

Difficult-to-control asthma: Clinical characteristics of steroid-insensitive asthma

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Background: Although widely used, little is known regarding the patterns of response that subjects with severe asthma exhibit to oral glucocorticoid (GC) therapy.

Methods: We retrospectively reviewed the charts of 164 consecutive adolescents admitted to the National Jewish Medical and Research Center for difficult-to-control asthma. Data collected included medical history, pulmonary function measures by plethysmography, methacholine challenge results, AM cortisol levels, serum IgE, total eosinophil counts (TEC), serum eosinophil cationic protein (ECP), soluble IL-2 receptor (sIL-2R), and spirometry.

Results: Eighty-seven patients (53%) required a GC burst during the hospitalization secondary to poor asthma control. Those requiring a GC burst had a significantly longer history of asthma, a greater degree of bronchial hyperresponsiveness, and lower pulmonary function. Twenty-one patients (24%) failed to respond with a greater than 15% improvement in their AM prebronchodilator FEV₁ after the GC burst and were termed steroid insensitive (SI). Although those with SI asthma had a similar duration of asthma, they required oral GC therapy at a younger age, required a larger maintenance oral GC dose on admission, and were more likely to be African-American, compared with those with steroid-sensitive asthma. Furthermore, two distinct spirometry patterns were noted among the SI asthmatic subjects: "chaotic" and "non-chaotic." Patients with the chaotic pattern were characterized by a significant degree of variability (greater than 30%) in daily pulmonary function, whereas those with nonchaotic, SI asthma were characterized by less than 15% variability in daily lung function. Those with nonchaotic SI were diagnosed with asthma and treated with oral GCs at a later age.

Conclusions: This retrospective study suggests that SI asthma is quite common (25%) among adolescents with severe asthma evaluated at a national referral center. In addition, two distinct patterns of SI asthma have been identified that may constitute different pathophysiologic processes. Finally, the overrepresentation of African-Americans in the SI group supports the need for further epidemiologic studies investigating the prevalence of SI asthma and the impact

early asthma intervention may have on this severe form of asthma. (*J Allergy Clin Immunol* 1998;101:594-601.)

Key words: Steroid-sensitive asthma, steroid-insensitive asthma, steroid-resistant asthma, glucocorticoid, inflammation

Many studies have shown inhaled and systemic glucocorticoid (GC) therapy to be effective in the treatment of chronic asthma.¹ Although the majority of asthmatic subjects respond to systemic GCs, a subpopulation fails to derive clinical benefit from GC therapy, and these individuals have been termed "steroid resistant" (SR). SR asthma was first described by Schwartz et al.² in 1968, when the investigators identified a group of six subjects with severe asthma who displayed a poor response to intravenous cortisol and a decreased eosinopenic response.

In 1977, Turner-Warwick³ described patterns of GC response among asthmatic subjects in a few patients. On the basis of data obtained from serial peak flow measurements, she described the "brittle" asthmatic subjects and the "irreversible" asthmatic subjects. The "brittle" asthmatic subject was characterized by intractable asthma with "chaotic" fluctuations in peak expiratory flow rate despite the use of high-dose GCs. The "irreversible" asthmatic subject was characterized as an asthmatic subject who, despite a bronchodilator response, continued to display a component of irreversibility after a course of systemic GC therapy. Carmichael et al.⁴ in 1981 defined SR asthma as a lack of improvement in the AM prebronchodilator FEV₁ of greater than 15% after a 7-day course of 20 mg/day of prednisolone or its equivalent. Those with SR asthma were more likely to have a positive family history of asthma and a longer duration of asthma. A recent symposium on steroid resistance in asthma stressed the critical need to better understand the natural history and cause of SR asthma.⁵ In addition, the symposium authors concluded that asthmatic subjects poorly responsive to GC therapy should be termed "steroid insensitive" (SI) rather than SR because resistance has the connotation of being absolute.

Given the paucity of information in the literature characterizing the response of subjects with severe asthma to systemic GC therapy, especially in children and adolescents, we retrospectively reviewed the treatment course of all adolescent patients admitted to the National Jewish Medical and Research Center with the diagnosis of severe asthma to better define patterns of GC response and their clinical characteristics as well as to determine the prevalence of SI.

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Abbreviations used

BHR:	Bronchial hyperresponsiveness
ECP:	Eosinophil cationic protein
GC:	Glucocorticoid
iGC:	Inhaled glucocorticoid
Raw:	Airway resistance
Sgaw:	Airway conductance
sIL2R:	Soluble IL-2 receptor
SR:	Steroid resistant
SI:	Steroid insensitive
SS:	Steroid sensitive
TEC:	Total eosinophil count

METHODS

This retrospective study was undertaken by reviewing the clinical course of 164 consecutive patients admitted to the National Jewish Medical and Research Center's adolescent unit in Denver between July 1993 and February 1997 for difficult-to-control asthma. Information collected included patient demographics such as age, sex, race, and family history of asthma or atopy. Historical information included age at the time of asthma diagnosis, age of first exposure to oral GCs, average number of GC bursts per year, duration of chronically administered oral GCs, previous history of intubations, the use and frequency of inhaled/nebulized β -agonist therapy, and the dosage of inhaled and oral GCs. Data collected upon admission and during the hospitalization included AM cortisol, serum IgE, total eosinophil count (TEC), eosinophil cationic protein (ECP), and soluble IL-2 receptor (sIL2R). In addition, number of positive allergen prick skin test results and methacholine challenge results were collected. Spirometry values were measured three times per day (mornings, afternoons, and evenings) in all the patients. Body plethysmography was obtained early after admission for measurements of total lung capacity (TLC), thoracic gas volume (TGV), residual volume (RV), airway resistance (Raw) and specific airway conductance (Sgaw). In all patients, an evaluation of potential aggravating factors including gastroesophageal reflux and sinusitis was performed, and when identified appropriate treatment was rendered.

The patients were then divided into two groups: those who required an oral GC burst during their hospitalization because of poor asthma control and those who did not require a prednisone burst during their hospitalization (Fig. 1). Because this was a retrospective study, uniform criteria were not used by the clinicians when deciding whether a GC burst was indicated. In reviewing the charts of those who required a GC burst, poor pulmonary function, wheezing, active asthma symptoms, and nocturnal hypoxemia or awakening were the most commonly cited reasons. Also, for the purpose of this study, a patient was defined as having required a prednisone burst if he or she received a minimum of 40 mg per day of prednisone or its equivalent for at least 7 consecutive days. Data collected serially on all patients who performed spirometry at least three times per day were plotted versus day of prednisone therapy. Depending on their response to GC therapy, the patients were divided into those who were steroid sensitive (SS) and those who were SI. SS asthmatic subjects were defined as those whose AM prebronchodilator FEV₁ improved by greater than 15% after the GC burst. The formula for calculating the mean change in

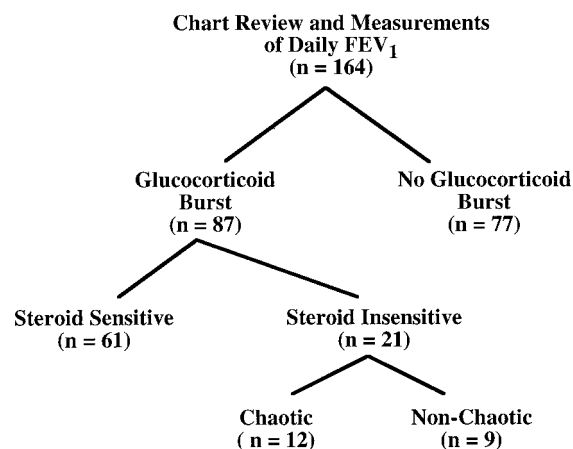


FIG. 1. Flow diagram of study analysis. Of 164 patients admitted to National Jewish Medical and Research Center with difficult-to-control asthma, 87 received a GC burst because of poor asthma control. Of those who received burst therapy, 61 demonstrated a greater than 15% increase in their AM prebronchodilator FEV₁ after the burst and were considered SS. Of the remaining 26 patients who failed to respond with a greater than 15% improvement, 21 were considered SI. Five patients who failed to respond to the GC burst were excluded from further analysis because of their nearly normal pulmonary function. Two distinct patterns of SI asthma were identified and termed chaotic and nonchaotic.

FEV₁ before versus after GC burst was as follows: $(FEV_{1\text{ postburst}} - FEV_{1\text{ preburst}}) / FEV_{1\text{ preburst}} \times 100\%$. Those with baseline FEV₁ values less than 85% of predicted and who failed to respond with greater than 15% improvement in their AM prebronchodilator FEV₁ after the oral GC burst were termed SI. When the spirometry graphs of the SI asthmatic subjects were evaluated, two distinct patterns were identified and were termed "chaotic" and "nonchaotic." The chaotic pattern was defined as those individuals who, despite an oral GC burst continued to display wide daily variation (coefficient of variation or CV of greater than 30%) in their FEV₁ values. The CV of FEV₁ is the SD/mean $\times$ 100 (to yield a percent) and was calculated by all prebronchodilator FEV₁ values after the GC burst. Those that displayed less than 30% CV of FEV₁ (prebronchodilator) values after the GC burst were termed nonchaotic.

Blood for ECP quantitation was obtained in serum separator tubes that were incubated at room temperature for 60 minutes before centrifugation at 2000 rpm for 10 minutes. ECP levels were determined with the Pharmacia CAP System, a fluorescence enzyme immunoassay (FEIA) (Pharmacia Diagnostics AB, Uppsala, Sweden). The manufacturer states that the detection limit of the assay is less than 0.5 mg/L, and the intraassay and interassay coefficients of variation are equal to or less than 7% and 8%, respectively. Soluble IL-2 receptor levels were performed by enzyme immunoassay (Cellfree IL-2R Test Kit, T Cell Diagnostics, Cambridge, Mass.). The manufacturer states that the detection limit of this assay is 50 U/ml, and the intraassay and interassay variation coefficients are equal to or less than 3.5% and 6%, respectively.

The data were analyzed with JMP (SAS Institute Incorporated) and are presented as medians and interquartile ranges (25th and 75th percentiles). Comparative analysis of variance between individual groups was performed with ANOVA/Student's *t* test for parameters with normality and the nonpara-

TABLE I. Clinical characteristics of the study population ($n = 164$)

Admission demographic data	Median (IQR)*
Age (yrs)	14.0 (13.0, 15.5)
Sex (m/f)	45%/55%
Race	75% Caucasian, 17% African-American, 7% Hispanic, 1% American Indian
Duration of asthma (yrs)	11.9 (8.0, 13.0) years
Inhaled GC dose	1500 (840, 2,213) $\mu\text{g}/\text{d}$
Maintenance oral GC	
% of study population	51
admission dose (prednisone or equivalent)	15 (5, 30) mg/d
Pulmonary function	
Admission AM FEV ₁ (% predicted)	77 (61, 90)
Total lung capacity (% predicted)	113 (103, 124)
Residual volume (% predicted)	204 (158, 260)
Laboratory	
Allergy skin prick test	73% positive (>3 positive test responses)
AM cortisol	3.8 (0, 11.1) $\mu\text{g}/\text{dl}$ (normal, 5-20)
Total eosinophil count	176 (35, 405) mm^3 (normal, 0-450)
IgE	208 (56, 544) IU/ml (normal, 1.6-456)
Serum ECP (ng/ml)	14.0 (8.2, 23.9) ng/ml (normal, 0-10)
Serum soluble IL-2 receptor (U/ml)	630 (419, 874) U/ml (normal, 145-913)

IQR, Interquartile range; the 25th and 75th percentiles are indicated in parentheses.

*Data presented as median values.

metric Wilcoxon rank sums test when the assumption of normality was not made. Measurements of strength of linear relationships between two variables were performed with the Pearson product moment correlation coefficient for parametric measures and the Spearman's ρ coefficient for nonparametric measures by computing the rank of the data. Tests of proportions (or percentages) between groups were performed by the Pearson's Chi square test. Statistical significance was observed when probabilities were 0.05 or less.

RESULTS

Study population

The charts from a total of 164 adolescent patients with severe asthma were evaluated. The median age of the study population was 14.0 years, with a relatively equal sex distribution (Table I). The racial distribution was 75% Caucasian, 17% African-American, 7% Hispanic, and 1% American Indian. The group had a long history of asthma, were on high-dose inhaled GC (iGC) therapy, and more than 50% of the individuals required maintenance oral GC therapy. Despite the history of high-dose inhaled GC therapy and chronic oral GC treatment in more than 50% of the patients, baseline pulmonary function studies indicated the presence of hyperinflation, air trapping, and airflow obstruction. In addition, the study population used a median of 40 puffs of inhaled β -agonist per week. Although the TEC was within the normal limits, the median ECP level was elevated at 14.0 ng/ml (normal range 0 to 10 ng/ml), whereas the sIL2R was within the normal range at 630 U/ml (normal range 145 to 913 U/ml). Nearly three quarters of the individuals were atopic as defined by positive reactions to more than three standard allergens on prick skin testing. There were inverse correlations between admission oral GC dosage and admission AM

cortisol level ($p < 0.0001$) and the markers of inflammation ECP ($p = 0.053$), sIL2R ($p = 0.039$), and TEC ($p < 0.0001$).

Clinical characteristics of patients requiring a GC burst

From this study population of severe asthma, 87 (53%) required an oral GC burst because of poor asthma control. There were several features distinguishing those individuals requiring an oral GC burst versus those who did not. The group requiring a burst had a significantly longer duration of asthma (11.5 vs 10 years; $p = 0.008$), demonstrated a significantly greater degree of bronchial hyperresponsiveness compared with the group not requiring a burst as evidenced by a median methacholine PC₂₀ value of 0.26 versus 0.66 mg/ml ($p = 0.016$), and had significantly greater airflow obstruction as indicated by their baseline AM prebronchodilator FEV₁ (% predicted) being significantly lower (64% vs 89% of predicted) than the group not requiring a GC burst. Overall, the group demonstrated a significant improvement in their AM prebronchodilator FEV₁ after the GC burst, with the median FEV₁ increasing to 87% (IQR 78, 99) of predicted, a value similar to the admission FEV₁ noted in the nonburst group. In addition, a positive correlation was found between the PC₂₀ value and the admission AM prebronchodilator FEV₁ in the group that required a GC burst ($r = 0.35$; $p = 0.03$). In assessing markers of inflammation, the ECP levels were slightly elevated in both groups, with no statistically significant difference between the two groups (data not shown). In contrast, the sIL2R values in both groups were within the normal range and again, were not statistically different from each other.

TABLE II. Distinguishing features between those with SI versus those with SS asthma

	SI asthma (n = 21)	SS asthma (n = 61)	p Value
African-American (%)	38	11.5	0.007*
Duration of asthma (yrs)	12.0 (10, 13.8)	11.4 (9.5, 13.0)	0.09
Age at first oral GC use (yrs)	5.0 (3.0, 6.0)	8.0 (3.0, 10.0)	0.025*
Admission oral GC dose (mg/day)‡	20 (5, 58)	10 (2.5, 25)	0.025*
Admission β -agonist use (inhalations/wk)	50 (30, 140)	50 (30, 100)	0.35
AM prebronchodilator FEV ₁			
Preburst (% predicted)	60 (54.4, 68.5)	64 (56, 76.5)	0.26
Postburst (% predicted)	63 (55, 70.5)	93 (84, 103.5)	0.0001*
Δ FEV ₁ Postburst (%)†	7.0 (1.0, 11.0)	44.8 (29, 63)	0.0001*
TLC (% predicted)	103 (87, 115)	117 (107, 125)	0.005*
Raw (% predicted)	110 (83, 137)	82 (62, 104)	0.02*
Eosinophil cationic protein (ng/ml)	11.5 (9.3, 18.1)	15.5 (9.9, 26.8)	0.095
Soluble IL ₂ receptor (U/ml)	641 (328, 932)	626 (468, 847)	0.62

Data are presented as median values.

IQR, Interquartile range: the 25th and 75th percentiles are indicated in parentheses.

*p values < 0.05 are statistically significant.

† Δ FEV₁ calculated as shown in the Results section.

‡Dosage expressed in milligrams per day of prednisone or its equivalent.

Characteristics of SI asthma

Of the 87 patients who required a GC burst, 61 (70%) demonstrated a greater than 15% increase in their AM prebronchodilator FEV₁ after the oral GC burst, whereas the FEV₁ in the remaining 26 failed to respond, with a less than 15% improvement. Of these 26 patients, five patients, although failing to respond with a greater than 15% change in their FEV₁, had baseline AM prebronchodilator FEV₁ values greater than 85% of predicted. Despite nearly normal FEV₁ values in these five cases, three were given a GC burst secondary to hyperinflation and air trapping noted with plethysmography, while a GC burst was administered in another secondary to decreased β -agonist response, and in one case there was not a clearly defined reason. Because these individuals had nearly normal pulmonary function before the GC burst, these patients were excluded from further analysis.

Although the patients with SI asthma had a similar duration of asthma compared with the SS group (12.0 vs 11.4 years), they required systemic GC therapy at a much earlier age (5 vs 8 years; $p = 0.025$) and were more likely to be African-American (38% vs 11.5%; $p = 0.007$) and to require a greater amount of oral GC as their maintenance dose (20 vs 10 mg/d; $p = 0.025$) (Table II). Of some surprise, those with SI asthma did not require more frequent use of inhaled β -agonists than those with SS asthma (median number of β -agonist puffs per week was 50 for each group). Also, there was no difference in admission AM prebronchodilator FEV₁ values among the SI and SS groups. By definition, those with SS asthma demonstrated a significant improvement in their AM prebronchodilator FEV₁ (% predicted), with a 45% improvement in their pulmonary function after the GC burst compared with only a 7% improvement among those with SI asthma ($p < 0.0001$). The

ECP and sIL2R values at baseline were not statistically different between the two groups.

Nonchaotic versus chaotic spirometry pattern among those with SI asthma

Two distinct spirometric profiles were observed in the 21 patients with SI asthma during and after the oral GC burst. Nine (43%) patients displayed a chaotic pattern characterized by greater than 30% variability in their daily prebronchodilator FEV₁, whereas the remaining 12 (57%) displayed very little fluctuation in their pulmonary function, which we have termed nonchaotic (Fig. 2). Those with the nonchaotic pulmonary function profile were diagnosed with asthma at a significantly later age (3.5 vs 1.5 year of life; $p = 0.05$) and had first received oral GCs at a much later age (5.5 vs 1.5 years; $p = 0.03$) compared with those SI asthmatic subjects with the chaotic pulmonary function profile (Table III). In addition, there was a significantly greater percentage of African-Americans (58% vs 11%, $p = 0.027$) in the nonchaotic SI asthma group. Of note, there were no statistically significant differences between the two groups in terms of family history of allergy or asthma, degree of bronchial hyperresponsiveness (BHR), or admission pulmonary function. There were also no statistically significant differences between IgE or any of the markers of inflammation (TEC, sIL2R, and ECP) at baseline, which could have differentiated between the two groups.

DISCUSSION

This is the first study to describe distinct patterns of response to oral GC therapy in adolescents with asthma. It is also the first study to provide information on the prevalence and the clinical characteristics of GC insensitivity among adolescents with severe asthma. The

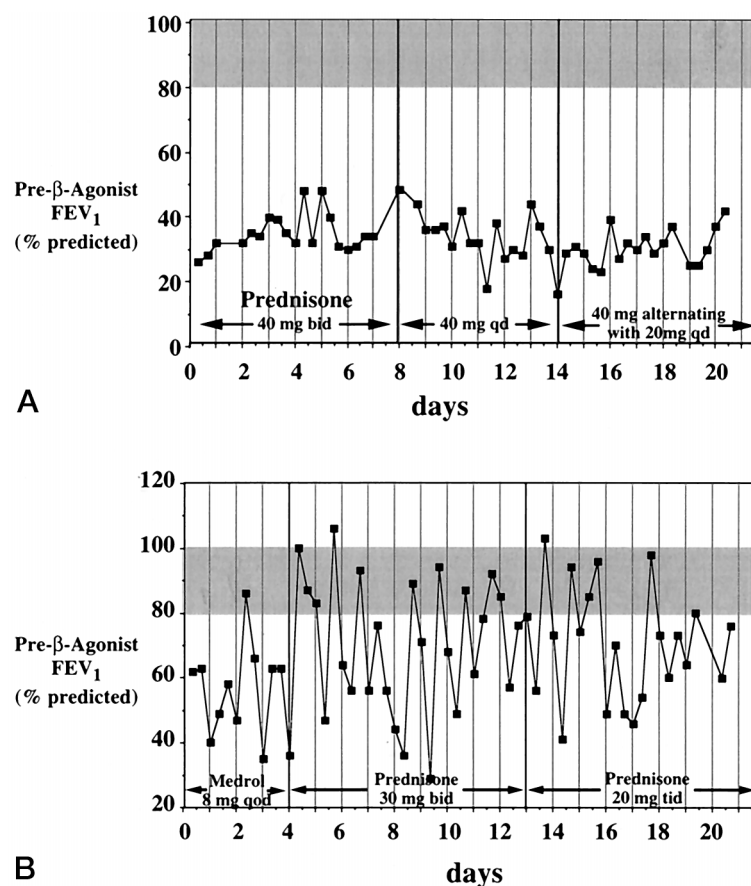


FIG. 2. Examples of two spirometric patterns noted among patients with SI asthma. Pre- β -agonist FEV₁, reported as percent predicted, is plotted versus days of observation. FEV₁ measurements were obtained three times a day (morning, noon, and evening), and the vertical lines represent AM values. SI asthma is defined by 15% or greater change in AM FEV₁ after a GC burst with 40 mg/day or more of prednisone or its equivalent for a minimum of 7 consecutive days. **A**, Nonchaotic pattern is defined by 30% or greater variability in daily FEV₁ after oral GC burst. **B**, Chaotic pattern is defined by greater than 30% variability in daily FEV₁ after oral GC burst.

ethnic composition of our population reflected that of the United States.⁶ The study group as a whole had asthma for much of their lives, 90% were receiving high-dose inhaled GC therapy, and more than 50% were receiving maintenance oral GC. The group displayed moderate airflow obstruction with airtrapping on admission, and roughly 75% were atopic as defined by allergen prick skin test positivity. The 75% prevalence of positive prick skin tests among our study population is similar to what has been previously reported. Zimmerman et al.⁷ reported a positive skin prick test prevalence of 65% among 123 children with asthma evaluated in their clinic. Similar results were noted by Montgomery Smith,⁸ whereas Tuchinda et al.⁹ reported a much higher prevalence with more than 90% of 2000 Thai children with asthma having positive prick skin tests to major allergens. More than half of the study population required a course of high-dose oral GC therapy because of poor asthma control during their admission. Not surprisingly, those requiring a GC burst displayed significantly lower

pulmonary function and greater bronchial hyperresponsiveness.

Of significance, 24% of the patients were found to be SI, failing to respond to the GC burst with a less than 15% improvement in their AM prebronchodilator FEV₁. It should be stressed that this was a retrospective cohort study, and as a consequence, it has a number of inherent weaknesses. First, the issue of population bias must be acknowledged. Given the tertiary referral status of our institution, the study population most likely represents adolescents with the most severe asthma. Thus it is difficult to know whether the prevalence of SI asthma among the general population of asthmatic subjects is similar to the results of this study. Second is the issue of confounding variables, especially as it pertains to potential explanations for the overrepresentation of African-Americans among those with SI asthma. Several factors including allergen exposure (cockroach exposure in inner cities), socioeconomic status, lack of adequate care, as well as genetic predisposition could all

TABLE III. Distinguishing features between those with nonchaotic versus those with chaotic SI asthma

	Nonchaotic (<i>n</i> = 12)	Chaotic (<i>n</i> = 9)	<i>p</i> Value
CV of FEV ₁ post GC burst (%)	8 (3, 12)	40 (32, 66)	0.0001*
African-American (%)	58	11	0.027†
Age of asthma diagnosis (yrs)	3.5 (2, 4)	1.5 (1, 3)	0.046*
First use of oral GC (yr)	5.5 (2.9, 9.3)	1.5 (1, 3)	0.033*
Previously intubated (%)	25	11	0.42
Family history of allergy/asthma (%)	89/80	67/71	0.3/0.7
Methacholine challenge (PC ₂₀ mg/ml)	0.18 (0.11, 0.46)	0.26 (0.21, 0.28)	0.33
Admission oral GC dose (mg/day)‡	20 (9, 76)	20 (3, 40)	0.5
Admission AM prebronchodilator FEV ₁ (% predicted)	59 (54, 73)	60 (50, 68)	0.41
Eosinophil cationic protein (ng/ml)	11.6 (7.4, 13.0)	11.4 (9.7, 21.8)	0.13
Soluble IL ₂ receptor (U/ml)	480 (282, 1089)	653 (513, 880)	0.52

Data presented as median values.

IQR, Interquartile range; the 25th and 75th percentiles are indicated in parentheses.

*Statistics calculated with the Wilcoxon nonparametric rank sum test with *p* values < 0.05 being statistically significant.

†Statistics calculated with Pearson's chi square with *p* value < 0.05 being statistically significant.

‡Dosage expressed in milligrams per day of prednisone or its equivalent.

contribute. Also, as both early onset of oral GC use and greater likelihood of being of African-American ethnicity were found among the SI group, it is difficult to differentiate between the effect of race and the onset of GC use on the development of SI asthma.

Another potential weakness of our study comes from how the definition of SI asthma was made. It has become more apparent over time that SI asthma most likely represents an extreme end of a continuum of steroid responsiveness, and as such, any attempt at a definition will be "arbitrary." The same is true for the length of time GC are administered before determining whether a patient has failed to respond to that therapy. It should be noted that all studies on this topic have used similar definitions.^{4, 7, 10} In fact, a recent symposium on SI asthma addressed this specific issue⁵ and stressed that when evaluating an individual with suspected SI asthma, one should ensure that the patient indeed has asthma, that compliance is ensured, and that the patient receive an adequate dose of GC (40 or more mg/d) for an adequate period of time (1 to 2 weeks). In addition, lack of improvement in pulmonary function (less than 15% increase in prebronchodilator FEV₁) after GC treatment was also deemed helpful in defining response.⁵ Our working definition of SI asthma met all the criteria as recently proposed. In addition, and unlike other studies, compliance with oral GC therapy was ensured because all patients received their medications under direct supervision.

Although information is available on the immunopathogenesis of SI asthma,¹⁰⁻¹⁵ there are no published epidemiologic studies describing the prevalence of SI asthma. The results of our study suggest that the prevalence of SI asthma among adolescents with severe asthma may be higher than expected. However, these results are consistent with a previous study suggesting that the "at risk" population for GC insensitivity may be quite high as in vitro resistance to the suppressive effects

of prednisolone on mitogen-induced lymphocyte proliferation has been identified in up to 25% of normal control subjects.¹¹

In addition to the paucity of information regarding the prevalence of SI asthma, there is almost no information regarding the clinical characteristics of SI asthma and no information regarding steroid insensitivity among adolescents. Our results suggest that SI asthmatic subjects are more likely to be African-American (*p* = 0.007), to have required systemic GC therapy at an earlier age, and to require greater amounts of maintenance oral GC compared with their SS peers. One could speculate that SI asthmatic subjects had severe disease from an early age, as suggested by the early use of systemic GC therapy, and that their disease continues to be severe, as reflected by their higher maintenance oral GC requirement. Most patients who are poorly responsive to GC have a relative, not an absolute, resistance to GC. Those with SI asthma were similar to those with SS asthma in terms of airflow obstruction on admission, methacholine PC₂₀ values, presence of atopy, and family history of allergy or asthma. Pulmonary function data obtained shortly after admission (and before the GC burst) revealed those with SI asthma to have smaller lung volumes and a greater degree of airway resistance. Of some surprise, the markers of inflammation we chose to evaluate (total eosinophil count, serum ECP, and sIL2R drawn at admission) had no predictive value in differentiating SS from SI asthma.

On the basis of review of the FEV₁ plots from those with SI asthma, there were two distinct and evenly distributed profiles: an irreversible or nonchaotic profile and a chaotic profile. Those with the nonchaotic profile, although demonstrating a significant bronchodilator response, displayed little diurnal variability in their pulmonary function throughout their hospitalization. In contrast, those with the chaotic profile had wide swings in their FEV₁ values throughout the day that were refrac-

tory to the GC burst. Those with nonchaotic SI asthma were much more likely to be African-American, to have been diagnosed with asthma at a later age, and to have been treated with systemic GC at a later age. Although speculative, those asthmatic subjects with nonchaotic SI asthma may have developed significant airway remodeling as a result of possible delay in diagnosis and delayed utilization of GC therapy. Alternatively, the persistent inflammation in this group may have led to a progression in severity. Postmortem studies from patients who died from status asthmaticus have demonstrated significant increases in bronchial smooth muscle volume, thickening of lamina reticularis, and increased mucus gland volume.¹⁶ Recent studies using bronchoscopy with bronchial biopsies from patients with chronic asthma have demonstrated epithelial destruction, increased numbers of lymphocytes and eosinophils in the lamina propria and submucosa, and subepithelial fibrosis.¹⁷⁻¹⁹ Because the nonchaotic SI group had relatively fixed airflow obstruction with little diurnal variation, it is possible that the airways of these patients have undergone significant airway remodeling leading to airway fibrosis.

In contrast to the nonchaotic group, those with the chaotic pattern had evidence for significant variability in lung function, with prebronchodilator FEV₁ values fluctuating greatly throughout the day. Of note, the swings in pulmonary function were not limited to the AM values; lability was documented at all periods of the day, and this variability was refractory to the GC burst. These individuals are analogous to those with "brittle" asthma as described by Dr. Turner-Warwick.³ A recent editorial has stressed the importance of monitoring for significant variability in asthma by using statistical PEF control charts.²⁰ With control charts, one can easily distinguish between common cause variation (i.e., day-to-day variability) and special cause variation (i.e., exposure to allergen, irritation, or viral infection). This method appears to be a more effective way of monitoring a patient's pulmonary function, especially as it pertains to the outpatient management of children with severe asthma. The cause of this chaotic pattern remains unclear at this time. Given that these individuals can achieve nearly normal FEV₁ values, it is unlikely that they have an irreversible component to their airflow obstruction. Do these individuals have ongoing airway inflammation that is contributing to their significant airway lability or do they have an intrinsic GC refractory component to their airway reactivity, as has been previously suggested?²¹

Of particular interest was the observation that African-Americans were overrepresented in those with SI asthma. To our knowledge, this has not been observed in past studies. This group appeared to have a higher level of asthma morbidity, possibly secondary to delay in access to care, subsequent delay in diagnosis, and treatment of their disease. In a review of data from the National Center for Health Statistics (NCHS) between 1980 and 1994, Sly and O'Donnell²² noted that the asthma mortality for African-Americans was much greater compared with Caucasians. There are many potential explanations for this observation, with socio-

economic, environmental, and genetic factors possibly contributing. The increased incidence in asthma morbidity and mortality among African-Americans has been noted most frequently in large urban areas of the United States, and it remains to be determined whether the increase in morbidity is due to poverty and the lack of adequate care as a result of that, and/or secondary to increased exposure to environmental allergens such as cockroach and dust mite.²³ Genetic factors may also contribute. A recent study by Ganier et al.²⁴ found African-Americans to be hyperresponsive to inflammatory mediators compared with Caucasians. Given the increase in asthma morbidity and mortality among African-Americans with asthma in general and the overrepresentation of African-Americans among those with SI asthma, there is an urgent need for further studies aimed at better understanding of these observations.

In summary, the prevalence of SI asthma among adolescents with severe asthma referred to our institution (roughly 25%) was substantially higher than we had expected. In all patients, an evaluation of potential aggravating factors was performed, and when identified appropriate treatment was rendered. Proper inhaled asthma medication technique was taught by trained nursing staff members and compliance with oral GC use was ensured. Despite ruling out confounding factors, treating associated conditions, and maximizing education, technique, and compliance, a significant percentage of patients remained SI. Those with SI asthma displayed either a chaotic or nonchaotic spirometric profile. Further studies are needed to determine whether these two patterns of SI asthma constitute different pathophysiologic processes. Despite advancements in our understanding of the pathophysiology of asthma, there remains a persistent trend of significant morbidity and mortality. This study supports the need for a more critical review of the algorithms of medication selection and further epidemiologic studies of the natural history and risk factors associated with asthma.

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