

Our study is also limited by the parents providing surrogate information for exposures that the child may or may not directly experience or indirectly be affected by. However, our findings coincide with previous studies regarding the potential impact of racism on asthma and, identifying potentially modifiable stressors in young children, which may allow intervention early on and improve health-related outcomes in the long term, is important. Further research is also needed to determine the impact of ACEs on asthma outcomes in children, because the exploration of ACEs within this context is less established than other psychosocial factors. Given the multifaceted and direct/indirect effects of racism and discrimination on the daily life of individuals and the compounded generational and community-level impact, this factor requires further rigorous consideration as a contributor to poor health outcomes in minoritized communities in the United States especially among young children in whom long-term effects may be cumulative.

Bridgette L. Jones, MD, MS^{*,†}

Vincent Staggs, PhD^{†,‡}

Brianna Woods-Jaeger, PhD[§]

^{*}Department of Pediatrics

Division of Allergy, Asthma and Clinical Immunology and Division of
Pediatric Pharmacology and Therapeutic Innovation
Children's Mercy

Kansas City, Missouri

[†]University of Missouri

Kansas City School of Medicine

Kansas City, Missouri

[‡]Health Services and Outcomes Research

Children's Mercy

Kansas City, Missouri

[§]Department of Behavioral Sciences and Health Education
Emory University Rollins School of Public Health
Atlanta, Georgia
bljones@cmh.edu

References

1. CDC. Most Recent Asthma Data 2017; 2015 National Health Interview Survey (NHIS) Data, Table 2013–2011 and Table 2014–2011. Available at: https://www.cdc.gov/asthma/most_recent_data.htm. Accessed March 1, 2019.
2. Beck AF, Huang B, Auger KA, Ryan PH, Chen C, Kahn RS. Explaining racial disparities in child asthma readmission using a causal inference approach. *JAMA Pediatr*. 2016;170(7):695–703.
3. Burchard EG. Medical research: missing patients. *Nature*. 2014;513(7518):301–302.
4. Barnhouse M, Jones BL. The impact of environmental chronic and toxic stress on asthma. *Clin Rev Allergy Immunol*. 2019. <https://doi.org/10.1007/s12016-019-08736-x>.
5. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: the Adverse Childhood Experiences (ACE) Study. *Am J Prev Med*. 1998;14(4):245–258.
6. Cronholm PF, Forke CM, Wade R, et al. Adverse childhood experiences: expanding the concept of adversity. *Am J Prev Med*. 2015;49(3):354–361.
7. Landrine H, Klonoff EA. The schedule of racist events: a measure of racial discrimination and a study of its negative physical and mental health consequences. May 1996. *J Black Psychol*. 1996;22(2).
8. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Int Med*. 2001;16(9):606–613.
9. Collins Jr JW, David RJ, Handler A, Wall S, Andes S. Very low birthweight in African American infants: the role of maternal exposure to interpersonal racial discrimination. *Am J Public Health*. 2004;94(12):2132–2138.
10. Brody GH, Yu T, Miller GE, Chen E. Discrimination, racial identity, and cytokine levels among African-American adolescents. *J Adolesc Health*. 2015;56(5):496–501.
11. Trent M, Dooley DG, Douge J, Section on Adolescent H. Council on Community P, Committee on A. The impact of racism on child and adolescent health. *Pediatrics*. 2019;144(2).

Effect of cysteinyl leukotriene receptor 1 blockade on aeroallergen-induced nasal recruitment of CD49d expressing neutrophils



Asthma and atopic diseases have been increasing worldwide.¹ One risk factor for the development of asthma and atopy is a severe respiratory viral infection in infancy. The viruses most associated with this risk are respiratory syncytial virus and rhinovirus. Using the murine parainfluenza virus Sendai virus (closely related to respiratory syncytial virus), we described a pathway that translates the severe respiratory viral infection into the development of atopy and airway disease in mice. Critical to this translation is the recruitment of a specific subset (CD49d expressing) of neutrophils to the airway.² We found that CD49d⁺ neutrophils are present in peripheral blood and nasal lavage of humans, and the presence of these cells correlates with atopic status.³ Furthermore, nasal allergen challenge increased frequency of these cells in nasal lavage in an allergen-specific fashion, and in individuals with symptoms of an upper respiratory tract infection, there were increased numbers of CD49d⁺ neutrophils.⁴

In our animal model, we noted that CD49d⁺ neutrophils coexpressed cysteinyl leukotriene receptor 1 (CysLTR1), 1 of 3 receptors for cysteinyl leukotrienes.⁴ Treating mice with a CysLTR1 antagonist prevented development of postviral airway disease. In humans, we found that CD49d⁺ neutrophils also coexpressed CysLTR1.⁴ We undertook this study to determine whether blockade of CysLTR1 would be sufficient to impair allergen-induced recruitment of CD49d⁺ neutrophils to the nasal lavage.

After providing consent, 34 atopic adults (median age, 31 years; age range, 23–58 years; 53% female; 97% white) underwent skin prick testing to dust mite, cat, Timothy grass, Bermuda grass, Kentucky bluegrass, and ragweed (Greer Laboratories) to confirm atopic status and determine appropriate allergen to which to challenge (per our previous work³). Individuals were excluded if they had fever or wheezing in the past 2 weeks, were pregnant, had ongoing persistent atopic symptoms, had a history of current or past suicidality, had hypersensitivity or intolerance to montelukast, had used an antihistamine within 5 days, had used intranasal corticosteroids within 2 weeks, or were treated with any biologic therapy within 6 months. On the basis of our prior work, 10 subjects should provide 80% power and 20 subjects should provide 98% power to detect a difference between

Disclosures: Dr Grayson has served on advisory boards for AstraZeneca, Novartis, and Genentech. No other disclosures were reported.

Funding Sources: This work was supported by grant R01 HL087778 (Dr Grayson) from the National Institutes of Health and The Abigail Wexner Research Institute at Nationwide Children's Hospital (Dr Grayson).

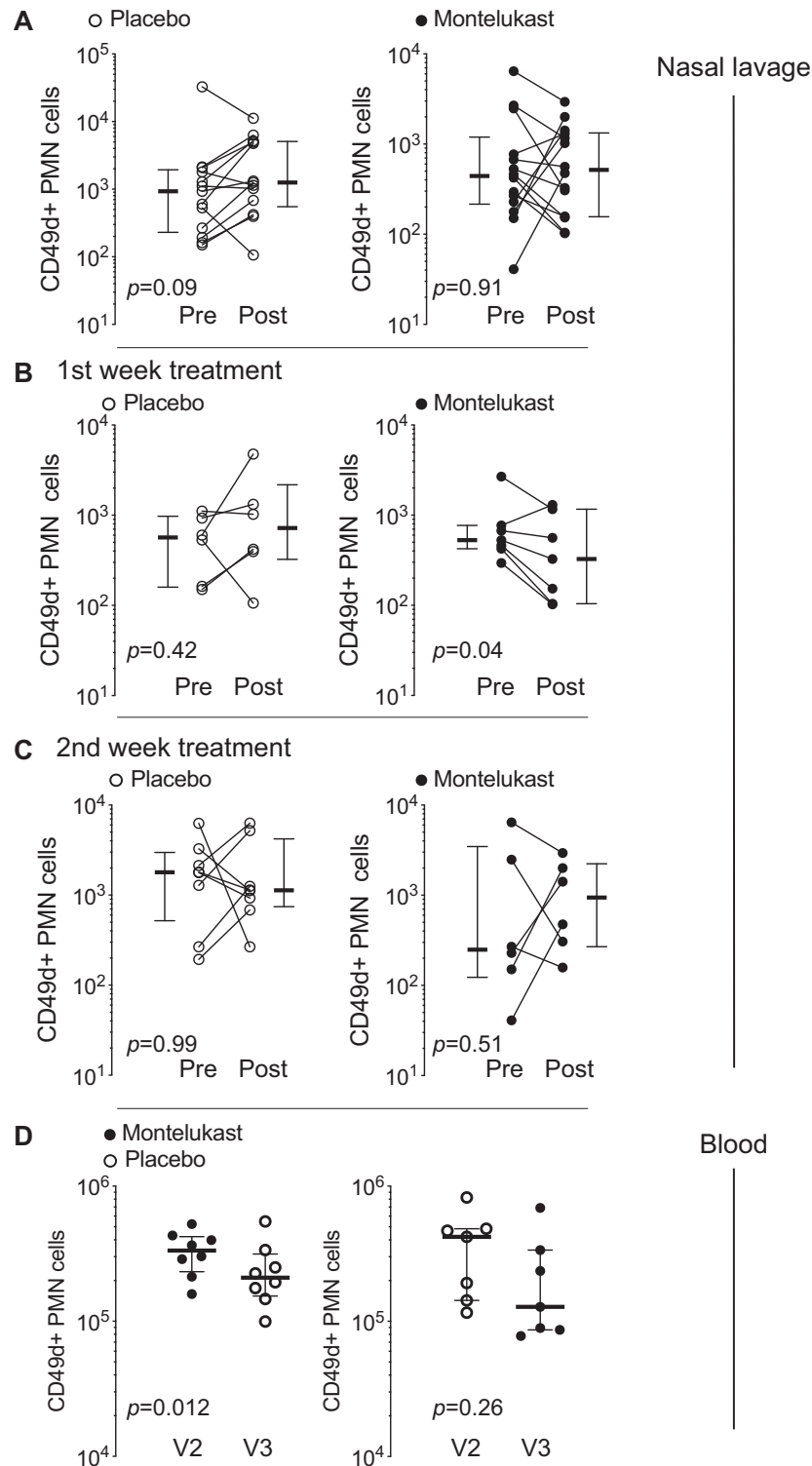


Figure 1. Effect of cysteinyl leukotriene receptor 1 antagonism on CD49d⁺ neutrophil accumulation in nasal lavage. A, Number of CD49d⁺ polymorphonuclear neutrophils in the nasal lavage before and after allergen challenge after 1 week of treatment with placebo (open circles) compared with montelukast (closed circles; $n = 16$, medians marked with bar) regardless of which week the individuals were treated with montelukast or placebo. B, CD49d⁺ neutrophils in nasal lavage before and after allergen challenge in individuals after receiving placebo (open circles) or montelukast (closed circles) for 1 week of therapy as their intervention for the first week of treatment. C, As for panel B but with individuals grouped based on the intervention they received in the second week of treatment (ie, the opposite of the treatment in panel B). D, Treatment with montelukast in the first week before allergen challenge increased peripheral blood CD49d⁺ neutrophils, but this was not seen when montelukast was used in the second week of the study. Number of CD49d⁺ neutrophils in 10 mL of peripheral blood from individuals treated with placebo (open circles) or montelukast (closed circles) grouped by whether montelukast was given before the first allergen challenge (left panel) or before the second challenge (right panel). V2 and V3 indicate the study visit (2, after first week of treatment [at the time of the first allergen challenge], or 3, after second week of treatment [at the time of the second allergen challenge], respectively) when the blood was drawn (data are shown for individuals with the median [interquartile range] for each group).

pretreatment and posttreatment nasal lavage CD49d⁺ neutrophil numbers.³

Participants were randomized in double-blind fashion to receive daily montelukast (10 mg) or placebo. One week later, participants underwent nasal lavage and peripheral blood draw, followed by nasal aeroallergen challenge (200 AU in 100 μ L, as outlined by Sigua et al³). Thirty minutes after allergen challenge, a 20-Item Sino-Nasal Outcome Test (SNOT20) survey was completed. Six hours after challenge, an additional nasal lavage was performed. Following this visit, individuals crossed over to the other treatment (montelukast or placebo) for 1 week, followed by additional nasal lavage and challenge (to same antigen as first challenge) 1 week later. A second SNOT20 survey was completed at this final visit. The study was approved by our local institutional review board and registered on [ClinicalTrials.gov](https://www.clinicaltrials.gov) (NCT03039101).

Nasal lavage and peripheral blood were processed as published.³ CD49d⁺ CD16⁺ neutrophils were determined by flow cytometry. Wilcoxon rank sum (nonparametric) and paired *t* test (parametric) statistics were used for analysis.

Although 34 individuals were enrolled in our study, only 23 completed all study visits and challenges. Of these 23, only 16 had samples suitable for analysis (the others had no identifiable cells or had evidence of sample contamination on flow cytometry). The most prevalent aeroallergen used for challenge was dust mite (44%), followed by ragweed (25%), Timothy grass (25%), and cat (6.3%). Mean SNOT20 and SNOT20 top 5 scores are given in [eTable 1](#). There were no statistical differences between placebo and montelukast-treated participants in terms of symptom scores, and we did not note any significant difference in clinical symptoms (ie, nasal itching and sneezing) between placebo and montelukast-treated participants, regardless of whether they were treated first or second with montelukast (data not shown). Of note, the SNOT20 questionnaire covers symptoms during the past 2 weeks, whereas individuals in our study only underwent a single week of treatment.

[Figure 1A](#) shows the number of CD49d⁺ neutrophils in nasal lavage before allergen challenge versus after allergen challenge stratified by participant treatment. There was a trend for increased CD49d⁺ neutrophils in nasal lavage after allergen challenge when individuals were taking placebo (median before challenge, 930; interquartile range [IQR], 230–1945; median after challenge, 1255; IQR, 552–5084; *P* = .09) compared with treatment with montelukast (median before challenge, 443; IQR, 216–1198; median after challenge, 518; IQR, 156–1327; *P* = .91). Compared with our previous work,³ this study generated a much less robust accumulation of CD49d⁺ neutrophils in the nasal lavage after allergen challenge with placebo treatment. One difference among the studies is that in this study we performed 2 allergen challenges with the same allergen 1 week apart (the previous study had a single allergen challenge). Therefore, it is possible that the first allergen challenge could have influenced the outcome of the second challenge. To examine this possibility, we looked at data for the first challenge ([Fig. 1B](#)) compared with data for the second challenge ([Fig. 1C](#)). In fact, those individuals given montelukast in the week before the first allergen challenge had a significant decrease in CD49d⁺ neutrophils with allergen challenge (median before challenge, 527.8; IQR, 425.1–770; median after challenge, 327; IQR, 104.3–1166; *P* = .04). This decrease was not seen in individuals treated with placebo (median before challenge, 565.7; IQR, 159.5–975; median after challenge, 722; IQR, 323.9–2179; *P* = .42)

([Fig. 1B](#)) before this first challenge. Supporting an effect of the first challenge on the second one, treatment with montelukast before the second challenge ([Fig. 1C](#)) was not associated with a reduction in CD49d⁺ neutrophils (median before challenge, 248.8; IQR, 123–3470; median after challenge, 944.3; IQR, 268.9–2235; *P* = .51). Similarly, treatment in the second week with placebo also failed to demonstrate an effect on CD49d⁺ neutrophils (median before challenge, 1792; IQR, 520.6–2982; median after challenge, 1131; IQR, 744.8–4220; *P* = .99) ([Fig. 1C](#)).

Further evidence of a differential effect of montelukast depending on when administered was found in the peripheral blood data ([Fig. 1D](#)). Treatment with montelukast for the first week (before the first allergen challenge) was associated with an increase in peripheral blood CD49d⁺ neutrophils compared with the levels in the same individuals when treated with placebo (montelukast group: median, 3.33×10^5 cells/mL; IQR, $2.32\text{--}4.23 \times 10^5$ cells/mL; placebo group: median, 2.10×10^5 cells/mL; IQR, $1.54\text{--}3.14 \times 10^5$ cells/mL; *P* = .01). If montelukast prevented migration of neutrophils to the nasal tissue, it might lead to an increase in peripheral blood neutrophils, but placebo would not prevent migration to the nasal tissue and the number of blood CD49d⁺ neutrophils would decrease. Similar to the nasal lavage, there appeared to be no difference between montelukast and placebo treatment in those individuals who received montelukast in the second week of the study (montelukast group: median, 1.28×10^5 cells/mL; IQR, $8.64\text{--}3.36 \times 10^5$ cells/mL; placebo group: median, 22×10^5 ; IQR, $1.43\text{--}4.84 \times 10^5$; *P* = .26).

Our data provide limited support for the hypothesis that human CD49d⁺ neutrophils use CysLTR1 for accumulation in the nasal tissue after an allergen challenge. However, our study has significant limitations: lack of robust symptoms during nasal allergen challenge, which suggests an impaired allergic response and may be reflected in the reduced recruitment of CD49d⁺ neutrophils, the carryover effect seen with the second allergen challenge, and the relatively small number of participants. Furthermore, we examined adults, whereas our animal model suggests that CysLTR1 antagonism is most relevant in infants. Additional studies are needed to determine whether the CysLTR1-dependent pathway identified in the mouse is applicable to the human.

Lisa M. Sammon, DO*

Syed-Rehan A. Hussain, PhD**†

Melinda Smith, BS, BSN, RN, CCRC‡

Michelle Rohlfing, BS**†

Jennifer L. Santoro, BS**†

Mitchell H. Grayson, MD**†

*Division of Allergy and Immunology, Department of Pediatrics
Nationwide Children's Hospital and The Ohio State University
Columbus, Ohio

†Center for Clinical and Translational Research, The Abigail Wexner
Research Institute at Nationwide Children's Hospital, Columbus, Ohio

‡Division of Clinical Research, Nationwide Children's Hospital
Columbus, Ohio
wheeze@allergist.com

Supplementary Data

Supplementary data related to this article can be found online at <https://doi.org/10.1016/j.anai.2019.08.019>.

References

1. Pawankar R. Allergic diseases and asthma: a global public health concern and a call to action. *World Allergy Organ J*. 2014;7(1):12.
2. Cheung DS, Ehlenbach SJ, Kitchens RT, et al. CD49d+ neutrophils induce FcεRI expression on lung dendritic cells in a mouse model of postviral asthma. *J Immunol*. 2010;185(9):4983–4987.
3. Sigua JA, Buelow B, Cheung DS, et al. CD49d-expressing neutrophils differentiate atopic from nonatopic individuals. *J Allergy Clin Immunol*. 2014;133(3):901–904.e5.
4. Cheung DS, Sigua JA, Simpson PM, et al. Cysteinyl leukotriene receptor 1 expression identifies a subset of neutrophils during the antiviral response that contributes to postviral atopic disease. *J Allergy Clin Immunol*. 2018;142(4):1206–1207.e5.

Factors associated with effective inhaler technique among children with moderate to severe asthma



Guidelines recommend that children and families receive education about and demonstration of effective inhaler technique as part of asthma self-management education.¹ For youth, improved inhaler technique is associated with better quality of life and decreased health care use,^{2,3} yet technique remains suboptimal.² To understand potential reasons for differences in inhaler skills, this study examined individual- and health care–level factors associated with effective inhaler technique among children.

This cross-sectional study analyzed baseline data from Improving Technology-Assisted Recording of Asthma Control in Children (iTRACC), a randomized clinical trial conducted from 2016 to 2018. Recruitment of parent-child dyads was conducted at 5 pediatric clinics (3 primary care, 1 pulmonary, and 1 allergy) in Chicago, Illinois. Enrolled children were 4 to 17 years old, had persistent asthma, were prescribed daily inhaled corticosteroids for 1 year or more, and experienced 1 or more exacerbations that required oral corticosteroids in the prior year. The study excluded children who were non-English speaking, had comorbid respiratory conditions (eg, bronchopulmonary dysplasia), or participated in other technology-based research. Lurie Children's Hospital's Institutional Review Board approved the protocol. The trial was registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT02994238).

At enrollment, inhaler technique, the primary outcome, was assessed by observing how participants used a metered-dose inhaler with spacer or a metered-dose inhaler with spacer and mask. Trained research staff scored technique with validated checklists that included 12 steps for inhaler and spacer and 10 steps for inhaler, spacer, and mask.⁴ One point was given for each step completed correctly. For analysis, effective inhaler technique was defined as more than 75% of steps performed correctly (spacer only: ≥ 10 of 12 steps; spacer and mask: ≥ 8 of 10) vs misuse (spacer only: < 10 of 12; spacer and mask: < 8 of 10).^{4,5} Parent-child dyads also completed the Asthma Control Test or Childhood Asthma Control Test (ACT/cACT), based on child's age. Age, sex, race, and insurance were obtained from electronic health records.

Univariate statistics summarized participants' characteristics and inhaler technique. Multivariable logistic regression models were fitted to evaluate the association of effective inhaler technique and covariates, including age, sex, race, insurance, clinic site, and

asthma control. The model adjusted for potential clustering of children by family. Testing was 2-tailed with $\alpha = .05$. Analyses used Stata SE 15.1 software (StataCorp).

Of 252 children enrolled in iTRACC, 141 parent-child dyads demonstrated inhaler technique. We restricted the sample to 130 dyads who completed all parts of the technique assessment. Children's mean (SD) age was 9.5 (3.5) years, and more than one-third of children were female (35.4%). Participants were 36.9% Hispanic, 20.0% non-Hispanic white, and 30.0% non-Hispanic black. Approximately 60% had public insurance, and roughly half had uncontrolled asthma (ACT/cACT < 20).

Among 59 participants using inhaler with spacer only, the mean (SD) number of steps completed correctly was 9.7 (2.1) (range, 5–12). The most commonly missed steps in this group were breathing out fully (50.8%), breathing out away from inhaler or spacer (44.1%), breathing normally between puffs (28.8%), and breathing in slowly (27.1%). Among 71 participants using inhaler with spacer and mask, the mean (SD) number of steps completed correctly was 9.0 (1.4) (range, 4–10). In this group, the most commonly missed steps were breathing normally between puffs (32.4%), breathing in or out 6 times (18.3%), and removing mask before breathing normally (15.5%) (eTable 1).

Overall, 73.1% of children demonstrated effective inhaler technique, with 54.2% of the 59 children using spacer only and 88.7% of 71 children using spacer and mask. Children who used the inhalers effectively were significantly younger than those who misused inhalers (mean age, 8.9 vs 11.3 years; $P < .001$). There were no statistically significant differences in sex, race, insurance, primary/subspecialty care, or asthma control among children with effective inhaler technique versus misuse ($P > .05$ for all). In multivariable analysis, age was the only variable associated with effective use, showing that adolescents (14–18 years old) had 80% lower odds of effective inhaler technique vs children 4 to 8 years old (odds ratio, 0.2; 95% CI, 0.06–0.5) (Table 1).

This study among diverse children identified an association between age and effective inhaler technique. No other individual or health system factors were significantly associated with effective inhaler use among youth.

We found effective inhaler technique was less likely among adolescents compared with younger children. These findings are in contrast to a prior study that found that older children were significantly more likely to perform inhaler steps correctly.⁶ However, this previous study differed in terms of participants' ages (4–17 vs 8–16 years old), location (urban Chicago vs nonurban North Carolina), and outcome metrics (proper use or misuse vs all steps). Other studies have found no association between inhaler technique and age.⁷ One possible explanation is that the association between inhaler technique and age is mediated through other factors that play a role in medication use, for example, level of parental involvement or amount of self-management education received. Our findings reinforce the need to engage not only parents but also children in their asthma care and also emphasize the importance of

Disclosures: Dr. Kan was supported by grant K12 HS026385-01 from the Agency for Healthcare Research and Quality. Dr. Gupta reports receiving grants from the National Institutes of Health, Stanford University, and Aimmune Therapeutics during the conduct of the study; serving as a medical consultant/adviser for DBV, Aimmune, Before Brands, Pfizer, Mylan, and Kaleo Inc during the past 3 years; and receiving grants from the National Institutes of Health, Allergy and Asthma Network, Food Allergy Research & Education, Rho Inc, Northwestern University Clinical and Translational Sciences Institute, Thermo Fisher, UnitedHealth Group, Mylan, and the National Confectioners Association outside the submitted work.

Funding Sources: The Improving Technology-Assisted Recording of Asthma Control in Children Trial was funded by UnitedHealth Group.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality.

eTable 1

SNOT20 Survey Scores for Placebo vs Montelukast Groups After Nasal Allergen Challenge

Allergen	Age, y/sex	Placebo		Montelukast	
		SNOT20	TOP5	SNOT20	TOP5
Timothy grass	58/M	5	5	15	12
Timothy grass	31/M	21	15	17	13
Timothy grass	41/F	15	14	11	11
Timothy grass	27/F	22	12	44	15
Dust mite	27/M	14	13	21	19
Dust mite	32/F	28	15	44	20
Dust mite	39/F	26	18	32	17
Dust mite	26/M	16	10	11	7
Dust mite	28/F	17	2	15	2
Dust mite	28/M	11	10	17	12
Dust mite	28/M	8	8	7	7
Dust mite	42/M	5	5	6	5
Ragweed	35/M	12	8	8	7
Ragweed	30/M	21	8	13	7
Ragweed	39/F	21	11	29	15
Cat	27/F	32	18	31	15

Abbreviations: SNOT20, 20-Item Sino-Nasal Outcome Test; TOP5, top 5 most bothersome symptoms.