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Identification of Asthma Phenotypes in a Tertiary Care Medical Center

James Lee Kuhlen Jr., M.D.,

Department of Medicine, Medical University of South Carolina

Amy E. Wahlquist, M.S.,

Department of Public Health Sciences, Medical University of South Carolina

Paul J. Nietert, Ph.D., and

Department of Public Health Sciences, Medical University of South Carolina

Sonia N. Bains, M.D.

Division of Pulmonary, Critical Care, Sleep and Allergy, Department of Medicine, Medical University of South Carolina

Abstract

Background—Asthma affects 5–10% of the population and its severity is assessed using four parameters: lung function, symptom frequency, rescue inhaler use, and number of asthma exacerbations^{1–2}. Asthma is increasingly recognized as a clinical syndrome rather than a single disease³. However, the current classification system fails to reflect the heterogeneous characteristics of the disease⁴.

Methods—A retrospective chart review of 139 patients with mild, moderate, and severe persistent asthma was performed. Variables including baseline and maximal FEV1 (percent predicted), and age of asthma onset were used to classify patients.

Results—This yielded five clusters(C) similar to SARP. Subjects in C1 (n=32) and C2 (n= 47) had early onset atopic asthma and reduced lung function but differed in medication requirement and health care utilization (HCU). C3 (n=32) consisted of older obese women with late onset asthma, less atopy, and mildly reduced FEV1. Members of C4 (n=20) and C5 (n=8) had atopic asthma with severe obstruction but differed in bronchodilator response, age of onset, and oral corticosteroid use. Compared to SARP, our subjects were older, had a higher percentage of African Americans and obesity, and less severe asthma ($p < 0.05$). The observed clusters differed from SARP clusters in the following: 1) More frequent asthma exacerbations and medication use among C1 and 2, 2) Lower medication use in C3 and 4, 3) Although total HCU was similar, there were fewer ED visits in C3 ($p < 0.05$).

Corresponding author information: Sonia Noreen Bains M.D., 96 Jonathan Lucas Street, CSB Suite 812, MSC 630, Charleston, SC 29425, Tel: (843) 792-3712, Fax: (843) 792-0732, bains@musc.edu.

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Conclusion—The SARP algorithm may be used to classify diverse asthmatic populations into a clinically reproducible phenotypic cluster.

Introduction

Asthma affects 5–10% of the population in many developed countries and its prevalence is rising⁶. Asthma is associated with a significant socioeconomic burden, costing the US \$20.7 billion in 2008 alone^{6–7}. Physicians follow the National Asthma Education and Prevention Program and Global Initiative for Asthma Guidelines (GINA) to assess asthma severity using four parameters: lung function, frequency of symptoms (daytime and nocturnal), rescue inhaler use, and the number of asthma exacerbations^{1–5}. Despite strict adherence to guideline recommended treatment strategies up to 42% of adolescents experience at least one exacerbation annually^{8–9}. Asthma is increasingly recognized as a clinical syndrome rather than a single disease⁵. However, the current classification system fails to reflect the heterogeneous characteristics of the disease⁶.

Asthma is a heterogeneous disorder. Asthma patients frequently present with diverse symptom profiles which often do not correlate with lung function¹⁰. Furthermore, altered responses to medications have been observed, with close to 50% of patients with mild asthma not responding to inhaled corticosteroids and only subsets of asthmatics responding to newer biologics such as Omalizumab^{11–13}. In patients with mild persistent asthma that were randomized to placebo or an inhaled corticosteroid there was no difference between frequency of exacerbations, asthma control, or asthma-related quality of life¹³. Economically, analysis of healthcare utilization (HCU) associated with asthma shows large variances based on a patient's age and gender; more specifically, it is higher in women and the elderly^{14–16}. The current asthma severity classification system does not take into account these differences and therefore fails to distinguish such patients. The identification and classification of asthmatic patients into clinically reproducible phenotypes can increase our knowledge of the pathophysiology, diagnosis and disease specific treatment of asthma^{17–19}.

The identification of distinct asthma phenotypic groups has been achieved through cluster analysis utilizing both demographic and clinical information^{17–18}. Dr. Moore and the Severe Asthma Research Program (SARP) performed cluster analysis using 34 clinical and demographic variables and identified 5 distinct phenotypic clusters;¹⁷ cluster 1: mild atopic asthma; cluster 2: mild to moderate atopic asthma; cluster 3: late-onset non-atopic asthma; cluster 4: severe atopic asthma; and cluster 5: severe asthma with fixed airflow. Differences between clusters included age of asthma onset, gender, atopy, lung function, asthma control and HCU. Given the complexity of classifying patients into one of the five asthma phenotypes, they devised a simple algorithm using baseline lung function, maximal lung function, and age of asthma onset¹⁷. Applying this algorithm, they were able to assign patients into the appropriate cluster with 80% accuracy¹⁷. The simplicity of this algorithm makes it applicable in a clinical setting, however its utility has only been studied in a large Northeastern city¹⁸, never a suburban Southeast population.

The Medical University of South Carolina (MUSC) is a tertiary care center located in the Southeastern United States and is comprised of a vast network of inpatient and outpatient

facilities. Its patient base is comprised mostly of Caucasians and African Americans, although a small percentage of other racial/ethnic groups are represented. It represents a geographic region in which the simple SARP algorithm for assigning patients into an asthma phenotype has not been studied. We hypothesized that applying the simple SARP algorithm to patients seen at MUSC would yield five phenotypic clusters similar to those seen in the SARP cohort. Application of the simple algorithm yielded five asthma phenotypes that, despite some differences, were similar enough to the SARP cohort, to suggest consistently reproducible asthma phenotypes utilizing the simple SARP algorithm. The differences we observed are reported in the text below.

Methods

Patients

A retrospective chart review of 213 consecutive patients seen at the Medical University of South Carolina outpatient allergy clinic between January 2010 and May 2012 was performed after institutional review board (IRB) approval was obtained. Patients with a physician diagnosis of mild, moderate or severe persistent asthma (based on the National Asthma Education and Prevention Program guidelines) were included²⁻⁵. Patients were excluded if they were younger than 12 years old (n=48) or if they were missing one or more variables necessary for cluster classification (n=26). All patients were seen by a clinician with experience in asthma diagnosis and management. Demographic and clinical data collected included: age, gender, body mass index (BMI), race, age of asthma onset, atopy, lung function, number of controller medications, use of oral corticosteroids, vitamin D level, serum IgE level, number of asthma exacerbations (over the past year), comorbidities, and HCU (over the past year). Atopy was defined as a positive skin prick test to an inhalant allergen using standardized reagents when available (from Greer, NC) with a wheal of 3 mm or greater than the negative control (saline). HCU was further defined by number of oral corticosteroid courses (OCS), emergency department (ED) visits, and hospital admissions (HA) over the past year for each patient. This data was entered into a centralized web-based database developed using REDCap (© 2009, Vanderbilt University) and is displayed in Table 1. Patients were assigned into one of five clusters by applying the algorithm proposed by Moore et al. (Figure 1). This algorithm utilizes three variables: baseline percent predicted FEV1 (pre BD), maximal percent predicted FEV1 (post BD), and age of asthma onset¹⁷.

Statistical Analysis

Cluster characteristics were described using medians (for continuous variables) and percentages (of affected individuals). To compare the clusters with respect to demographics and clinical characteristics, Kruskal-Wallis tests and chi square² tests were used. To compare the demographics and clinical characteristics between our clusters and the SARP clusters, one sample z-tests and χ^2 goodness-of-fit tests were utilized. All statistical analyses were conducted using SAS v9.3 (Cary, NC) and p-values <0.05 were considered statistically significant.

Results

Subject Characteristics

Complete demographic and clinical information was collected for 139 asthma subjects meeting study criteria. Their demographics and clinical characteristics are summarized in Table 1. The subjects' median age was 47 years, two-thirds of subjects were female, and one-third were African American. The majority of subjects were obese, with over half having a BMI greater than 30. The most frequent comorbidity seen in the patient population was physician diagnosed allergic rhinitis with 70% of subjects affected.

Phenotypic Clusters

Application of the simple SARP algorithm (Figure 1) classified our patients into five phenotypic clusters. Cluster 1 (N=32) consisted of mostly female (75%) patients with early onset asthma, well-preserved lung function (FEV₁ median=103%) and a high rate of atopy. Cluster 2 (N=47) consisted of patients with early onset asthma, normal to mild reduction in lung function (FEV₁, median =84%) and a high rate of atopy. Cluster 3 (N=32) was comprised mainly of older, obese women with later onset of asthma, and a lower rate of atopy. Cluster 3 also had the highest percentage of smokers (63%). Cluster 4 (N=20) was comprised of early onset asthmatics with moderate reduction in lung function (FEV₁ median=59%) a normal bronchodilator response and the highest prevalence of atopy (74%). Cluster 5 (N=8) consisted of the largest percentage of patients who were African American (63%), the second longest disease duration (median=26.5 years), and the most severe reduction of lung function (FEV₁ median=47%) and fixed airflow obstruction. Cluster 5 also had the second highest rate of atopy and the highest proportion of patients with sleep apnea (88%).

Asthma Control

Asthma control was determined by looking at the patient's most recent asthma control test (ACT) questionnaire for the frequency of daytime and nocturnal asthma symptoms and use of short acting beta agonists (SABA). Cluster 1 consisted of a high percentage of patients with daytime symptoms (>twice/week) (44%) and SABA use (>twice/week) (31%) despite their normal lung function. Cluster 2 had nearly identical frequency of daytime asthma symptoms (45%) as cluster 1 patients but had a slightly higher rate of nocturnal symptoms (23%). Cluster 2 also had a higher percentage of patients with SABA use (38%). Cluster 3 had a lower percentage of patients with daytime asthma symptoms (28%), nocturnal symptoms (19%) and SABA use (28%) compared to clusters 1 and 2. Cluster 4 had the lowest percentage of patients with daytime asthma symptoms (25%) but the second highest rate of nocturnal symptoms (35%) and SABA use (40%). Cluster 5 had the most frequent daytime symptoms (75%), nocturnal symptoms (50%), and SABA use (75%).

Medication Use

Asthma medication use was determined by chart review and is displayed in Table 2. Overall the majority of patients were on at least one controller medication (CM) for asthma. Inhaled corticosteroids (ICS) were the most commonly prescribed controller medication (94% of

total population), followed by long acting beta agonist (LABA, never prescribed as monotherapy) medications (68%). The least prescribed controller medication was theophylline (1%) and its use was seen only in cluster 5 (25%). The frequency of patients on 3 CM varied greatly between clusters, with the highest percentage of patients on 3 CM being in cluster 5 (75%) and the lowest percentage of patients 3 CM being in cluster 1 (22%). Cluster 2 had a larger percentage of patients on 3 CM (43%) compared to cluster 1. Cluster 4 had the third highest rate of patients on 3 CM (40%) after clusters 5 and 2. Cluster 1 had the lowest frequency of montelukast (25%) and Omalizumab (6%) use. Allergen immunotherapy use was most prevalent among clusters 1 (13%) and 2 (15%). ICS use was most frequent in cluster 5 (100%) followed by cluster 2 (98%). Cluster 2, had the second highest frequency of Omalizumab (17%) after cluster 5 (63%). Cluster 3, had the second highest frequency of oral corticosteroid use (OCS) (22%) after cluster 5 (50%). All of cluster 5 patients were on ICS and it was the only cluster that had patients using theophylline. Cluster 5 also had the highest frequency of LABA use (88%); montelukast use (50%), OCS use (50%), and Omalizumab use (63%). Not surprisingly, cluster 5 had the highest percentage of patients on 3 or more CM (75%).

Healthcare Utilization and Asthma Exacerbations

HCU and asthma exacerbations over the past year rose in a step wise fashion from cluster 1 to 5. Patients who had not had an ED visit, HA or ICU admit or been prescribed an OCS burst over the past year were defined as having no (none) HCU. HCU defined as ED visits or HA, increased from cluster 1 to cluster 5 with $p < 0.05$. Cluster 5 had the most frequent ED visits, HA, and intensive care unit (ICU) admissions Cluster 1 had the lowest rate of HCU (See Figure 2). The frequency of asthma exacerbations, defined by the need of an OCS burst increased from cluster 1 (56%) to cluster 5 (88%) with the exception of cluster 3 (50%). However, cluster 3 patients did have a higher frequency (28%) of patients with more than one oral corticosteroid burst than cluster 1 patients (16%). Overall, 58% of patients had at least one asthma exacerbation requiring an OCS burst in the previous year. The frequency of patients with 3 asthma exacerbations over the previous year increased steadily from cluster 1 to cluster 5 (See Figure 2)..

Comparison of MUSC Clusters to SARP Clusters

Compared to SARP, MUSC clusters displayed overall less severe asthma, an older population, a higher percentage of African Americans, and a higher prevalence of obesity ($p < 0.05$). Asthma exacerbations were more frequent in MUSC clusters 1 and 2. Overall, MUSC's clusters also had less atopy, a later age of disease onset and a higher frequency of females.

The analysis of medication use between MUSC and SARP revealed some similarities and differences. Omalizumab use at MUSC was higher compared to SARP. The largest percentage of patients on 3 or more CM at both MUSC (75%) and SARP (60%) was in cluster 5. Clusters 1 and 2 of MUSC patients had higher medication use than the SARP patients. However, CM use was lower in MUSC cluster 3 and 4 compared to SARP. All of these differences were statistically significant ($p < 0.05$). A comparison of HCU between MUSC and SARP yielded fairly similar results for clusters 1,2 and 5. On the other hand,

HCU was lower in MUSC clusters 3 and 4 as compared to SARP clusters 3 and 4 (See Figure 3).

Limitations

Our study does have several limitations. A clinical diagnosis of asthma was used in subjects (n=34, or 24%) that did not meet bronchodilator criteria for asthma. One possible explanation for why these patients may not have met bronchodilator criteria for asthma is that their asthma was well controlled when the spirometry was obtained. Furthermore, this diagnosis contrasts the SARP cohort, in which methacholine challenge testing was performed to establish the diagnosis of asthma; however, our resulting clusters were similar in phenotype to the SARP clusters, suggesting the SARP algorithm can accurately be applied to patients on chronic medications with a clinical diagnosis of asthma¹⁷⁻¹⁸. Another limiting factor of our study was our access to only SARP's published, not raw, data, a fact which could have impacted the finer details of comparison. Finally, we were limited by the low power to detect differences between MUSC and SARP clusters given the sample sizes of MUSC's clusters. One limitation of the algorithm proposed by SARP is that it does not include current medication use which can influence FEV1. Future studies may investigate the application of this algorithm to patients that have newly diagnosed asthma and are on no controller medication.

Discussion

Classifying asthma patients at MUSC utilizing the SARP algorithm, which had never before been tried in this patient population, yielded five groups similar to the SARP cohort. Our cluster analysis and comparisons both between MUSC clusters and with the SARP clusters yielded further the similarities between the two studies.

Classification of asthma severity and management is currently achieved through guideline recommended strategies^{1,19}. However, this system does not account for the heterogeneous characteristics of asthma nor the newly recognized multiple phenotypes within the disease⁶. These asthma phenotypes may differ in disease severity and response to treatment, illustrating the importance of classifying asthmatics into the appropriate phenotype²⁰.

SARP's cluster analysis used both clinical and demographic variables and identified five distinct phenotypic clusters¹⁷. They then devised a simplified algorithm for classifying patients into an asthma phenotype that is easily applicable in the clinical setting¹⁷. The population of asthmatics at MUSC is mostly obese, Caucasian females residing in a suburban Southeastern city differing from previous populations studied using the SARP algorithm¹⁷⁻¹⁸. Despite minor differences, the MUSC study classified subjects into five asthma phenotypes of similar nature to the SARP cohort, suggesting the existence of distinct, well-defined and consistently reproducible asthma phenotypes.

There were many similarities between the SARP and MUSC clusters. Cluster 1 patients had early onset, mild atopic asthma and cluster 2 patients had later onset atopic asthma and a mild reduction in lung function (Table 1)¹⁷. Cluster 3 consisted of obese, female patients with late onset asthma and a lower rate of atopy (Table 1)¹⁷. Cluster 4 consisted of early

onset asthmatics with moderate to severe reduction in lung function and a high rate of atopy (Table 1)¹⁷. Cluster 5 consisted of patients with the longest duration of disease, the most severe reduction of lung function, fixed airflow obstruction and a high frequency of obesity, medication use, and HCU (Table 1, Table 2, Figure 2)¹⁷.

There were also noticeable differences between the SARP and MUSC clusters. The MUSC clusters displayed overall less severe asthma, an older population, a higher percentage of African Americans, and a higher prevalence of obesity ($p<0.05$). Asthma exacerbations were more frequent in MUSC cluster 1 and 2 compared to SARP which may explain the higher medication requirement observed in MUSC clusters 1 and 2 compared to SARP (Table 2)¹⁷. SABA use was also higher in MUSC clusters 1 and 2 as compared to SARP. MUSC's cluster 3 had neither the highest BMI nor the highest percentage of obese patients (Table 1). HCU was lower among MUSC's cluster 4 compared to SARP (Figure 3) which may be due to decreased lung function in the SARP cohort¹⁷.

Classifying patients with asthma into phenotypic clusters utilizing the SARP algorithm has potential clinical significance. The next step for applying this algorithm would be to perform an efficacy study to show and confirm the differences between clusters. It would also be helpful to study the efficacy of ICS, LABA, antileukotriene agents, lebrikizumab, mepolizumab, omalizumab, anti-GM-CSF therapy, bronchial thermoplasty and asthma biomarkers (periostin and fractional excretion of nitric oxide) among the various asthma phenotypes.

Conclusions

Our study and its results suggest the application of the simple SARP algorithm, to a clinically and demographically distinct population than prior studies, yields phenotypic clusters that are similar to the SARP cohort. Our data supports the use of this algorithm for classification of diverse asthmatic populations into a clinically reproducible phenotypic cluster. Further validation of this algorithm for practical clinical use will require large scale prospective studies in diverse populations.

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Acronym Glossary (in order of appearance)

HCU	health care utilization
SARP	Severe Asthma Research Program
MUSC	Medical University of South Carolina

IRB	Institutional Review Board
BMI	body mass index
OCS	oral corticosteroids
ED	emergency department
HA	hospital admissions
FEV1	forced expiratory volume over first second
Pre BD	prior to receiving bronchodilator
Post BD	after receiving bronchodilator
ACT	asthma control test
SABA	short acting beta agonists
CM	controller medication
ICS	inhaled corticosteroids
LABA	long acting beta agonist
ICU	intensive care unit

*adapted from Moore, et al.

Figure 1. Severe Asthma Research Program Simple Algorithm.*

Patients were classified into one of five clusters using three variables: Baseline FEV1 percent predicted, maximal FEV1 percent predicted after 4 puffs Albuterol, and age of asthma onset.

Figure 2. Healthcare Utilization in the Last Year at MUSC

Asthma exacerbations were defined by the need of an oral corticosteroid (OCS) burst. The percentage of patients with ≥ 3 OCS bursts over the past year rose in a step wise fashion from cluster 1 (9%) to cluster 5 (38%). Health care utilization (HCU) defined as ED visits or hospital admissions (HA), also increased from cluster 1 to cluster 5 with $p < 0.05$. Cluster 5 had the most frequent ED visits (63%), HA (38%), and intensive care unit (ICU) admissions (13%). Cluster 1 had the lowest rate of HCU.

Figure 3. Healthcare Utilization in the Last Year at MUSC vs. SARP

HCU over the past year (defined by the number of ED visits and HA) was lower in MUSC clusters 3 and 4 compared to SARP clusters 3 and 4. Although the frequency of ED visits was statistically lower in MUSC's cluster 3 ($p < 0.05$), comparing OCS, HA, or ICU admits between MUSC cluster 3 and SARP cluster 3 yielded results of no statistical significance.

Table 1

Demographics and Clinical Characteristics of Asthma Patients at MUSC

	Total	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	P value
	N=139	N=32	N=47	N=32	N=20	N=8	
Age at enrollment, median (IQR) ^a	47 (29–58)	33 (22–43)	36 (20–48)	62 (55–66)	51 (31–56)	61 (48–71)	<0.01
Gender, N (%)							0.54
Female	92 (66)	24 (75)	27 (57)	21 (66)	14 (70)	6 (75)	
Male	47 (34)	8 (25)	20 (43)	11 (34)	6 (30)	2 (25)	
Race/Ethnicity, N(%)							0.26
Caucasian	89 (65)	19 (61)	36 (77)	20 (65)	11 (55)	3 (38)	
African American	45 (33)	12 (39)	11 (23)	9 (29)	8 (40)	5 (63)	
Hispanic	1 (<1)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	
Asian/Other	2 (1.5)	0 (0)	0 (0)	1 (3)	1 (5)	0 (0)	
BMI ^b >30, N (%)	72 (52)	14 (44)	24 (51)	18 (56)	10 (50)	6 (75)	0.58
H/O ^c Smoking, (%)	15	16	21	63	35	38	<0.01
Co-morbidity, N (%)							
GERD	68 (49)	11 (34)	25 (53)	15 (47)	11 (55)	6 (75)	0.23
Sleep Apnea	40 (29)	4 (13)	13 (28)	10 (31)	6 (30)	7 (88)	<0.01
Allergic rhinitis	97 (70)	26 (81)	34 (72)	16 (50)	16 (80)	5 (63)	0.05
Atopy ^d	83 (65)	20 (67)	29 (66)	15 (50)	14 (74)	5 (100)	0.18
Age of asthma onset, median (IQR)	26 (8–46)	15 (4–31)	19 (7–30)	54 (46–60)	17 (5–29)	10 (8–57)	<0.01
Asthma duration, median (IQR)	11 (5–22)	11 (5–21)	14 (7–25)	6 (4–11)	29 (8–41)	27 (11–48)	<0.01
Asthma Classification mild/moderate/severe N	14/59/66	3/18/11	4/17/26	7/15/10	0/7/13	0/2/6	
FEV ₁ % predicted ^e , median (IQR)	83 (70–92)	100 (94–112)	83 (75–91)	83 (75–86)	61 (55–65)	46 (37–59)	<0.01
FEV ₁ /FVC ^f , median (IQR)	73 (68–79)	76 (73–82)	75 (68–79)	73 (68–79)	69 (61–73)	58 (45–75)	<0.01
Daytime Symptoms, N (%) 2 days/week	55 (40)	14 (44)	21 (45)	9 (28)	5 (25)	6 (75)	<0.01
Nocturnal symptoms, N (%) 2 days/week	34 (24)	6 (19)	11 (23)	6 (19)	7 (35)	4 (50)	0.39
SABA ^g use, N (%) 2 days/week	51 (37)	10 (31)	18 (38)	9 (28)	8 (40)	6 (75)	0.54

	Total	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	P value
	N=139	N=32	N=47	N=32	N=20	N=8	
Asthma exacerbation, N (%) ^a in prior year	80 (58)	18 (56)	27 (57)	16 (50)	12 (60)	7 (88)	0.44

Key:

- ^a =IQR is the interquartile range (25th percentile – 75th percentile),
- ^b =BMI, body mass index;
- ^c =H/O, history of;
- ^d =represents positive skin test to at least one perennial aeroallergen, data missing for 11 subjects,
- ^e =FEV₁ % predicted; forced expiratory volume in one second percent predicted;
- ^f =FVC, forced vital capacity;
- ^g =SABA, short acting beta agonist

Table 2

Medication use within MUSC Clusters

	Total	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	P value
Medication:	N=139	N=32	N=47	N=32	N=20	N=8	
ICS ^a , N (%)	131 (94)	30 (94)	46 (98)	29 (91)	18 (90)	8 (100)	0.51
LABA ^b , N (%)	94 (68)	16 (50)	33 (70)	21 (66)	17 (85)	7 (88)	0.06
Montelukast, N (%)	49 (35)	8 (25)	21 (45)	10 (31)	6 (30)	4 (50)	0.34
OCS ^c , N (%)	21 (15)	3 (9)	5 (11)	7 (22)	2 (10)	4 (50)	0.03
Zileuton, N (%)	5 (4)	0 (0)	3 (6)	1 (3)	1 (5)	0 (0)	0.61
Theophylline, N (%)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (25)	0.00
Omalizumab, N (%)	22 (16)	2 (6)	8 (17)	4 (13)	3 (15)	5 (63)	0.00
AIT ^d , N (%)	12 (9)	4 (13)	7 (15)	1 (3)	0 (0)	0 (0)	0.15
Patients on 3 CMTs^e, N (%)	51 (37)	7 (22)	20 (43)	10 (33)	8 (40)	6 (75)	0.055

Key:

^a =ICS: inhaled corticosteroid (low, medium or high dose);

^b =LABA: long acting beta agonist;

^c =OCS: oral corticosteroids;

^d =AIT:allergen immunotherapy;

^e =CMTs: controller medications