

The changing face of severe childhood asthma: A comparison of two cohorts of children evaluated at National Jewish Health over the past 20 years

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ABSTRACT

Novel asthma pharmacotherapy has changed the management of severe childhood asthma. This study determined whether the introduction and use of second-generation inhaled glucocorticoids (GCs), long-acting beta-agonists (LABAs), and combination inhaled GC/LABA (iGC/LABA) products and leukotriene receptor antagonists (LTRAs) have impacted children with severe asthma. A retrospective review of children (aged 6–18 years) referred to National Jewish Health for severe asthma between 2003 and 2007 (current cohort) was performed ($n = 65$); the results were compared with a published cohort from 1993 to 1997 (historic cohort; $n = 164$). When comparing the current cohort to the historic cohort, the percentage requiring chronic oral GC therapy (28% versus 51%; $p = 0.001$), average dose (3.7 ± 2.4 mg/dose versus 16.7 ± 1.4 mg/dose; $p < 0.0001$), and duration of oral GC use (17.8 ± 8.6 months versus 33.7 ± 3.5 months; $p = 0.09$) were less. Ninety-seven percent of the current cohort was on a second-generation iGC either alone or in combination with an LABA, 76% were on an LTRA, and 66% were on combination iGC/LABA product, while none of the historic cohort received these medications. In addition, the current cohort had a higher forced expiratory volume in 1 second ($84 \pm 2.5\%$ versus $76 \pm 2\%$ of predicted; $p = 0.008$), required less albuterol (33 ± 9 inhalations/week versus 71 ± 7 inhalations/week; $p = 0.0007$), had fewer intubations in the past (13% versus 21%; $p = 0.13$) and had fewer GC-induced adverse effects compared with the historic cohort. The current cohort required less chronic oral GCs, had better asthma control, and had fewer GC-induced adverse effects compared with the historic cohort studied 10 years ago. This is most likely because of the use of more effective medications for childhood asthma.

(Allergy Asthma Proc 35:119–125, 2014; doi: 10.2500/aap.2014.35.3727)

Asthma is regarded to be one of the most common chronic diseases of childhood.¹ Patients with severe asthma comprise a small percentage of all childhood asthma; however, these patients account for a great deal of asthma morbidity, health care use, and health care costs.² The cost of illness related to asthma is estimated to be \$6.2 billion, with the majority of this cost attributed to emergency department visits, hospitalizations, and death secondary to the disease.^{2–5}

National Jewish Health (NJH) has long been a tertiary referral center for the evaluation of children with severe asthma. In 1998, Chan *et al.*⁶ characterized the clinical characteristics of children with severe asthma who underwent Day Program evaluations at NJH. This study examined 163 children from 1993 to 1997. This “historic cohort” comprised of children with difficult-to-control asthma who showed significant asthma burden as evidenced by the need for chronically administered oral glucocorticoid (GC), high-dose inhaled GC

(iGC) use, and frequent usage of rescue albuterol. These severe asthmatic patients were treated primarily with high doses of first-generation inhaled steroids including beclomethasone dipropionate (BDP), triamcinolone acetonide, and flunisolide delivered *via* a metered-dose inhaler using chlorofluorocarbon as the propellant. Recently, we have noticed that there has been a decline in the number of children with severe asthma requiring admission who require chronically administered prednisone. We hypothesized that this was a result of the development and use of more effective asthma medications including the second-generation iGC medications fluticasone propionate (FP), budesonide (BUD), and mometasone furoate, and combination iGC/long-acting β -agonist (LABA) medications such as fluticasone/salmeterol combination and BUD/formoterol combination. In addition, BDP is now available in a solution beclomethasone dipropionate-hydrofluoroalkane (BDP-HFA), which not only enhances its delivery to the lungs but also leads to peripheral airway deposition.

These advances in asthma therapy are another step in the quest to improve the quality of life and reduce the morbidity associated with chronic oral GC therapy in children with severe asthma. Shortly after the initiation of orally administered GCs for the treatment of asthma in the 1950s, it became apparent that chronic usage of these medications was associated with signif-

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The authors have no conflicts of interest to declare pertaining to this article

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icant adverse effects such as growth suppression, osteoporosis, Cushingoid stigmata, and cataracts. The usage of so called "second-generation" iGCs by virtue of their enhanced potency and greater first-pass metabolism, especially when used in combination with LABA in a single device, has allowed for significant sparing of both inhaled and oral GC therapy. The first-generation iGCs were less potent and had high oral bioavailability and significant side effects when compared with the second-generation iGCs^{7,8} that are in current use. The second-generation iGCs have increased GC-receptor specificity and have a more efficient first-pass metabolism,^{9–11} thus resulting in decreased potential for systemic side effects and have significantly impacted the need for chronic oral steroids in severe asthma.^{12–14} A second advance in asthma control came with the development of combination second-generation iGC/LABA products.^{15–19}

We hypothesized that the development of increasingly effective medications in the past 10 years has altered the phenotypic expression and the clinical course of children with severe asthma. Specifically, the development of second-generation iGC and combination iGC/LABA products have resulted in improved asthma control, fewer adverse effects from chronically administered oral GCs, and have altered the natural history of severe childhood asthma.

METHODS

We performed a cross-sectional, retrospective chart review of all children aged 6–18 years who were admitted to the Day Program for the evaluation and treatment of severe asthma from 2003 to 2007. This group made up the "current cohort." The Day Program is a national referral center for children with severe asthma, with all of the patients referred to the program for further evaluation of their disease. Charts with a primary ICD-9 code for asthma were initially screened. Established asthma or MD-diagnosed asthma was defined by the presence of symptoms plus any of the following: the use of an inhaled bronchodilator; prior documented β -agonist reversibility or PC₂₀ methacholine of ≤ 12.5 mg/mL.

The "historic cohort" consisted of a retrospective review of all children with severe asthma evaluated at National Jewish from 1993 to 1997. The result of this study has been previously published.⁶ Both the historic and current cohorts had similar data collection performed during their Day Program admissions, which included demographic information such as age, sex, race, height, weight, and body mass index (BMI). Medical history included age at asthma diagnosis, duration of asthma diagnosis, number of hospitalizations, intensive care unit admissions, and if there was a history of intubation. Asthma burden was evaluated by the fre-

quency of β -agonist use, daily oral steroid use, the number of prednisone bursts in the past year, the need for chronic prednisone, and the use of controller medications (iGC type and dose; combination iGC/LABA type and dose; use of leukotriene receptor antagonists, omalizumab, and tiotropium/ipratropium). Both cohorts had objective clinical assessments of asthma performed during their admission including spirometry, body box plethysmography, and methacholine challenge. Allergic inflammation was assessed by measuring serum IgE level, number of positive skin-prick tests, and level of circulating eosinophils. The patients also had pH probe, radiography with chest and sinus computed tomography, and bone densitometry performed. Objective and subjective reports of steroid-induced adverse effects were also collected.

Exclusion criteria included an age of <5 years and >18 years, concomitant respiratory disease or cardiac disease, neuromuscular disease, and those unable to perform reliable reproducible spirometry. Both studies were approved by the NJH Institutional Review Board.

Statistical Analysis

Analyses were performed with the use of JMP Version 9.0.0 (SAS 2010; SAS Institute, Inc., Cary, NC). The *p* values were derived to compare the historic cohort versus the current cohort of children with severe asthma from either chi-square tests (for categorical variables), Fisher's exact test (for categorical variables with small expected numbers), analysis of variance (for normally-distributed continuous variables), or Wilcoxon rank sum test (for variables that were not normally distributed). Given the significant difference in age between the two cohorts, multiple regression analysis adjusting for age was used to compare the outcomes between the two cohorts. Data in the text and tables are presented as means $\pm$ SEM.

RESULTS

The current cohort consisted of all patients with severe asthma who were evaluated at NJH from 2003 to 2007 consisting of 65 patients, and the historic cohort from 1993 to 1997, consisted of 163 patients (Table 1). The current cohort was younger (mean age of 11.3 ± 0.3 years versus 14.1 ± 0.2 years; $p < 0.0001$), had an earlier age of onset (2.9 ± 0.4 years versus 3.8 ± 0.3 years), and had greater percentage of male subjects (59% versus 45%; $p = 0.05$) when compared with their historic peers. In addition, the current cohort had a shorter duration of asthma (8.5 ± 0.5 years versus 10.3 ± 0.3 years). There was a similar race breakdown in the current cohort when compared with the historic cohort (Table 1).

The use of oral and iGC varied between the current and historic cohorts (Table 2). A smaller percentage of

Table 1 Demographics

Parameter	Current Cohort (n = 65)	Historic Cohort (n = 163)	p Value
Age (yr)	11.3 ± 0.3*	14.1 ± 0.2	<0.0001
Gender (male), %	59	45	0.05
Race/ethnicity (%)			
White	67	75	
Black	16	17	
Hispanic	14	7	
Other	3	13	
Age at asthma diagnosis (yr)	2.9 ± 0.4	3.8 ± 0.3	
Asthma duration (yr)	8.5 ± 0.5	10.3 ± 0.3	0.001
Inhaled steroid (%)			<0.0001
Beclomethasone	0	29	
Triamcinolone	0	33	
Flunisolide	0	35	
Beclomethasone HFA	3	0	
Fluticasone/salmeterol	66	0	
Fluticasone	16	1	
Budesonide	16	2	
Mometasone	3	0	
Leukotriene modifying agent (%)	77	0	
Omalizumab (%)	9	0	
Tiotropium (%)	8	0	

*Data are expressed as mean ± SD of the mean unless otherwise stated.

HFA = hydrofluoroalkane.

children in the current cohort required chronically administered prednisone compared with the historic cohort (28% versus 51%; $p = 0.002$). In addition, children who required chronically administered oral GC therapy in the current cohort required chronic oral GC therapy for a shorter duration (18 ± 9 months versus 34 ± 4 months; $p = 0.09$) and required a smaller dose (4 ± 2 mg/day versus 17 ± 1 mg/day; $p < 0.0001$) than those children in the historic cohort. In addition, the current cohort was on a lower daily iGC dose than their historic counterparts (764 ± 124 µg/day versus 1691 ± 82 µg/day; $p < 0.0001$). The current cohort was also noted to require more frequent courses of oral GC therapy per year compared with the historic cohort (11 ± 1 versus 7 ± 1 GC courses/yr; $p = 0.003$; Table 2).

The vast majority of the current cohort was on a second-generation iGC, most of which were also on a LABA. In contrast, nearly all of the patients in the historic cohort were taking a first-generation iGC (Table 1). The current cohort required less rescue albuterol for asthma symptoms than their historic peers (33 ± 9 versus 71 ± 7 inhalations/wk; $p = 0.0007$).

When comparing lung function (Table 3), the current cohort had a higher forced expiratory volume in 1 second (FEV₁) than their historic counterparts ($84 \pm 3\%$ versus $76 \pm 2\%$ of predicted; $p = 0.008$). In addition, the total lung capacity and residual volume were in-

creased in the current cohort (total lung capacity, $123 \pm 2\%$ versus $113 \pm 1\%$ [$p < 0.0001$], and residual volume, $260 \pm 11\%$ versus $216 \pm 7\%$ [$p = 0.001$]) compared with the historic cohort. The current cohort had increased airway resistance (R_{aw}) when compared with their historic counterparts (163 ± 6 versus 92 ± 4 ; $p < 0.0001$). When evaluating both cohorts for atopy (defined by three or more positive skin-prick tests), roughly 75% of patients were atopic (Table 3). Both cohorts had similar levels of circulating eosinophils and serum IgE.

With respect to steroid-induced adverse effects (Table 2), the current cohort was less growth suppressed (53rd percentile versus 39th percentile; $p = 0.002$), less likely to have cataracts (0% versus 21%; $p < 0.0001$), and less likely to have Cushingoid stigmata (2% versus 75%; $p < 0.0001$) when compared with the historic cohort. Both cohorts were as likely to have adrenal suppression, osteopenia, and osteoporosis and as likely to have an increased BMI. Finally, fewer children from the current cohort required intubation and mechanical ventilation for respiratory failure compared with the historic cohort (13% versus 21%; $p = 0.13$; Table 3).

DISCUSSION

By comparing two well-characterized cohorts of children with severe asthma evaluated at NJH sep-

Table 2 Steroid usage and steroid-related side effects

Parameter	Current Cohort (n = 65)	Historic Cohort (n = 163)	p Value
Chronic oral steroid (%)	28%	51%	0.002
Duration (mo)	18 ± 9	34 ± 4	0.09
Dose (mg/day)	4.0 ± 2.0	17.0 ± 1.0	<0.0001
Inhaled GC dose (μg/day)	764 ± 124	1691 ± 82	<0.0001
Rescue prednisone (courses/yr)	11 ± 1	7 ± 1	0.003
Steroid-induced adverse effects			
Height (percentile)	53 ± 4	39 ± 2	0.002
Height (SDS)	0.17 ± 0.2	-0.59 ± 0.1	0.0003
Weight (percentile)	71 ± 4	68 ± 2	0.52
BMI (percentile)	77 ± 2	74 ± 3	0.37
Cushingoid stigmata (%)	2	75%	<0.0001
Myopathy/myalgia (%)	36	51	0.04
Cataracts (%)	0	21	<0.0001
Cortisol suppression (%)	51	56	0.53
Vertebral BMD (Z score)	-1.0 ± 0.2	-0.9 ± 0.1	0.74
Osteopenia (-1 to -1.99), %	51	46	0.51
Osteoporosis (less than -2.0), %	18	18	0.97

*Data are expressed as mean ± the standard deviation of the mean unless otherwise stated.

BMI = body mass index; BMD = bone mineral density; SDS = standard deviation score.

Table 3 Morbidity, pulmonary function, and atopy

Parameter	Current Cohort (n = 65)	Historic Cohort (n = 163)	p Value
Albuterol (inhalations/wk)	33 ± 9	71 ± 7	0.0007
Past intubation (%)	13	21	0.13
Admission FEV ₁ (% predicted)	84 ± 3	76 ± 2	0.008
Lung function			
TLC (% predicted)	123 ± 2	113 ± 1	<0.0001
FRC (% predicted)	122 ± 4	123 ± 3	0.83
RV (% predicted)	260 ± 11	216 ± 7	0.001
R _{aw} (% predicted)	163 ± 6	92 ± 4	<0.0001
Sgaw (% predicted)	62 ± 4	83 ± 2	<0.0001
Measures of allergic inflammation			
Circulating eosinophils	370 ± 43	283 ± 31	0.10
Serum IgE	641 ± 221	661 ± 147	0.95
Atopy (more than three positive skin tests)	75%	76%	0.83

*Data are expressed as mean ± the standard deviation of the mean unless otherwise stated.

FEV₁ = forced expiratory volume in 1 s; TLC = total lung capacity; FRC = functional residual capacity; RV = residual volume; Sgaw = specific airways conductance.

arated by over 10 years, we found significant differences in type of therapy required to maintain asthma control in the current compared with the historic cohorts. The current cohort had less asthma impairment as manifest by their higher admission FEV₁, less need for rescue β-agonist therapy, and less need for chronically administered oral GC therapy. In addition, the current cohort had fewer steroid-associated adverse effects with less growth suppression and had fewer Cushingoid stigmata than their his-

toric peers. Although the length of time for each cohort was the same (4 years), the number of subjects evaluated in the current cohort was smaller than the number studied in the historic cohort. This finding could be the result of improved asthma control with current therapy and fewer children with refractory asthma requiring a NJH Day Program evaluation. Alternatively, referral patterns may have changed and insurance authorizations may be more difficult now compared with in the past.

We believe the significant improvement in asthma control as manifest by a roughly 50% reduction in need for rescue albuterol therapy and improved baseline FEV₁, the decreased need for chronically administered oral GCs, and fewer GC-associated adverse effect profiles in the current cohort is the result of the development of and widespread use of second-generation iGC and combination iGC/LABA therapy.

It could be argued that the smaller proportion of children requiring oral GC therapy is the result of the current cohort being significantly younger. To address this issue, we performed a *post hoc* analysis where we age matched the two cohorts. When matched for age, the two cohorts had similar ages of onset (3.8 versus 3.7; $p = 0.9$ years) and similar durations of asthma (10.2 versus 10.3; $p = 0.8$ years) for the historic and current cohorts, respectively. Fifty-one percent of the historic cohort required chronic oral steroid therapy versus 33% of the current cohort ($p = 0.04$). The historic cohort required a larger oral steroid dose (16.9 mg/day versus 3.6 mg/day; $p = 0.0003$), for a longer duration of time (33.7 months versus 22.1 months; $p = 0.02$). After correcting for age, the current cohort remained less growth suppressed than the historic group for both SD scores (-0.05 versus -0.58 ; $p = 0.03$) and height percentiles (49 percentile versus 39 percentile; $p = 0.05$). When all other parameters were corrected for age, the differences remained significantly different between the two cohorts except for baseline FEV₁ where the historic cohort FEV₁ was 76.2 and the current cohort FEV₁ was 82.1% predicted with a value of $p = 0.08$.

With that said, several studies have established the oral steroid-sparing effect of the second-generation iGC. Noonan *et al.* were among the first to show the substantial reduction in need for and dose of prednisone in a group of steroid-dependent asthmatic patients who received therapy with high-dose inhaled FP.¹² Similar steroid-sparing effects have been noted with high-dose inhaled BUD and mometasone furoate.^{13,14} Over 95% of the current cohort was on a second-generation inhaled steroid versus 3% of the historic cohort. We believe that the high percentage of children in the current cohort who received a second-generation iGC, 66% in combination with an LABA allowed for a substantial reduction in need for chronic oral GC, while improving asthma control.

The addition of an LABA to a second-generation iGC provides more benefits than iGC therapy alone. The Formoterol And Corticosteroids Establishing Therapy trial showed that adding formoterol to BUD resulted in the greatest decrease of asthma exacerbations¹⁶ in patients with moderate/severe asthma when compared with alternate therapy regimens. The Optimal Treatment for Mild Asthma study in patients with mild/moderate asthma showed that a greater benefit was noted when formoterol was added to the iGC

patients were receiving rather than doubling the iGC dose.¹⁷ The Gaining Optimal Asthma Control study showed that uncontrolled asthmatic patients are more likely to achieve asthma control when treated with combination fluticasone/salmeterol therapy than when treated with fluticasone alone.¹⁵

There has been significant controversy surrounding the use of LABA in asthma, and whether they confer an increased risk of death. Many studies have not supported this contention,^{20,21} and the rate of fatal or near-fatal attacks since the introduction of LABAs has not increased.²² Studies have concluded that it is the overuse of short-acting β -agonists in patients with severe asthma, rather than LABA therapy, that places patients at the greatest risk of mortality.^{23–25} The Salmeterol Multicenter Research Trial has been at the center of the LABA controversy, showing increased frequency in the deaths of asthmatic patients treated with salmeterol versus placebo.²⁶ Less than one-half of the participants in the Salmeterol Multicenter Research Trial study were on an iGC as a part of their asthma controller regimen, and the patients who were not on iGC therapy showed higher frequency of death on salmeterol versus placebo. A study by Mann *et al.*²⁷ suggested that high-dose formoterol may be associated with increased risk of severe asthma exacerbation; however, a subsequent study²⁸ published to address these concerns showed that there was an increase in exacerbation on low-dose, not high-dose formoterol, and high-dose formoterol was associated with improved asthma control and a reduction in exacerbations in subjects on concomitant iGC therapy. As previously mentioned, many well-controlled studies have shown improved asthma control and fewer exacerbations in subjects with combination iGC/LABA therapy when compared with iGC monotherapy.^{15–19} The predominance of data suggests that use of LABA therapy in combination with iGC therapy decreases the risk of hospital admission for asthma although large studies are currently underway to determine whether there is an increased risk for life-threatening events in patients treated with combination iGC/LABA versus iGC therapy alone.

It is known that chronically administered GC therapy is associated with a range of adverse effects.²⁹ Common adverse effects include adrenal suppression, growth suppression,^{30–33} osteoporosis,³⁴ cataracts³⁵ myopathy,³⁶ and the development of Cushingoid stigmata (moon facies, buffalo hump, central obesity, extremity wasting, skin atrophy, and hirsutism). The current cohort had a decreased number of GC-associated adverse effects when compared with the historic cohort. This is likely secondary to the reduced dosage and improved therapeutic index associated with the second-generation iGC⁹ and the overall decreased requirement for chronic oral GC in the current cohort. Although the current cohort did require more frequent

rescue prednisone courses, these were for shorter duration than using chronic oral steroids, also likely contributing to fewer adverse effects. The current cohort was less likely to have growth suppression, cataracts, and Cushingoid stigmata when compared with the historic cohort.

Although the current cohort had an overall reduction in the number of GC-associated adverse effects, they were as likely as the historic cohort to have adrenal suppression, osteopenia, and osteoporosis and an increased BMI. High-dose iGC therapy can result in significant suppression in the hypothalamic-pituitary axis,³⁷ and FP specifically seems to have a greater effect on hypothalamic-pituitary-adrenal-axis suppression than other iGCs.^{7,38,39} Because the current cohort were primarily managed with FP, either alone or in combination with salmeterol, and required frequent courses of prednisone, it is not surprising that they displayed evidence of adrenal suppression.

Given that this is a retrospective and cross-sectional study, there are several inherent limitations. First, there may have been several changes in referral patterns and insurance authorizations for admission into the Day Program in the 10 years that elapsed between the two cohorts. Second, physician, patient, and system variables were not controlled for, including physicians' perception of asthma severity, preference of step-up therapy, and choice of medications; role of insurance in choice of medication regimen; and patient adherence to a proposed medication regimen. Third, environmental exposures that are known to contribute to asthma severity including tobacco smoke, air quality, and home allergen exposure were not controlled for in this study. Fourth, there were significant differences in the ages of children studied with the historic cohort being older than the current cohort. Finally, clinical practice may have changed since our current cohort was studied, because we had only a small percentage of children treated with BDP-HFA and omalizumab. BDP-HFA is being used more frequently because of its ability to reach the distal airways. Omalizumab is currently not indicated for the treatment of children <12 years old and may explain why it was not used frequently in our cohort.

Novel therapies introduced within the past 15 years appear to have improved the natural history of severe childhood asthma. The current cohort of children with severe asthma evaluated at NJH have better-controlled asthma than their historic counterparts based on decreased need for rescue albuterol and significant reduction in the need for chronic GC use. The current cohort is less likely to have growth suppression and fewer patients have myopathy and Cushingoid stigmata. Unfortunately, the current cohort continues to have significant asthma morbidity as evidenced by their need for a greater number of rescue prednisone courses per

year and their greater lung hyperinflation and air trapping than their historic peers and are as likely to suffer from adrenal suppression, osteopenia, and osteoporosis. The advent of second-generation iGC with and without LABA has greatly reduced the burden of severe asthma; however, continued improvements to current therapy will need to be made over time to further improve control and decrease adverse effects.

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