Original Article

Patients With Asthma Only Sensitized to *Staphylococcus aureus* Enterotoxins Have More Exacerbations, Airflow Limitation, and Higher Levels of Sputum IL-5 and IgE

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What is already known about this topic? Sensitization to Staphylococcus aureus enterotoxin (SE) has been detected in late-onset asthma, and several studies have suggested a link between sensitization to SE and asthma exacerbations and lower lung function.

What does this article add to our knowledge? Isolated sensitization to SE is associated with a higher exacerbation rate and nasal polyposis, higher fractional exhaled nitric oxide, sputum IgE, and sputum IL-5 levels, and elevated serum IgE to levels well above those observed in patients sensitized only to common aeroallergens.

How this study impact current management guidelines? Our study suggests that asthma specialists should measure specific IgE directed against SE during the phenotyping process of intrinsic asthma because it may allow the identification of a subgroup of patients with more exacerbations, polyposis, and intense type 2 inflammation.

BACKGROUND: *Staphylococcus aureus* enterotoxins (SE) may act as superantigens and induce an intense T-cell activation, causing local production of polyclonal IgE and resultant eosinophil activation.

OBJECTIVE: To assess whether asthma with sensitization to SE but not to common aeroallergens (AAs) displays different inflammatory characteristics.

METHODS: We conducted a prospective study on a series of 110 consecutive patients with asthma recruited from the University Asthma Clinic of Liège. We compared clinical, functional, and inflammatory characteristics of this general population of patients with asthma categorized into 4 groups according to sensitization to AAs and/or SE. We also compared sputum supernatant cytokines in patients sensitized to SE or not.

RESULTS: Patients with asthma sensitized only to AAs represented 30%, while 29% were sensitized to both AAs and SE. One-fifth of the population had no specific IgE. Sensitization to SE but not to AA (21%) was associated with later onset of disease, higher rate of exacerbations, nasal polyps, and more severe airway obstruction. As for airway type 2 biomarkers, patients presenting with specific IgE against SE displayed higher fractional exhaled nitric oxide, sputum IgE, and sputum IL-5 levels but not IL-4. We confirm that the presence of specific IgE against SE is associated with elevated serum IgE to levels well above those observed in patients sensitized only to AAs.

CONCLUSIONS: Our study suggests that asthma specialists should measure specific IgE against SE during the phenotyping process because it may allow the identification of a subgroup of patients with more asthma exacerbations, more nasal polyposis and chronic sinusitis, lower lung function, and more intense type 2 inflammation. **(J Allergy Clin Immunol Pract 2023;11:3055-61)**

Key words: *Asthma; Staphylococcus aureus enterotoxins; Allergy; Induced sputum; IL-5; IgE; Exhaled nitric oxide; Aeroallergens; Exacerbations; Airflow obstruction*

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Abbreviations used
AA- aeroallergen
FENO- exhaled nitric oxide
ILC2- type 2 innate lymphoid cell
SE- Staphylococcus aureus enterotoxin

INTRODUCTION

Asthma is a chronic heterogeneous inflammatory disease of the airways characterized by airway hyperresponsiveness toward various environmental factors. Previous studies suggest that the respiratory tract microbiome may underlie the development of asthma.[1] We previously reported that patients with asthma presenting with diffuse eosinophilic inflammation in the blood and in the sputum were characterized by later onset of the disease, were more frequently associated with chronic rhinosinusitis with nasal polyposis, had poorer lung function, poorer asthma control, higher exacerbation rates, and higher total serum IgE levels despite the absence of evidence of a clear sensitization to common aeroallergens (AAs).[2] In these hypereosinophilic patients, it has been hypothesized that type 2 innate lymphoid cells (ILC2s) could directly activate B cells, with subsequent IgE production in an antigen-independent manner.[3]

Staphylococcus aureus may trigger type 2 inflammation because *Staphylococcus aureus* enterotoxins (SE) may act as superantigens and induce an intense T-cell activation, causing local production of polyclonal IgE and resultant eosinophil activation. SE can also activate eosinophils, epithelial cells, and ILC2s, resulting in a cytokine storm.[4] Sensitization to SE has been detected in late-onset asthma and could even predict the development of severe asthma.[5,6] Moreover, several studies have suggested a link between sensitization to SE and asthma exacerbations, lower lung function,[6,7] and chronic rhinosinusitis and nasal polyps frequently associated with more severe asthma outcomes.

Whether asthma with sensitization to SE but not to common AAs displays different clinical and inflammatory characteristics and outcomes as compared with patients sensitized to common AAs or both has not yet been studied. The objective of this study was to compare clinical and inflammatory characteristics and outcomes of patients according to their sensitization status to common AAs and/or SE, in a well-characterized general population of patients with asthma taking into account ear, nose, and throat comorbidities such as chronic rhinosinusitis with or without nasal polyps or allergic rhinitis, and to assess sputum supernatant cytokines to characterize bronchial inflammation in these different subgroups.

METHODS

Study design

We conducted a prospective study on a series of 110 consecutive patients with asthma recruited from the University Asthma Clinic of Liège between June 7, 2018, and June 26, 2020. The patients were addressed by their general practitionner or pulmonologist to the University Asthma Clinic where they were evaluated by 2 clinicians involved in asthma. Entry criteria were any patients with asthma who accepted to undergo detailed investigation at the Asthma Clinic.

Asthma was diagnosed on the basis of presence of chronic respiratory symptoms such as cough, breathlessness, or dyspnea together with the demonstration of airflow variability. The latter was defined by airway hyperresponsiveness shown by 1 or more of the following: increase in FEV_1 of more than 12% and 200 mL following inhalation of 400 μg salbutamol or inhaled concentration of methacholine provoking a 20% fall in FEV_1 of less than 16 mg/mL. Methacholine challenge was performed according to a standardized methodology as previously described.[8] All patients gave a blood sample for the measurement of blood leukocytes and total and specific IgE levels. Subjects were characterized as atopic if they had at least 1 positive specific IgE (>0.35 kU/L; Phadia, Uppsala, Sweden) for at least 1 common AA (cat, dog, house dust mites, grass pollen, tree pollen, and a mixture of molds). Following the technical limitations of the earlier assays, the specific IgE detection threshold was 0.35 kU/L and is still used by laboratories for common AAs. The current modern assays such as ImmunoCAP, however, can reliably identify IgE levels as low as 0.1 kU/L.[9,10] Total serum IgE and specific IgE against *Staphylococcus enterotoxin* A, *Staphylococcus enterotoxin* B, and toxic shock syndrome toxin were measured with the ImmunoCAP 100 system. The lower limit of SE detection was set as 0.10 kU/L. We defined 4 groups according to sensitization to AAs and SE: AA+/SE+, AA+/SE−, AA−/SE+, and AA−/SE−. PAQ-years was calculated as the number of cigarettes smoked per day divided by 20 and multiplied by the number of years patient has been smoking.

Outcomes

Exacerbation in the previous year was defined by a course of oral corticosteroids for at least 3 days in case of asthma worsening. Patients experiencing an exacerbation treated with oral corticosteroids or antibiotics during the last 6 weeks were excluded.

Patients underwent fractional exhaled nitric oxide (FENO) measurement at a flow rate of 50 mL/s according to the European Respiratory Society/American Thoracic Society recommendations (NIOX, Aerocrine, Sweden). FENO was first measured and followed by spirometry with bronchodilation, sputum induction, and blood sampling. All tests were performed on the same day. Quality of life was assessed using the self-administered Asthma Quality of Life Questionnaire[11] and asthma control by the Juniper Asthma Control Questionnaire[12] and Asthma Control Test.[13]

Sputum was induced and processed as previously reported[14] and was successful in 83% of the patients encountered in our asthma clinic, which is similar to the rate found in the previous report. Cell count were estimated on samples centrifuged (Cytospin) and stained with Diff Quick after counting 500 cells (Dade, Brussels, Belgium) in all patients with successful induced sputum. In a subset of patients not receiving biological treatment, we measured type 2 cytokines in sputum supernatant. IgE sputum level was measured using Human IgE ELISA kit (Abcam, Cambridge, UK) with a detection limit of 28.5 pg/mL. Sputum IL-5 was assessed with a Luminex Performance High Sensitivity kit (Panel B FCSTM14-01 from Biotechne, Dublin, Minn) with a detection limit of 0.9 pg/mL, and IL-4 was detected using an XL Cytokine Luminex Performance kit (FCSTM18-01, Biotechne, Minn) with a detection limit of 1.3 pg/mL.

This study was conducted with the approval of the Ethics Committee of CHU Liège.

Statistical analyses

Data were expressed as count and percentage for categorical variables and as median (interquartile range) for quantitative variables. Comparisons were performed using a Pearson χ^2 test or Fisher

TABLE I. Demographic characteristics of patients classified according to their sensitization to SE and common AAs

	STAPH+ > 0.1/ATOPY+ > 0.35				
Demographic characteristic	**AA−/SE−**	**AA+/SE−**	**AA−/SE+**	**AA+/SE+**	***P* value**
N (%)	22 (20)	33 (30)	23 (21)	32 (29)	
Age (y)	62 (47.5- 69.5)	49 (29-61)	56 (52.5-64)	49 (40-64.2)	.056
Age at diagnosis (y)	43.5 (28.6- 57)	26 (5-47.8)	52 (49-59)*	15 (5- 34.7)†‡	<.0001
Sex (male)	5 (23)	12 (36)	13 (57)	13 (41)	.130
BMI (kg/m^2)	25.8 (22.8- 28.6)	27.1 (23.9- 29.7)	25.3 (23- 27.9)	25.6 (23.1- 29.1)	.846
Rhinitis	4 (18)	20 (61)‡	14 (61)‡	16 (50)‡	<.01
Nasal polyposis	1 (5)	5 (15)	11 (48)*‡	10 (31)	<.01
Chronic sinusitis	2 (9)	8 (24)	13 (57)*‡	10 (31)	<.01
Exacerbations per patient	1 (0-2)	0 (0-2)	1.5 (1-2.8)*	0 (0-2)†	.028
ACT score	13 (10-15.5)	16 (13-20)	16 (9-23)	14.5 (10.8- 18)	.124
ACQ score	2.6 (1.4-3.3)	1.9 (0.9-2.7)	2 (0.6-3.6)	2 (1.1-3.1)	.203
AQLQ score	4.1 (3.5-4.9)	4.6 (3.8-5.5)	4.5 (3.1-5.8)	3.9 (3.3-5)	.300
PAQ-Y	18.8 (0-39.4)	0 (0-0)‡	11 (2-25)*	0 (0-5.4)†‡	<.0001
Smoking status					.0001
Nonsmokers	7 (32)	26 (79)‡	6 (26)*	21 (66)†	
Ex-smokers	11 (50)	4 (12)	15 (65)	7 (22)	
Smokers	4 (18)	3 (9)	2 (9)	4 (12)	
ICS	14 (64)	23 (70)	19 (83)	26 (81)	.358
ICS (μg)	800 (0-2000)	1000 (0- 2000)	1500 (725- 2000)	1000 (437.5-2000)	.813
OCS	5 (23)	3 (9)	7 (30)	3 (9)	.093
LABA	14 (64)	23 (70)	19 (83)	26 (81)	.352
SABA	20 (91)	23 (70)	18 (78)	24 (75)	.319
LAMA	3 (14)	2 (6)	2 (9)	1 (3)	.600
LTRA	8 (36)	12 (36)	8 (35)	10 (31)	.977
Anti-IgE	0 (0)	2 (6)	0 (0)	6 (19)	.027
Anti−IL-5	1 (5)	2 (6)	0 (0)	4 (12)	.291

ACT, Asthma Control Test; *ACQ*, Asthma Control Questionnaire; *AQLQ*, Asthma Quality of Life Questionnaire; *BMI*, body mass index; *ICS*, inhaled corticosteroid; *IQR*, interquartile range; *LABA*, long-acting β-agonist; *LAMA*, long-acting muscarinic agent; *LTRA*, leukotriene receptor antagonist; *OCS*, oral corticosteroid; *PAQ-Y*, quantification of cigarette smoking; *SABA*, short-acting β-agonist.
Values are median (IQR) or n (%).
*$P < .05$, comparison with STAPH−/ATOPY+.
†$P < .05$, comparison with STAPH+/ATOPY−.
‡$P < .05$, comparison with STAPH−/ATOPY−.

exact test for categorical variables, an ANOVA test for parametric variables, and a Kruskal-Wallis test for nonparametric variables. A *P* value of less than .05 was considered statistically significant. Statistical analyses were performed using Rstudio Team (Rstudio: Integrated Development for R; Rstudio, Inc, Boston, Mass).

RESULTS

Study population

The demographic, functional, and inflammatory characteristics of the study population (n = 110) are summarized in Tables I and II. Mean age was 53 years, and 61% of the participants were female with a mean body mass index of 26.7 kg/m^2. Regarding comorbidities and contributing factors, 12% were current smokers, 30% suffered from chronic rhinosinusitis, and 25% had comorbid nasal polyposis. The Mean Asthma Control Test score was 16, and 26% of the population studied had good asthma control according to the Asthma Control Test.

Prevalence of sensitization to SE and/or AAs

In the overall population, 59% of patients with asthma had specific IgE for AAs of greater than or equal to 0.35 kU/L and 50% had at least 1 specific IgE directed against SE of greater than or equal to 0.1 kU/L while 29% were sensitized to both AAs and SE (Table III). The use of specific IgE cutoff of greater than or equal to 0.10 kU/L or greater than or equal to 0.35 kU/L for both AAs and SE did not change the results (see Tables E1 and E2 in this article's Online Repository at www.jaci-inpractice.org). The change in cutoffs of course impacted the prevalence of sensitization, with 32 patients (29%) considered SE+ with a cutoff of 0.35 kU/L for specific IgE directed against SE. Regarding AAs, 67% were defined as sensitized with the specific IgE greater than or equal to 0.1 kU/L definition.

We classified patients into 4 groups according to sensitization to SE and AAs (Tables I and II). We identified a group of 23 patients representing 21% of the total study cohort who were sensitized only to SE (AA−/SE+). A subgroup of 32 patients (29%) was sensitized to both SE and AA (AA+/SE+). Patients sensitized only to AA (AA+/SE−) represented 30%, whereas nonsensitized patients (AA−/SE−) represented one-fifth of the population.

Clinical, functional, and inflammatory characteristics according to sensitization to SE and/or AAs

AA−/SE+ patients with asthma had a later onset of the disease, more intense smoking history (higher pack-years), more exacerbations in the previous year, higher FENO and total serum

TABLE II. Functional and inflammatory characteristics of patients classified according to their sensitization to SE and common AAs

Functional and inflammatory characteristic	STAPH+ > 0.1/ATOPY+ > 0.35				
	AA−/SE−	AA+/SE−	AA−/SE+	AA+/SE+	*P* value
N (%)	22 (20)	33 (30)	23 (21)	32 (29)	
FENO (ppb)	21 (14.2-24.8)	18 (11, 31)	47.5 (16.5-80.5)*	22 (15-41.5)	.045
FEV_1 (pre) (%)	70 (57-85.2)	93 (73-103)†	72.5 (63-93.8)	80.5 (68.5-87.5)	.004
FEV_1 (post) (%)	77.5 (63-93.8)	96 (82-109)†	81 (72-98)	84 (72-93)	.011
FVC (pre) (%)	75 (60.2-88.8)	97 (85-107)†	89 (77.8-99)	87.5 (79.5-97.2)	.002
FVC (post) (%)	80 (68-91.8)	97 (84-108)†	95.5 (83.2-101)	91 (77.5-97.5)	.014
FEV_1/FVC (pre) (%)	74.5 (68-82)	82 (71-86)	70 (61.5-80)	75 (71-81)	.056
FEV_1/FVC (post) (%)	76.5 (70.2-83)	85 (76-88)	73 (64.2-81.8)*	78 (73-86)	.022
Reversibility (%)	7.5 (5-17.2)	3 (2-10)	7.5 (3.2-18)	6 (3.5-10.5)	.119
Blood leukocytes ($\times 10^3/\mu L$)	7.8 (6.3-9.8)	7.8 (6.8-9)	8.4 (7.4-9.6)	7 (6.1-8.4)	.072
Blood neutrophils ($\times 10^3/\mu L$)	4.5 (3.3-6.4)	4.4 (3.4-5.5)	5.1 (4-6.2)	4 (3.2-5.2)	.21
Blood lymphocytes ($\times 10^3/\mu L$)	2.2 (1.8-2.7)	2.4 (2.2-2.9)	2.4 (1.6-3.2)	2.1 (1.8-2.8)	.17
Blood monocytes ($\times 10^3/\mu L$)	0.5 (0.4-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.7)	0.5 (0.4-0.7)	.39
Blood eosinophils ($\times 10^3/\mu L$)	0.2 (0.1-0.4)	0.1 (0.1-0.3)	0.3 (0.2-0.6)	0.2 (0.1-0.3)	.23
Blood basophils ($\times 10^3/\mu L$)	0 (0-0)	0 (0-0.1)	0.1 (0-0.1)	0 (0-0)	.09
Blood neutrophils (%)	57.1 (52-66.5)	56.3 (48.1-63.2)	57 (51.9-65.9)	56.9 (51.3-66.7)	.705
Blood lymphocytes (%)	31 (21.6-37.3)	33.3 (26.1-40.8)	29.8 (20.4-35.5)	32 (22.4-38.2)	.425
Blood monocytes (%)	7.7 (5.8-9.1)	7.1 (5.9-9.1)	7.2 (6.1-8.2)	7.2 (5.4-8.4)	.961
Blood eosinophils (%)	2 (1.6-4.5)	2 (1.4-4)	4.5 (1.6-6.2)	2.6 (1.2-3.8)	.401
Blood basophils (%)	0.5 (0.3-0.6)	0.4 (0.4-0.7)	0.6 (0.4-0.7)	0.4 (0.3-0.6)	.559
IgE (kU/L)	32 (22.2-54.2)	93 (52-175)†	219 (112-316)†	380 (272.5-734.5)*†	<.0001
Total sputum cell count ($\times 10^6$/g)	2.6 (0.8-6.4)	1.9 (0.9-6.7)	2.9 (0.7-9.3)	1.2 (0.3-5.3)	.652
Sputum macrophages (%)	13.3 (8.6-25.4)	17.6 (8.6-35.9)	12.6 (6-29.2)	19.5 (8.3-37.9)	.484
Sputum lymphocytes (%)	0.6 (0.4-1)	0.6 (0.2-1.6)	0.6 (0-2.3)	0.4 (0-1)	.767
Sputum neutrophils (%)	66.9 (53.9-89.1)	74.6 (49.1-83.2)	61.8 (36.7-77.5)	65.7 (43.6-78.6)	.447
Sputum eosinophils (%)	1.3 (0.1-11.7)	2 (1-4)	5.5 (0.9-22.9)	2.2 (0.7-4.9)	.379
Sputum epithelial cells (%)	1.2 (0.6-3.4)	2 (0.7-3.8)	3.9 (1.9-6.5)	2.9 (1.6-7.4)	.059

FVC, Forced vital capacity; *IQR*, interquartile range.
Values are median (IQR) or n (%).
*$P < .05$, comparison with STAPH−/ATOPY+
†$P < .05$, comparison with STAPH−/ATOPY−.

TABLE III. Prevalence of sensitization to SE and common AAs

Sensitization to SE and AA	AA−/SE−	AA+/SE−	AA−/SE+	AA+/SE+
SE-specific serum IgE, n (%)				
SE A	0 (0)	0 (0)	7 (30)	22 (69)
SE B	0 (0)	0 (0)	12 (52)	27 (84)
SE TSST	0 (0)	0 (0)	18 (78)	26 (81)
AA-specific serum IgE, n (%)				
House dust mite	0 (0)	23 (70)	0 (0)	23 (72)
Cat	0 (0)	12 (36)	0 (0)	16 (53)
Dog	0 (0)	10 (30)	0 (0)	20 (69)
Grass pollenmix	0 (0)	17 (53)	0 (0)	18 (62)
Mixed molds	0 (0)	5 (16)	0 (0)	6 (21)
Birch pollen	0 (0)	11 (35)	0 (0)	8 (29)

SE A, *Staphylococcus aureus* enterotoxin A; *SE B*, *Stahylococcus aureus* enterotoxin B; *TSST*, toxic shock syndrome toxin.

IgE levels, and lower FEV_1/forced vital capacity ratio as compared with AA+/SE− patients. Moreover, AA−/SE+ patients had chronic rhinosinusitis and nasal polyps more frequently. AA+/SE+ patients with asthma had the highest level of total serum IgE. AA+/SE− patients were characterized by earlier onset of the disease, lower exacerbation rate, less intense smoking history (with 79% nonsmokers), and better lung function. AA−/SE− patients had the most intense smoking

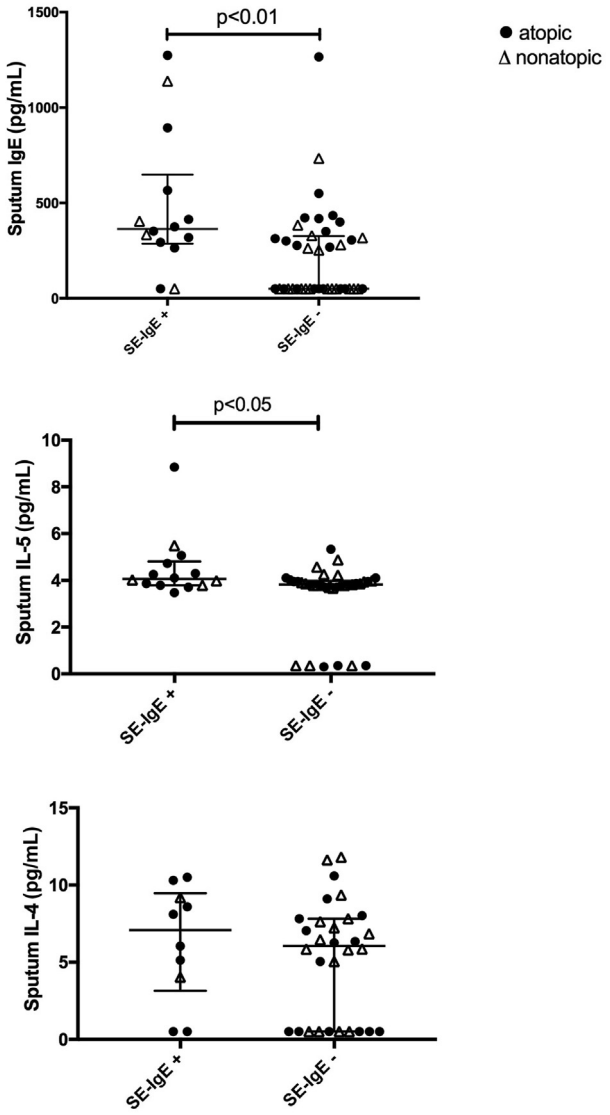

FIG 1. Sputum supernatant levels of IgE, IL-5, and IL-4 in patients according to the presence of sensitization to SE (n = 14) or not (n = 40). *SE-IgE*, Specific IgE against SE.

history (18.8 person-year), more airflow obstruction, the lowest levels of total serum IgE, and the lowest rate of ear, nose, and throat comorbidities. There was no significant difference in other characteristics including demographic characteristics, asthma control and quality of life, and blood and sputum counts (Tables I and II). The exclusion of biologics-treated patients (n = 15) did not change the results on characteristics of patients according to their sensitization status (see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

Sputum cytokines according to SE sensitization status

After exclusion of patients treated with biologics, we measured sputum supernatant levels of IgE, IL-5, and IL-4 in a subset of patients according to the presence of sensitization to SE (n = 14) or not (n = 40) and irrespective of sensitization to AAs. SE+ patients had higher levels of sputum IgE, higher levels of sputum IL-5, and similar levels of sputum IL-4 compared with SE− asthmatic patients (Figure 1).

DISCUSSION

Our study shows that one-third to one-half of a general population of patients with asthma is sensitized to SE. Our study suggests that physicians taking care of patients with asthma should measure SE-specific IgE during the phenotyping process of patients with asthma because AA−/SE+ patients with asthma are characterized by later onset of disease, higher rate of exacerbations, chronic rhinosinusitis and nasal polyps, and more severe airway obstruction. This could have treatment implications. As for airway type 2 inflammation biomarkers, SE+ patients display higher FENO, sputum IgE, and sputum IL-5 levels but not IL-4. Sensitization to SE is associated with serum IgE levels well above levels observed in AA+/SE− patients.

Being sensitized to SE without sensitization to common AAs is not infrequent because one-fifth of our general population of patients with asthma seen in a secondary care center had this phenotype. Bachert et al[7] previously found exactly the same proportion in a population of patients with severe asthma where 21% were sensitized to SE but had no other sensitization. This is of importance because these patients would have been classified as nonatopic or intrinsic patients with asthma if SE sensitization had not been looked for. Remarkably, this pattern was mainly observed in those who were nonatopic with high total serum IgE, which accounts for 20% of nonatopic patients with asthma.[15] SE+ patients have also raised sputum IgE levels. The question as to whether these patients with severe asthma may also benefit from treatment with anti-IgE requires further studies, but there are some reports showing that nonatopics with total IgE above the normal range may benefit from a treatment with omalizumab.[16] We also found that SE+ patients had higher levels of sputum IL-5. In a recent study,[17] we found that patients suffering from severe asthma and presenting with high sputum IL-5 levels were more prone to reach remission when receiving anti−IL-5 treatments. Whether SE+ patients with severe asthma are good candidates for anti−IL-5 or anti−IL-5(R) treatments remains to be studied. Moreover, future studies will also be necessary to determine whether patients with sensitization to Staphylococus enterotoxins may respond to any form of desensitization.

Our study confirms in a general population of patients with asthma that patients with asthma sensitized to SE have a later onset of the disease, higher exacerbation rate, and lower FEV_1/forced vital capacity. In addition, those sensitized to SE more often suffer from chronic sinusitis and nasal polyposis than patients sensitized only to common AAs. Sensitization to SE was previously detected in late-onset asthma and could even predict the development of severe asthma.[5,6] Moreover, several studies have suggested a link between sensitization to SE and asthma exacerbations and lower lung function.[6,7] Our study goes a step further with the comparison of patients sensitized to SE and patients with asthma sensitized to common AAs. Our data support the idea that sensitization to SE may contribute to asthma severity in those patients with eosinophilic asthma as is the case for molds and aspergillus in particular. We previously found that patients with elevated sputum and blood eosinophils

had later onset of the disease, poorer lung function, and higher levels of total serum IgE without any evidence of sensitization to common AAs, and were more often associated with chronic rhinosinusitis with nasal polyps.[2] Previous studies found levels of specific IgE directed against SE to be significantly greater in patients with chronic rhinosinusitis and nasal polyps,[18] a frequent comorbidity associated with more severe asthma outcomes.[19] This once more highlights the concept of the united airway diseases because sensitization to SE has been associated with both type 2 asthma and comorbid nasal polyposis.

Moreover, patients sensitized to SE had persistent high FENO levels despite being treated with high doses of inhaled corticosteroids. This could be due to the more frequent association with chronic rhinosinusitis and nasal polyps.[20] It might also be that activation of epithelial cells in patients sensitized to SE without sensitization to common AAs may induce the production of thymic stromal lymphopoietin and IL-33, thereby activating ILC2s, which could then induce the production of exhaled nitric oxide by production of IL-13. Patients with asthma sensitized to SE also exhibited higher total serum IgE, sputum IgE, and sputum IL-5 levels. Our study is the first to look at cytokines present in the sputum supernatant of patients with asthma sensitized to SE as compared with those who are not. Previous studies found that SE can activate eosinophils, epithelial cells, and ILC2s, resulting in a cytokine storm.[4] They indeed bind directly to the T-cell β-chain receptor, outside of the native antigen-binding site and bypass the human leukocyte antigen class II MHC complex of antigen-presenting cells. This direct binding pathway results in excessive and uncoordinated T-cell response with simultaneous B-cell proliferation, causing local production of polyclonal IgE and resultant eosinophil activation.[21,22] The attraction of eosinophils and their release of extracellular traps[23] and galectin 10 into the epithelial layer forming Charcot-Leyden crystals contributes to maintain inflammatory response.[24] The absence of increase in IL-4 could be surprising because IL-4 is essential for IgE production. We however did not measure serum IL-4, which might be more tightly related to the global IgE production in the body. We found elevated levels of sputum IgE in patients sensitized to SE. In a previous study, we reported that eosinophilic asthma phenotype was characterized by raised sputum IgE together with raised IL-5 and IL-13 compared with healthy subjects and to paucigranulocytic asthma.[25] Here, we also found increased levels of IL-5 in sputum of patients with serum SE-specific IgE. Increased levels of IL-5 have also been previously detected in nasal polyps.[26]

Our study has limitations. The limited number of patients included in the subanalysis of sputum cytokines did not allow to look at 4 subgroups and may have reduced the power of the analysis. Furthermore, the measurement of other cytokines more related to non−type 2 inflammation would be of interest. Our study identified specific characteristics of patients sensitized to SE as compared with AAs. It would be very interesting to perform a longitudinal multicentric study to evaluate whether SE+ patients show a different response to targeted treatments as compared with SE− patients with asthma.

Our study suggests that physicians taking care of patients with asthma should measure SE-specific IgE during the phenotyping process of asthma without sensitization to common AAs because it may allow, when positive, the identification of a subgroup of patients with more asthma exacerbations, more polyposis and chronic sinusitis, and more intense type 2 inflammation. This is not an unfrequent condition because it represented one-fifth of our general population of patients with asthma seen in a secondary care center. Sensitization to SE is associated with elevated serum IgE levels well above levels observed in patients with asthma sensitized only to common AAs.

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TABLE E1. Demographic, functional, and inflammatory characteristics of patients classified according to their sensitization to SE and common AAs defined with a cutoff of 0.35 kU/L for both SE and AA

Demographic, functional and inflammatory characteristic	STAPH+ > 0.35/ATOPY+ > 0.35				
	STAPH−/ATOPY−	STAPH−/ATOPY+	STAPH+/ATOPY−	STAPH+/ATOPY+	*P* value
N (%)	36 (33)	42 (38)	9 (8)	23 (21)	
Age (y)	58.5 (51.2-68)	49 (34-62.5)	56 (53-64)	48 (40-61)	.07
Age at diagnosis (y)	50 (38-58)	15 (5-45)	53.7 (49-60.8)	16.5 (5-34.7)	<.0001
Sex (male)	13 (36)	15 (36)	5 (56)	10 (43)	.66
BMI (kg/m^2)	25.9 (23.4-28.6)	26.8 (23.7-29.7)	22.9 (21.8-27.4)	25.9 (23.4-28.5)	.66
Exacerbations per patient	1 (0-2)	0 (0-2)	1 (1-3)	0 (0-1.8)	.03
ACT score	13 (10-19)	16 (12.2-19)	16 (9-23)	15 (11-19)	.63
ACQ score	2.3 (1.3-3.4)	1.9 (1-2.7)	2 (0.6-3.4)	2 (1.1-2.9)	.57
AQLQ score	4.3 (3.3-5.1)	4.3 (3.7-5.1)	4.5 (2.2-5.9)	4.1 (3.2-5.4)	.80
PAQ-Y	13.8 (0-31)	0 (0-0)	16 (6-20)	0 (0-6.4)	<.0001
Smoking status					<.001
Nonsmokers	11 (31)	33 (79)	2 (22)	14 (61)	
Ex-smokers	20 (56)	5 (12)	6 (67)	6 (26)	
Smokers	5 (14)	4 (10)	1 (11)	3 (13)	
ICS	26 (72)	30 (71)	7 (78)	19 (83)	.81
ICS (μg)	900 (125-2000)	1000 (0-2000)	1600 (950-2200)	1000 (750-2000)	.73
OCS	10 (28)	4 (10)	2 (22)	2 (9)	.10
LABA	26 (72)	30 (71)	7 (78)	19 (83)	.79
SABA	33 (92)	32 (76)	5 (56)	15 (65)	.03
LAMA	3 (8)	2 (5)	2 (22)	1 (4)	.30
LTRA	13 (36)	14 (33)	3 (33)	8 (35)	.99
Anti-IgE	0 (0)	2 (5)	0 (0)	6 (26)	<.01
Anti−IL-5	1 (3)	2 (5)	0 (0)	4 (17)	.17
FENO (ppb)	21.5 (15-48.8)	20 (11.2-37)	46.5 (16.8-83.5)	20.5 (15-39.5)	.44
FEV_1 (pre) (%)	73 (59-88.5)	91 (72.2-101.8)	70 (63-79)	80 (68-87)	.01
FEV_1 (post) (%)	81.5 (62.8-95.2)	95 (78.2-108.5)	77 (74-91.5)	84 (75-92.2)	.04
FVC (pre) (%)	86 (68.8-94.2)	92.5 (83-106.8)	83 (75.2-93.8)	88 (79-96.5)	.01
FVC (post) (%)	88.5 (71.8-99)	96.5 (82.2-108)	87 (81-99)	90.5 (78-96.8)	.13
FEV_1/FVC (pre) (%)	74 (64.8-79.5)	79.5 (71-86)	71.5 (64.5-81.2)	74 (71-80)	.12
FEV_1/FVC (post) (%)	76 (67-83)	83 (76-87.8)	74 (70.2-82.8)	77.5 (73.8-86.5)	.06
Reversibility (%)	7.5 (3-18)	4 (1.2-10)	8 (5.8-18)	6.5 (5-9.2)	.11
Blood leukocytes ($\times 10^3$/μL)	8 (7-9.5)	7.8 (6.8-9)	8 (7.2-9.9)	6.8 (6.1-8.1)	.13
Blood neutrophils (%)	57.1 (52.6-67.7)	56.3 (48.5-63.2)	52.1 (50.7-62.1)	56.9 (48.6-66.6)	.71
Blood lymphocytes (%)	30 (22.1-37.1)	32.6 (25.4-38.8)	30.3 (17.9-36.1)	32 (23.4-38.2)	.42
Blood monocytes (%)	7.2 (5.8-8.8)	7 (5.7-8.4)	7.2 (6.9-8.1)	7.7 (6.6-8.8)	.68
Blood eosinophils (%)	2.1 (1.4-5.7)	2.2 (1.4-4.6)	5.3 (4.5-7.6)	2.4 (1.1-3.5)	.10
Blood basophils (%)	0.5 (0.3-0.6)	0.4 (0.4-0.7)	0.5 (0.4-0.6)	0.4 (0.3-0.6)	.50
Blood neutrophils ($\times 10^3$/μL)	4.7 (3.7-6.6)	4.5 (3.4-5.5)	5 (3.6-5.8)	3.9 (3.2-5.2)	.29
Blood lymphocytes ($\times 10^3$/μL)	2.3 (1.7-2.8)	2.4 (2.1-2.9)	2.1 (1.5-3.3)	2.1 (2-2.7)	.58
Blood monocytes ($\times 10^3$/μL)	0.6 (0.5-0.7)	0.5 (0.4-0.7)	0.6 (0.5-0.7)	0.5 (0.5-0.7)	.53
Blood eosinophils ($\times 10^3$/μL)	0.2 (0.1-0.4)	0.2 (0.1-0.4)	0.5 (0.3-0.7)	0.1 (0.1-0.2)	.06
Blood basophils ($\times 10^3$/μL)	0 (0-0.1)	0 (0-0.1)	0 (0-0.1)	0 (0-0)	.17
IgE (kU/L)	51.5 (28.8-150.2)	110 (56-259)	229 (219-456)	442 (323.5-1145.5)	<.0001
Total sputum cell count ($\times 10^6$/g)	2.7 (0.9-7.5)	1.8 (0.8-12.2)	4.7 (0.6-9.7)	1.1 (0.6-4.4)	.58
Squamous cells (%)	8.5 (1-15.8)	12.5 (7.2-24.5)	30 (24-47)	20.5 (3.8-32.5)	.03
Sputum viability (%)	77.5 (63.5-89)	79 (65-86)	52 (12-79)	69.5 (53.8-78.5)	.13

(continued)

TABLE E1. *(Continued)*

Demographic, functional and inflammatory characteristic	STAPH+ > 0.35/ATOPY+ > 0.35				
	STAPH−/ATOPY−	STAPH−/ATOPY+	STAPH+/ATOPY−	STAPH+/ATOPY+	*P* value
Sputum macrophages (%)	13.8 (7.2-29.8)	17.6 (6.8-35)	9.4 (6.9-14.5)	20 (12.3-38.7)	.18
Sputum lymphocytes (%)	0.5 (0.1-1.2)	0.4 (0.2-1.1)	1.4 (0.2-5.6)	0.6 (0.1-1)	.66
Sputum neutrophils (%)	63.6 (49-86.3)	70.1 (45.9-82.8)	71.3 (38.1-77.5)	67.6 (49.7-76)	.92
Sputum eosinophils (%)	2.2 (0.2-16.8)	2.1 (0.9-5.2)	8.9 (3.4-21.2)	2.2 (0.9-3.3)	.38
Sputum epithelial cells (%)	1.8 (0.6-4.6)	2.1 (0.9-4.6)	4.5 (3.4-6.5)	2.8 (1.8-6)	.11

ACT, Asthma Control Test; *ACQ*, Asthma Control Questionnaire; *AQLQ*, Asthma Quality of Life Questionnaire; *BMI*, body mass index; *FVC*, forced vital capacity; *ICS*, inhaled corticosteroid; *IQR*, interquartile range; *LABA*, long-acting β-agonist; *LAMA*, long-acting muscarinic agent, *LTRA*, leukotriene receptor antagonist; *OCS*, oral corticosteroid; *PAQ-Y*, quantification of cigarette smoking; *SABA*, short-acting β-agonist.
Values are median (IQR) or n (%).

TABLE E2. Demographic, functional, and inflammatory characteristics of patients classified according to their sensitization to SE and common AAs defined with a cutoff of 0.10 kU/L for both SE and AA

Demographic, functional and inflammatory characteristic	STAPH+ > 0.1/ATOPY+ > 0.1				
	STAPH−/ATOPY−	STAPH−/ATOPY+	STAPH+/ATOPY−	STAPH+/ATOPY+	*P* value
N (%)	19 (17)	36 (33)	17 (15)	38 (35)	
Age (y)	64 (43.5-69)	49 (32-61)	55 (52-64)	54.5 (41.2-64.8)	.16
Age at diagnosis (y)	50 (38-60)	22.5 (5-40.4)	50 (46.8-58.3)	18 (5-51.2)	<.001
Sex (male)	4 (21)	13 (36)	7 (41)	19 (50)	.20
BMI (kg/m^2)	25 (22.9-28.4)	27.2 (23.8-29.7)	25.3 (23.2-27.5)	25.6 (22.9-29.8)	.73
Exacerbations per patient	1 (0-2)	0 (0-2)	1.5 (1-4.5)	0 (0-2)	.03
ACT score	13.5 (10.8-16.5)	16 (12.8-19.2)	16 (6-23)	15 (11-18.8)	.49
ACQ score	2.3 (1.3-3.3)	1.9 (0.9-2.8)	2.3 (0.9-4.3)	1.9 (1.1-2.7)	.42
AQLQ score	4.5 (3.9-5)	4.4 (3.7-5.2)	4.5 (2.7-5.5)	3.9 (3.3-5.3)	.53
PAQ-Y	20 (0-42.5)	0 (0-0.1)	11 (0-20)	0 (0-7.5)	<.01
Smoking status					.02
Nonsmokers	6 (32)	27 (75)	6 (35)	21 (55)	
Ex-smokers	9 (47)	6 (17)	9 (53)	13 (34)	
Smokers	4 (21)	3 (8)	2 (12)	4 (11)	
ICS	12 (63)	25 (69)	14 (82)	31 (82)	.35
ICS (μg)	650 (0-1750)	1000 (0-2000)	1500 (850-2000)	1000 (425-2000)	.73
OCS	4 (21)	4 (11)	4 (24)	6 (16)	.60
LABA	12 (63)	25 (69)	14 (82)	31 (82)	.35
SABA	17 (89)	26 (72)	15 (88)	27 (71)	.27
LAMA	3 (16)	2 (6)	2 (12)	1 (3)	.19
LTRA	6 (32)	14 (39)	7 (41)	11 (29)	.76
Anti-IgE	0 (0)	2 (6)	0 (0)	6 (16)	.13
Anti−IL-5	1 (5)	2 (6)	0 (0)	4 (11)	.72
FENO (ppb)	21 (12-24.5)	18 (11.8-31.5)	47.5 (17.2-81.2)	24 (15-54)	.07
FEV_1 (pre) (%)	74 (49.5-87)	91 (71-102.2)	69.5 (62.8-93.2)	80.5 (69.5-88.5)	.04
FEV_1 (post) (%)	83 (52.5-95.5)	95 (78.8-107.5)	79 (66-100.8)	84 (73-93)	.05
FVC (pre) (%)	83 (58-89.5)	92.5 (76.8-106.2)	89 (75-99.2)	87.5 (80-97.8)	.04
FVC (post) (%)	80 (67-95)	95 (82.8-108)	92.5 (78.8-102)	91 (79-98)	.08
FEV_1/FVC (pre) (%)	74 (67-84)	79.5 (71.8-86)	69.5 (59.8-81.2)	74 (70.2-80.5)	.09
FEV_1/FVC (post) (%)	76 (69-83.5)	83 (76.8-88)	74.5 (63.8-82.2)	78 (72-84)	.05
Reversibility (%)	7 (4.5-13.5)	4 (2-10.5)	7.5 (3.8-20)	7 (2-11)	.35
Blood leukocytes ($\times 10^3/\mu L$)	7.3 (6.2-8.7)	7.8 (7-9.1)	9 (7.4-9.6)	7.3 (6.4-8.5)	.11
Blood neutrophils (%)	56.9 (50.7-62.1)	56.3 (48.4-63.9)	56.6 (51.7-61.2)	57.4 (52.4-66.9)	.91
Blood lymphocytes (%)	31.8 (24.9-37.5)	32.3 (25.8-37.9)	31.9 (23.2-36.1)	30.4 (20.8-37.3)	.76
Blood monocytes (%)	7.9 (6.7-9.2)	7 (5.8-8.6)	7.2 (6.1-7.2)	7.3 (5.4-8.5)	.59
Blood eosinophils (%)	2.2 (1.6-5.2)	1.9 (1.3-4)	4.5 (1.9-5.8)	2.6 (1.2-3.9)	.41
Blood basophils (%)	0.5 (0.3-0.6)	0.4 (0.4-0.7)	0.6 (0.4-0.7)	0.4 (0.3-0.6)	.55
Blood neutrophils ($\times 10^3/\mu L$)	4.5 (3.1-5.7)	4.5 (3.5-5.6)	5.1 (3.7-6.6)	4.3 (3.2-5.5)	.53
Blood lymphocytes ($\times 10^3/\mu L$)	2.2 (1.8-2.6)	2.4 (2.2-2.9)	2.5 (2-3.1)	2.1 (1.7-2.8)	.18
Blood monocytes ($\times 10^3/\mu L$)	0.5 (0.4-0.7)	0.5 (0.5-0.7)	0.6 (0.5-0.7)	0.5 (0.4-0.7)	.56
Blood eosinophils ($\times 10^3/\mu L$)	0.2 (0.1-0.4)	0.2 (0.1-0.3)	0.3 (0.2-0.5)	0.2 (0.1-0.4)	.32
Blood basophils ($\times 10^3/\mu L$)	0 (0-0)	0 (0-0.1)	0.1 (0-0.1)	0 (0-0)	.13
IgE (kU/L)	32 (20-67.7)	87.5 (50.8-151.8)	175 (98-229)	380 (259-675)	<.0001
Total sputum cell count($\times 10^6$/g)	3.7 (0.9-6)	1.8 (0.9-8.4)	2.9 (0.8-7.7)	1.3 (0.5-6.8)	.79
Squamous cells (%)	5.5 (0.8-12.5)	11 (6.8-17)	18 (3-32)	20 (5.5-33)	.08
Sputum viability (%)	88 (70-89.8)	79 (65-87.5)	67 (48.8-80.8)	69 (58.5-82)	.08
Sputum macrophages (%)	14 (12.8-26.7)	16.2 (7.2-33)	8.8 (4.5-18.4)	20 (11-37)	.19
Sputum lymphocytes (%)	0.6 (0.4-1.2)	0.6 (0.2-1.3)	1 (0.1-2.2)	0.4 (0-1)	.72
Sputum neutrophils (%)	65.8 (53.1-79.2)	76.3 (50.8-85.5)	70.8 (38-79.1)	62.4 (41.2-78.4)	.41
Sputum eosinophils (%)	2 (0.2-10.3)	2 (0.9-4.1)	7 (2-29.1)	2.2 (0.6-4.6)	.19
Sputum epithelial cells (%)	2 (0.7-4.2)	1.4 (0.6-3.5)	3.6 (1.8-5.2)	3.2 (1.6-8.8)	.05

ACT, Asthma Control Test; *ACQ*, Asthma Control Questionnaire; *AQLQ*, Asthma Quality of Life Questionnaire; *BMI*, body mass index; *FVC*, forced vital capacity; *ICS*, inhaled corticosteroid; *IQR*, interquartile range; *LABA*, long-acting β-agonist; *LAMA*, long-acting muscarinic agent, *LTRA*, leukotriene receptor antagonist; *OCS*, oral corticosteroid; *PAQ-Y*, quantification of cigarette smoking; *SABA*, short-acting β-agonist.
Values are median (IQR) or n (%).

TABLE E3. Demographic, functional, and inflammatory characteristics of patients classified according to their sensitization to SE and common AAs after exclusion of biological-treated patients (n = 95)

Demographic, functional and inflammatory characteristic	STAPH+ > 0.1/ATOPY+ > 0.35				
	STAPH−/ATOPY−	STAPH−/ATOPY+	STAPH+/ATOPY−	STAPH+/ATOPY+	*P* value
N (%)	21 (22)	29 (31)	23 (24)	22 (23)	
Age (y)	64 (47-70)	49 (29-61)	56 (52.5-64)	51 (40.2-64.8)	.07
Age at diagnosis (y)	39 (27.4-58)	28 (10-47.8)	52 (49-59)	15 (5-40.7)	<.0001
Sex (male)	5 (24)	10 (34)	13 (57)	10 (45)	.14
BMI (kg/m^2)	26.6 (22.9-28.7)	27.1 (23.9-29.7)	25.3 (23-27.9)	25.9 (22.9-28.6)	.90
Exacerbations per patient	1 (0-2)	0 (0-2)	1.5 (1-2.8)	0 (0-1.2)	.03
ACT score	13 (10.2-15.8)	16 (13-20)	16 (9-23)	15 (11.2-18)	.23
ACQ score	2.4 (1.4-3.3)	1.9 (0.9-2.6)	2 (0.6-3.6)	1.9 (1.1-3)	.29
AQLQ score	4.2 (3.7-4.9)	4.7 (3.9-5.5)	4.5 (3.1-5.8)	4.2 (3.5-4.9)	.50
PAQ-Y	17.5 (0-40)	0 (0-0)	11 (2-25)	0 (0-2.5)	<.001
Smoking status					<.001
Nonsmokers	7 (33)	23 (79)	6 (26)	15 (68)	
Ex-smokers	10 (48)	3 (10)	15 (65)	5 (23)	
Smokers	4 (19)	3 (10)	2 (9)	2 (9)	
ICS	13 (62)	19 (66)	19 (83)	16 (73)	.43
ICS (μg)	650 (0-2000)	1000 (0-2000)	1500 (725-2000)	1000 (25-2000)	.62
OCS	5 (24)	3 (10)	7 (30)	2 (9)	.16
LABA	13 (62)	19 (66)	19 (83)	16 (73)	.43
SABA	19 (90)	20 (69)	18 (78)	15 (68)	.26
LAMA	3 (14)	2 (7)	2 (9)	0 (0)	.39
LTRA	8 (38)	10 (34)	8 (35)	7 (32)	.99
F_{ENO} (ppb)	21 (14-24)	17 (11-33)	47.5 (16.5-80.5)	22 (14.2-41)	.05
FEV_1 (pre) (%)	72 (60-86)	95 (79-105)	72.5 (63-93.8)	85.5 (72-92)	<.01
FEV_1 (post) (%)	80 (66-95)	98 (85-109)	81 (72-98)	88 (71-99)	.01
FVC (pre) (%)	79 (64-89)	99 (88-108)	89 (77.8-99)	87.5 (80-101)	<.001
FVC (post) (%)	80 (68-92)	98 (87-109)	95.5 (83.2-101)	91 (77-106)	<.01
FEV_1/FVC (pre) (%)	74 (68-79)	83 (71-87)	70 (61.5-80)	77.5 (71-82.8)	.04
FEV_1/FVC (post) (%)	76 (70-83)	85 (76-89)	73 (64.2-81.8)	81 (72-87)	.01
Reversibility (%)	8 (5-18)	3 (1-10)	7.5 (3.2-18)	6 (1-7)	.047
Blood leukocytes ($\times 10^3/\mu L$)	7.8 (6.4-10.1)	7.8 (7.1-9)	8.4 (7.4-9.6)	6.9 (6.1-8.3)	.07
Blood neutrophils (%)	57.3 (52.6-67.4)	56.3 (48.1-63.2)	57 (51.9-65.9)	56.6 (50.7-67.9)	.71
Blood lymphocytes (%)	30.2 (20.7-37.1)	33.3 (25.9-40.8)	29.8 (20.4-35.5)	32.2 (21.3-38.8)	.37
Blood monocytes (%)	7.5 (5.8-8.9)	7 (5.8-7.9)	7.2 (6.1-8.2)	6.8 (5.2-8.3)	.85
Blood eosinophils (%)	2.2 (1.5-4.5)	2.1 (1.5-4.6)	4.5 (1.6-6.2)	2.5 (1.5-4.1)	.60
Blood basophils (%)	0.5 (0.3-0.6)	0.4 (0.3-0.7)	0.6 (0.4-0.7)	0.4 (0.3-0.7)	.61
Blood neutrophils ($\times 10^3/\mu L$)	4.5 (3.6-6.6)	4.4 (3.4-5.5)	5.1 (4-6.2)	4 (3.2-5.1)	.20
Blood lymphocytes ($\times 10^3/\mu L$)	2.2 (1.8-2.7)	2.4 (2.2-3)	2.4 (1.6-3.2)	2 (1.7-2.5)	.17
Blood monocytes ($\times 10^3/\mu L$)	0.5 (0.4-0.7)	0.5 (0.4-0.7)	0.6 (0.5-0.7)	0.5 (0.4-0.6)	.23
Blood eosinophils ($\times 10^3/\mu L$)	0.2 (0.1-0.4)	0.2 (0.1-0.4)	0.3 (0.2-0.6)	0.2 (0.1-0.5)	.41
Blood basophils ($\times 10^3/\mu L$)	0 (0-0)	0 (0-0.1)	0.1 (0-0.1)	0 (0-0)	.13
IgE (kU/L)	32 (23-57)	93 (51.5-159.5)	219 (112-316)	323.5 (235-460.2)	<.0001
Total sputum cell count ($\times 10^6/g$)	2.6 (0.8-6.4)	1.9 (1-3.7)	2.9 (0.7-9.3)	1.4 (0.9-6.7)	.95
Squamous cells (%)	7 (0.5-13)	11 (7-16)	18 (3-35.2)	20 (7-32)	.14
Sputum viability (%)	84 (68-89)	80 (64-89.8)	68.5 (53-81.5)	70 (50-82)	.21
Sputum macrophages (%)	13.3 (8.6-25.4)	20 (6.8-38)	12.6 (6-29.2)	13.6 (7.8-37)	.70
Sputum lymphocytes (%)	0.6 (0.4-1)	0.6 (0.2-1.5)	0.6 (0-2.3)	0.6 (0.2-1)	.93
Sputum neutrophils (%)	66.9 (53.9-89.1)	72.6 (47.3-84.3)	61.8 (36.7-77.5)	62.4 (44.4-78.4)	.50
Sputum eosinophils (%)	1.3 (0.1-11.7)	2 (1-4.3)	5.5 (0.9-22.9)	2.2 (0.8-9.4)	.46
Sputum epithelial cells (%)	1.2 (0.6-3.4)	1.4 (0.5-3.4)	3.9 (1.9-6.5)	2.8 (1.6-8.8)	.048

ACT, Asthma Control Test; *ACQ*, Asthma Control Questionnaire; *AQLQ*, Asthma Quality of Lfe Questionnaire; *BMI*, body mass index; *FVC*, forced vital capacity; *ICS*, inhaled corticosteroid; *IQR*, interquartile range; *LABA*, long-acting β-agonist; *LAMA*, long-acting muscarinic agent, *LTRA*, leukotriene receptor antagonist; *OCS*, oral corticosteroid; *PAQ-Y*, quantification of cigarette smoking; *SABA*, short-acting β-agonist.
Values are median (IQR) or n (%).