patients with severe or difficult-to-treat asthma who were taking recommended long-term controller asthma medications.

The methods and baseline population characteristics of The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study have been previously described.[2] Briefly, TENOR was a prospective, observational, 3-year study conducted in the United States in patients with severe or difficult-to-treat asthma followed by asthma specialists. Study physicians subjectively categorized patients as having mild, moderate, or severe asthma. A patient was considered difficult to treat if the physician selected 1 or more of the following criteria at study entry: (1) complex treatment regimen, (2) multiple drugs required, (3) unable to avoid triggers, (4) frequent exacerbations, (5) severe exacerbations, and (6) unresponsive to therapy. Patients also had to have evidence of either high healthcare use (2 or more unscheduled care visits for asthma or 2 or more oral corticosteroid courses) or high medication use (currently requiring 3 medications to control asthma or long-term daily high doses of inhaled corticosteroids or use of 5 mg/d or more of oral prednisone), or both in the year before enrollment. No experimental intervention was involved; patients continued to receive asthma medications and treatments as recommended by their allergist or pulmonologist. At baseline, 4756 patients were enrolled at 283 study sites.

A total of 224 children, ages 6 to 11 years, and 1726 adolescents and adults, ages $\geq$12 years, were evaluated in this analysis. Patients were included if they had no missing data at follow-up assessments for spirometry and asthma-related healthcare use. Parents or guardians and adult participants gave written informed consent.

Data were collected at semiannual visits. Demographic, clinical, and medication data were collected by study coordinator interview and evaluation. Medication adherence was measured by using a proxy from the Asthma Therapy Assessment Questionnaire,[3] "What best describes how you take this medicine now?" Regular adherence was defined as "I take it every day" or "Some days I take it but other days I don't." Nonregular adherence was defined as "I used to take it but now I don't," "I only take it when I have symptoms," or "I never took it."

Spirometry was measured annually according to American Thoracic Society guidelines, and sites were required to have a certified instrument calibrated daily. Predicted values were race-adjusted.[4] For each age stratum, patients were categorized into 2 lung function strata on the basis of an Expert Panel Report (EPR)-3 guideline-defined normal (prebronchodilator percent predicted $FEV_1 > 80$ %) or abnormal (prebronchodilator percent predicted $FEV_1 \leq 80\%$) lung function at 2 consecutive assessments (baseline and month 12). Patients had to be in the same lung function stratum at baseline and month 12 to be included (patients who switched strata between the 2 assessments were excluded from analysis).

At study entry and at each 12-month visit, patients reported asthma-related healthcare use during the previous 3 months. Asthma exacerbations at months 12, 18, and 24 were defined as either (1) an overnight hospitalization or ED visit in the previous 3 months or (2) an oral corticosteroid steroid burst in the previous 3 months.

Descriptive statistics were generated for demographic and clinical variables at baseline. The frequency of asthma exacerbations was compared by age strata (6-11 years vs 12 years and older) and by lung function strata (>80% FEV_1% predicted vs $\leq$80% FEV_1% predicted). The Pearson χ^2 test (or Fisher exact test for cell counts n <5) was used to compare data. A 2-sided P value of .05 was considered statistically significant. All analyses were conducted by using SAS (version 9.1; SAS Institute Inc, Cary, NC).

Mean $\pm$ SD age (in years) was 9.6 ± 1.4 in children and 50.3 ± 16.2 in adolescents or adults with $FEV_1 \leq 80\%$, and 8.8 ± 1.7 in children and 40.9 ± 18.1 in adolescents or adults with $FEV_1 > 80\%$. Most patients were on 3 or more long-term controller asthma medications: 53% for children and 60% for adolescents or adults with $FEV_1 \leq 80\%$ ($P = .43$), and 63% for children and 57% for adolescents or adults with $FEV_1 > 80\%$ ($P = .19$).

In both normal and abnormal lung function strata, with the exception of month 12 for $FEV_1 \leq 80\%$, the frequency of ED visits or overnight hospitalizations was significantly and clinically meaningfully higher (approximately 2-fold to 3-fold) in children than in adolescents or adults (Table I). At the 18-month and 24-month visits, nearly one fourth of children in the $FEV_1 \leq 80\%$ stratum had experienced an ED visit or hospitalization in the previous 3 months, compared with only about 8% to 9% of adolescents or adults. The frequency of ED visits or overnight hospitalizations was significantly higher among adolescents or adults with abnormal lung function than among those with normal lung function. The effect among children was of similar magnitude, but only marginally higher, probably because of reduced power (Table II).

The frequency of oral corticosteroid courses was comparably high in both age and lung function strata (Table I). In the $FEV_1 \leq 80\%$ stratum, approximately 30% to 40% of both children and adolescents or adults experienced an oral corticosteroid burst in the 3 months before the 12-month and 18-month visits. At month 24, more than half (52%) of children had received an oral corticosteroid burst in the previous 3 months, compared with 31% of adolescents and adults ($P = .02$). In the $FEV_1 > 80\%$ stratum, about a fourth of children and adolescents or adults had received an oral corticosteroid burst in the 3 months before all visits. The frequency of oral corticosteroid courses was

TABLE I. Frequency of exacerbation outcomes in children age 6 to 11 years and adolescents and adults age 12 and older stratified by lung function

	FEV_1% predicted ≤80			FEV_1 % predicted >80		
	Age 6-11 y (n = 34)	Age 12+ y (n = 1081)	*P* value*	Age 6-11 y (n = 187)	Age 12+ y (n = 645)	*P* value*
ED visit or hospitalization (%)						
12 mo	14.7	9.9	.38†	11.3	5.9	.01
18 mo	23.1	8.8	.03†	11.9	5.4	.004
24 mo	22.2	8.7	.03†	13.4	5.1	.001
Oral corticosteroid course (%)						
12 mo	41.2	36.4	.57	26.3	24.1	.53
18 mo	26.9	31.4	.62	22.8	21.8	.80
24 mo	51.9	30.7	.02	26.1	22.6	.39

12+, Adolescents/adults.
**P* values compare differences between age groups.
†Derived from the Fisher exact test; other *P* values from the Pearson χ^2 test.

TABLE II. Frequency of exacerbation outcomes in lung function groups stratified by children age 6 to 11 years and adolescents and adults age 12 and older

	Age 6-11 y			Age 12+ y		
	FEV_1 % predicted ≤80 (n = 34)	FEV_1 % predicted >80 (n = 187)	*P* value*	FEV_1 % predicted ≤80 (n = 1081)	FEV_1 % predicted >80 (n = 645)	*P* value*
ED visit or hospitalization (%)						
12 mo	14.7	11.3	.57†	9.9	5.9	.004
18 mo	23.1	11.9	.13†	8.8	5.4	.01
24 mo	22.2	13.4	.24†	8.7	5.1	.02
Oral corticosteroid course (%)						
12 mo	41.2	26.3	.08	36.4	24.1	<.001
18 mo	26.9	22.8	.64	31.4	21.8	<.001
24 mo	51.9	26.1	.007	30.7	22.6	.001

12+, Adolescents/adults.
**P* values compare differences between lung function groups.
†Derived from the Fisher exact test; other *P* values from the Pearson χ^2 test.

significantly higher in abnormal than in normal lung function in children at the 24-month time point and in adolescents or adults at all time points (Table II).

There was no statistically significant difference between age or lung function strata with respect to medication adherence at baseline or month 12 follow-up. The majority of TENOR patients in our analysis (90% to 100%) were categorized as having regular adherence.

Independent of lung function, we report 2-fold to 3-fold higher frequencies of severe asthma exacerbations in children compared with adolescents or adults with severe or difficult-to-treat asthma (Table I), despite treatment with standard long-term controller asthma medications. The frequency of patients requiring oral corticosteroid courses was similar in children and adolescents or adults, with the exception of the month 24 visit, at which the frequency was higher in children with $FEV_1 \leq 80\%$ than in adolescents or adults in this same stratum (Table I). In addition, the frequencies of severe exacerbations and oral corticosteroid courses were marginally to significantly higher in children at varying time points and significantly higher at all time points in adolescents or adults with lower lung function (Table II).

These data indicate that asthma exacerbations are frequent in patients with severe or difficult-to-treat asthma, notwithstanding treatment with long-term asthma controllers, management by asthma specialists, and lung function above 80% predicted. Given the high incidence of severe exacerbations and oral corticosteroid courses in those with normal lung function, clinical impairment features in addition to lung function, as recommended by national guidelines, are needed to assess risk of asthma exacerbations in this normal lung function stratum of severe or difficult-to-treat asthma. Indeed, previous studies have shown that children with severe asthma, as determined by other outcomes, tend to have FEV_1 values near predicted normal[5] and demonstrate preserved pulmonary function.[6] In addition, in oral corticosteroid–dependent children, symptoms and episodic acute declines in lung function appear to precede chronic airflow limitation.[7] Given the limited power in this study, however, additional studies of exacerbations by lung function are needed in children with severe or difficult-to-treat asthma.

The similar-to-higher frequency of oral corticosteroid courses in children compared with adolescents and adults is of concern, given the potential for greater effects on growth of systemic corticosteroids in children.[8] Moreover, the higher frequency of severe asthma exacerbations requiring ED visits or hospitalizations despite similar to higher frequencies of oral corticosteroid use in children indicates greater limitations of systemic corticosteroids to prevent severe exacerbations in children compared with adults.

Our findings demonstrate an unmet need in children with severe or difficult-to-treat asthma given the high frequency of severe asthma exacerbations despite asthma specialist–prescribed optimal controllers and acute intervention with oral corticosteroids and the potential for adverse effects from frequent oral steroid courses and high-dose inhaled corticosteroids.[9,10] As such, either better use of present interventions with improved

objective adherence[11,12] or new therapeutic modalities to reduce asthma-related healthcare use would be advantageous.

We gratefully acknowledge Bryan Hains, PhD, of Genentech, Inc, who helped develop the first draft of this brief report with their assistance and extensive input.

Robert S. Zeiger, MD, PhD[a]
Bradley E. Chipps, MD[b]
Tmirah Haselkorn, PhD[c]
Lawrence Rasouliyan, MPH[d]
F. Estelle R. Simons, MD[e]
James E. Fish, MD[c]

From [a]Kaiser Permanente Southern California, San Diego; [b]the Capital Allergy and Respiratory Disease Center, Sacramento, Calif; [c]Genentech, Inc, South San Francisco, Calif; [d]ICON Clinical Research, San Francisco, Calif; and [e]the University of Manitoba, Winnipeg, Canada E-mail: Robert.S.Zeiger@kp.org

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens study is sponsored by Genentech, Inc, and Novartis Pharmaceuticals Corp.

Disclosure of potential conflict of interest: R. S. Zeiger is a consultant for Aerocrine, AstraZeneca, Dynavax, Genentech, GlaxoSmithKline, Merck & Co, Novartis, and Schering-Plough and receives research support from AstraZeneca, Merck & Co, GlaxoSmithKline, Teva Pharmaceuticals, Genentech, Aerocrine, and the National Heart, Lung, and Blood Institute. B. E. Chipps is a consultant for Alcon, Aventis, Genentech, AstraZeneca, GlaxoSmithKline, MedPoint, Novartis, Schering-Plough, Sepracor, and Merck & Co; is on the speakers' bureau for Alcon, Aventis, Genentech, AstraZeneca, Boehringer, GlaxoSmithKline, MedPoint, Novartis, Pfizer, Schering-Plough, Sepracor, and Merck; and receives grant support from Alcon, Aventis, Genentech, AstraZeneca, Boehringer, GlaxoSmithKline, Novartis, Schering-Plough, Sepracor, and Merck. T. Haselkorn is employed by Genentech. L. Rasouliyan is employed by ICON Clinical Research. F. E. R. Simons receives grant support from the Canadian Institutes of Health Research and is a consultant on The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens project for Genentech. J. E. Fish is employed by Genentech.

REFERENCES

1. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. N Engl J Med 2000;343:1054-63.
2. Dolan CM, Fraher KE, Bleecker ER, Borish L, Chipps B, Hayden ML, et al. TENOR Study Group. Design and baseline characteristics of The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study: a large cohort of patients with severe or difficult-to-treat asthma. Ann Allergy Asthma Immunol 2004;92:32-9.
3. Skinner EA, Diette GB, Algatt-Bergstrom PJ, Nguyen TTH, Clark RD, Markson LE, et al. The Asthma Therapy Assessment Questionnaire (ATAQ) for children and adolescents. Disease Management 2004;7:305-13.
4. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999;159: 179-87.
5. Bacharier LB, Strunk RC, Mauger D, White D, Lemanske RF Jr, Sorkness CA. Classifying asthma severity in children: mismatch between symptoms, medication use, and lung function. Am J Respir Crit Care Med 2004;170:426-32.
6. Paull K, Covar R, Jain N, Gelfand EW, Spahn JD. Do NHLBI lung function criteria apply to children? a cross-sectional evaluation of childhood asthma at National Jewish Medical and Research Center, 1999-2002. Pediatr Pulmonol 2005;39: 311-7.
7. Jenkins HA, Cherniack R, Szefler SJ, Covar R, Gelfand EW, Spahn JD. A comparison of the clinical characteristics of children and adults with severe asthma. Chest 2003;124:1318-24.
8. Leone FT, Fish JE, Szefler SJ, West SL. Systematic review of the evidence regarding potential complications of inhaled corticosteroid use in asthma: collaboration of American College of Chest Physicians, American Academy of Allergy, Asthma, and Immunology, and American College of Allergy, Asthma, and Immunology. Chest 2003;124:2329-40.
9. Zöllner EW. Hypothalamic-pituitary-adrenal axis suppression in asthmatic children on inhaled corticosteroids (Part 2)—the risk as determined by gold standard adrenal function tests: a systematic review. Pediatr Allergy Immunol 2007;18: 469-74.
10. Kelly HW, Van Natta ML, Covar RA, Tonascia J, Green RP, Strunk RC. CAMP Research Group. Effect of long-term corticosteroid use on bone mineral density in children: a prospective longitudinal assessment in the childhood Asthma Management Program (CAMP) study. Pediatrics 2008;122:53-61.
11. Rand C, Bilderback A, Schiller K, Edelman JM, Hustad CM, Zeiger RS. Adherence with montelukast or fluticasone in a long-term clinical trial: results from the mild asthma montelukast versus inhaled corticosteroid trial. J Allergy Clin Immunol 2007;119:916-23.
12. Strunk RC, Bacharier LB, Phillips BR, Szefler SJ, Zeiger RS, Chinchilli VM, et al. Azithromycin or montelukast as inhaled corticosteroid-sparing agents in moderate-to-severe childhood asthma study. J Allergy Clin Immunol 2008;122:1138-44.

Available online October 5, 2009.
doi:10.1016/j.jaci.2009.07.052

Bovine and porcine gelatin sensitivity in children sensitized to milk and meat

To the Editor:

Gelatin is a protein derived from collagen, and it is obtained principally from cow and pig bones, hides, and fish skin. It is a common ingredient in foods such as jellies, sweets, yogurt, and frozen desserts. It is also found in lunch meats, and it is used extensively as clarifying agents in wine, juices, and other beverages. Bovine and porcine gelatins, in particular, also have numerous applications throughout the pharmaceutical industry as integral components in drug capsules, plasma expanders, and stabilizers in vaccines, including measles, mumps and rubella (MMR), varicella, yellow fever, rabies, and some influenza vaccines. Severe allergic reactions, including anaphylaxis, have been reported after intravenous administration of modified fluid gelatins as plasma substitutes.[1] Postvaccination allergic reactions to MMR and varicella vaccines have been linked to the gelatin excipient.[2,3] Systemic allergic reactions have also been observed with the ingestion of gelatin-containing foods and administration of gelatin-containing medical products (eg, suppositories). These gelatin exposures have been associated with sensitization as evidenced by the induction of gelatin-specific IgE antibodies.[2-5]

American[6] and Finnish[7] groups have reported that 27% and 14% to 28%, respectively, of children who experienced systemic reactions after measles, mumps, and rubella vaccination had gelatin-specific IgE antibodies. In contrast, a Japanese study reported that at least 86% of children who manifested an immediate-type hypersensitivity reaction after receipt of a gelatin-containing vaccine (measles, rubella, mumps, or varicella) had detectable gelatin-specific IgE in their blood.[8] Type I hypersensitivity reactions to gelatin have even been reported with specific IgE levels as low as 0.8 kUa/L or kilo allergen-specific IgE units per liter.[8]

In the current study, we chose to not study fish gelatin sensitivity because the gelatins used in medical applications are almost exclusively bovine and porcine. We hypothesized that subjects who are sensitized to beef and pork meat and/or cow's milk are at greater risk for sensitization to bovine and porcine gelatin. Moreover, we hypothesized that there is cross-reactivity between bovine and porcine gelatin. These hypotheses were investigated by using serologic techniques to determine the prevalence and extent of cross-reactivity of bovine and porcine gelatin-specific IgE antibodies among children with confirmed sensitivity (IgE antibodies > 0.35 kUa/L) to pork or beef meat and cow's milk and a clinical history of cow's milk allergy.

Serum from children (n = 141; age, 3 months to 17 years; median age, 4 years; 74% boys; total IgE range, 19-49,457 kU/L; median, 909 kU/L) were selected for evaluation in the current study on the basis of a positive IgE antibody serology to cow's milk, beef, and/or pork meat. The exception was 1 subject who had a weak bovine and porcine gelatin-specific IgE <0.5 kUa/L in the absence of detectable milk, beef meat