

The Effect of Nasal Steroid and Antihistamine Use on Total Oxidative Stress and Antioxidant Status in the Treatment of Allergic Rhinitis

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Abstract

Introduction: The purpose of this study is to determine the post-treatment levels of total oxidant status (TOS) and total antioxidant status (TAS), that are increased due to pathophysiology, and to compare those with pre-treatment levels in allergic rhinitis patients.

Material-Methods: Among 84 patients clinically diagnosed with allergic rhinitis, 31 patients were started only on nasal steroid treatment (mometasone furoate), and 53 patients were started on nasal steroid and oral antihistamine treatment (mometasone furoate + rupatadine fumarate 10 mg). Blood samples were taken from the patients at the first examination and at post-treatment month 1. TAS and TOS were measured from the blood samples.

Results: While no significant change was determined in mean TAS levels with treatment, a statistically significant decrease was determined in TOS values in post-treatment period ($P < .01$). There was no significant change in TAS and TOS values of patients only using nasal steroids, while a significant decrease was determined in post-treatment TOS values of patients using both nasal steroids and oral antihistamines ($P < .001$). It was determined that TOS values of women were significantly lower compared to men, and it was also reduced in seasonal allergic rhinitis compared to perennial allergic rhinitis ($P < .05$ for both).

Conclusion: In allergic rhinitis patients, concomitant use of nasal steroids and antihistamines significantly decreases total oxidative stress. It may be stated that the addition of antihistamines to allergic rhinitis treatment positively affects treatment.

Keywords

allergic rhinitis, antihistamine, antioxidant, nasal steroid, oxidant, oxidative stress

Introduction

With oxygenic life, aerobic organisms have appeared and oxygen-sourced radicals were started to be formed. At that time, antioxidant defense systems were developed against oxidative damage in all aerobic organisms.

Molecules and atoms that have a nonshared (odd) number of electrons in their outer orbitals are called free radicals.¹ Free radicals are very reactive and short-lived. They may have positive, negative and neutral electrical charge.² Since they have high energy, electrons detach other electrons around them and damage their structure. This makes free radicals dangerous.³ Free radicals cause a high level of damage in cells and tissues.

DNA damage, changes in enzyme activities and lipid metabolism, disruption of membrane structure and functions through lipid peroxidation, and destruction of

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membrane proteins and carrier proteins are listed among the cellular damage they cause. Free radicals are recognized to play an efficient role in many pathological disorders such as aging, atherosclerosis, cancer, ischemia reperfusion, inflammation, rheumatoid arthritis, neurodegenerative diseases and liver diseases.^{2,4} Studies have revealed that free radicals cause aging and degenerative diseases.⁴ Radicals may be generated as by-products in all fractions of aerobic cells, during metabolism or pathological conditions, and they may cause various changes in cells. Serious cell, tissue and/or organ damage may occur as a result. Antioxidants prevent the negative effects of free radicals by stabilizing those or breaking down.

Oxidative stress is experienced when the balance between the levels of free radical and antioxidants is disrupted. The first determined effect of antioxidants was preventing the oxidation of polyunsaturated fatty acids in membrane structure, while in our day they are known to have protective effects on lipids, proteins, nucleic acids and other targeted macro molecules. In addition to various small molecules that are known to be antioxidants, enzymes such as glutathione peroxidase, catalase and superoxide dismutase and proteins binding metal ions are also included.⁵

Allergic rhinitis is an inflammatory nasal mucosal disease characterized with sneeze attacks, high level of fluid nasal discharge, nasal congestion and itching, which appears as a IgE-dependent, type I hypersensitivity reaction.⁶

Allergic rhinitis is a disease characterized with increased presence of eosinophils, basophils and mast cells in nasal secretion and nasal mucosa. Immunological or nonimmunological stimulation of these cells results in the production of free radicals such as superoxide anion, hydrogen peroxide and hydroxyl radicals.¹ The most important cells involved in the late phase of allergic rhinitis are eosinophils. In addition to causing tissue destruction, cytokines, chemokines and cations released from activated eosinophils also increase inflammation by autocrine and paracrine paths.^{7,8} Cytokines released from eosinophils in late phase reactions play a large role in the production of free oxygen radicals.⁸ Oxidative stress is considered to play an important role in the increasing continuation of inflammation after this stage.⁶⁻⁸ Emin et al. have compared 107 children with allergic rhinitis and 70 non-allergic children, and determined a significant increase in TAS and TOS rates.⁹ Similarly, Sim et al. have compared 90 children with allergic rhinitis and 90 healthy children, and they have determined that serum TAS and TOS levels of children with allergic rhinitis were significantly higher.¹⁰

The purpose of this study is to determine the post-treatment levels of total oxidant status (TOS) and total antioxidant status (TAS), that are increased due to pathophysiology, and to compare those with pre-treatment levels in allergic rhinitis patients.

Material-Method

A total of 84 patients who were diagnosed with allergic rhinitis (AR) between the dates January 2018 and June 2019 have been included in the study on a multicenter design containing Afyonkarahisar Sağlık Bilimleri University Medical Faculty Otorhinolaryngology Clinic, Emirdağ (Afyon, Turkey) Public Hospital Otorhinolaryngology Clinic and Serik (Antalya, Turkey) Public Hospital Otorhinolaryngology Clinic. The approval of Afyon Kocatepe University Ethics Committee was taken for the study (2017/8-207). The diagnosis of allergic rhinitis was determined with medical history and detailed ear, nose and throat physical examination (anterior rhinoscopy, nasal endoscopy, pharynx examination, autoscopy). Patients with appropriate history (at least two of nasal congestion, rhinorrhea, paroxysmal sneezing and itchy nose symptoms more than 1 hour in the day at least for 2 consecutive days) and examination findings (pale/hypertrophic turbinate, serous/mucous discharge) are diagnosed as AR and included in study. Pregnant patients, patients with significant septum deviation, active upper respiratory infection, nasal polyposis, and patients who have used nasal steroids and/or antihistamines in the last 4 weeks, have been excluded from the study.

Study details were explained to all patients included in the study, and informed consent forms were taken. Age, gender, detailed rhinoscopic examination findings, type of rhinitis (seasonal or year-round) have been recorded for patients diagnosed with allergic rhinitis. The state of conchae (pale-hypertrophic) and the state of nasal discharge (serous-mucoid) were determined with a detailed examination and recorded. In the first diagnostic examination, blood samples were taken from all patients into biochemistry tubes without using any agents. After first examination, 31 patients (16 females, 15 males) were started on only nasal steroid (mometasone furoate) treatment, and 53 patients (29 females, 24 males) were started on nasal steroid and oral antihistamine (mometasone furoate + rupatadine fumarate 10 mg) treatment. Patients were called for control after one month. Physical examination was repeated and the results have been recorded. Blood samples were taken from patients again for biochemistry. Blood samples were centrifuged, and serum parts were stored at - 80 degrees Celsius until the day of biochemical examinations.

Total Antioxidant and Total Oxidant Status Analyses in Blood Serum

Total Antioxidant Status Analysis: Total antioxidant status (TAS) of samples were measured with photometric method by using Rel Assay commercial kits (Rel Assay Kit Diagnostics, Turkey). A water-soluble

analogue of vitamin E, Trolox, was used as the calibrator. Results were stated in mmole Trolox equiv./L.

Total Oxidant Status Analysis: Total oxidant status (TOS) of samples were measured with photometric method by using Rel Assay commercial kits (Rel Assay Kit Diagnostics, Turkey). Hydrogen peroxide was used as calibrator. Results were stated in $\mu\text{mole H}_2\text{O}_2$ equiv./L.

Statistical Analysis

Descriptive statistics (percentage distribution, mean, standard deviation) were used in the analysis of data. Kolmogorov Smirnov and Shapiro Wilk tests were used to evaluate whether continuous data fit in normal distribution. Mann Whitney U Test was used for the comparison of median values of continuous data in independent groups, and Wilcoxon test was used for the comparison of repeating measures in dependent groups. SPSS V18 program was used in data analysis and significance level was assumed to be $p < 0.05$.

Results

Among the 84 patients included in the study, 39 (46%) were male and 45 (54%) were female. Mean age was 36 (min 10-max 69).

Mean TAS level was determined as 1.336 ± 0.270 at first blood measurement among 84 patients included in the study, and mean post-treatment measurement level was determined as 1.318 ± 0.275 ($p: 0.520$). Mean TOS level

was determined as 6.529 ± 1.512 at first blood measurement of the patients and as 5.901 ± 1.347 after the treatment, and it was determined to be statistically significantly lower compared to pre-treatment levels ($p: .009$) (Table 1).

Both nasal steroids and oral antihistamine treatment were applied to 53 patients (63%), while only nasal steroids were administered to 41 patients (37%). According to the applied treatment, only patients who were administered both nasal steroids and oral antihistamines were determined to have a significant decrease in post-treatment TOS level upon evaluating the measurement of pre- and post-treatment TAS and TOS levels (Table 2). In control all patients were asked whether they used their medication regularly. All female patients declared that they used medication properly as told. But few male patients declared that they could not use medication properly due to different reasons. Compliance of male patients to treatment were lower than female patients.

Upon evaluating measurements according to gender, a significant increase was determined in TOS value among women compared to pre-treatment values, while there was no significant difference for TAS value. No significant difference was determined with regard to TAS and TOS values in male patients (Table 3).

Sixty one patients (73%) were diagnosed with seasonal allergic rhinitis, while 24 patients (27%) were determined to have year-round (perennial) allergic rhinitis. Upon evaluating measurements in seasonal or perennial allergic rhinitis, it was determined that there was no significant difference between pre-and post-treatment TAS

Table 1. Blood Serum TAS and TOS Levels.

	First Measurement		Last Measurement		p
	Min $\pm$ Max	Mean $\pm$ SD	Min $\pm$ Max	Mean $\pm$ SD	
Total					
TAS	0.468–2.243	1.336 ± 0.270	0.493–2.033	1.318 ± 0.275	.520
TOS	2.255–11.418	6.529 ± 1.512	3.244–9.382	5.901 ± 1.347	.009

Table 2. Changes in TAS and TOS Levels According to Allergic Rhinitis Type.

Treatment					
	First Measurement		Last Measurement		p
	Min–Max	Mean $\pm$ SD	Min–Max	Mean $\pm$ SD	
Nasal steroids					
TAS	0.833–2.243	1.358 ± 0.300	1.026–2.033	1.365 ± 0.271	.724
TOS	2.255–9.309	6.276 ± 1.430	3.244–9.382	6.975 ± 1.539	.112
Nasal steroids and antihistamines					
TAS	0.468–1.902	1.323 ± 0.253	0.493–1.807	1.291 ± 0.276	.276
TOS	4.385–11.418	6.678 ± 1.552	3.796–7.782	5.273 ± 0.665	.000

Table 3. TAS and TOS Values According to Gender.

Gender	First Measurement		Last Measurement		p
	Min–Max	Mean $\pm$ SD	Min–Max	Mean $\pm$ SD	
Female					
TAS	0.775–2.243	1.345 $\pm$ 0.272	0.600–2.033	1.340 $\pm$ 0.279	.866
TOS	4.291–11.418	6.750 $\pm$ 1.531	3.244–9.018	5.853 $\pm$ 1.393	.021
Male					
TAS	0.468–1.902	1.326 $\pm$ 0.271	0.493–1.807	1.292 $\pm$ 0.272	.258
TOS	2.255–9.382	6.275 $\pm$ 1.468	3.913–9.382	5.956 $\pm$ 1.308	.276

Table 4. TAS and TOS Values of Patients According to Seasonal and Year-Round Allergic Rhinitis Status.

Allergic Rhinitis	First Measurement		Last Measurement		p
	Min–Max	Mean $\pm$ SD	Min–Max	Mean $\pm$ SD	
Seasonal					
TAS	0.468–2.243	1.303 $\pm$ 0.274	0.493–2.033	1.309 $\pm$ 0.280	.788
TOS	2.255–10.582	6.550 $\pm$ 1.484	3.244–9.055	5.942 $\pm$ 1.312	.032
Year-round					
TAS	0.996–1.902	1.425 $\pm$ 0.243	0.950–1.807	1.344 $\pm$ 0.265	.114
TOS	4.691–11.418	6.474 $\pm$ 1.617	3.913–9.382	5.793 $\pm$ 1.463	.248

values in seasonal allergic rhinitis, while a significant increase was determined in TOS value compared to pre-treatment period. No significant difference was determined between pre-treatment and post-treatment TAS and TOS values for patients with perennial allergic rhinitis (Table 4).

Discussion

Allergic rhinitis is the inflammatory disease of nasal mucosa due to IgE-mediated hypersensitivity reaction developed after encountering the allergen of susceptibility. Inflammation of nasal mucosa results in congestion, discharge, sneezing and itching, also it frequently causes complaints and symptoms such as itchy eyes and conjunctival discharge. Allergic rhinitis should be considered upon observing at least two of nasal congestion, rhinorrhea, paroxysmal sneezing and itchy nose symptoms more than 1 hour in the day at least for 2 consecutive days. The disease commonly involves all upper respiratory tract and conjunctiva, sometimes also lower respiratory tract, and it can coexist with asthma in the same person. In addition to being the most common chronic respiratory disease in childhood, it is also reported as the most common chronic disease among children in countries like USA.¹¹

Although the etiopathogenesis of allergic diseases are not completely clear, allergic rhinitis is known to be an immunopathological disorder characterized with nasal secretion and increased level of eosinophils, basophils and mast cells in nasal mucosa.^{2–6} Recent studies have reported that free oxygen radicals play a role in this inflammatory response.⁸

The rate of free radical generation and removal is balanced in the organism, and this is called oxidative balance. As long as oxidative balance is maintained, the organism is not affected by free radicals. Increased rate of radical formation or decreased rate of radical removal results in the disruption of this balance. In short, this status, which is called oxidative stress, shows a serious imbalance between free radical formation and antioxidant defense mechanism, and causes tissue damage in the result.¹²

Oxidative stress is responsible for the pathogenesis of many diseases, mainly cancer, and also diseases such as diabetes, cardiovascular and neurological diseases, atherosclerosis and inflammatory disorders.^{13–16} There are also studies showing the relation of oxidative stress and many diseases such as asthma, atopic dermatitis and allergic rhinitis.⁹

In the result of clinical and laboratory examinations in a study performed by Akbay et al.,¹⁷ enzymatic antioxidant myeloperoxidase (MPO), non-enzymatic antioxidants

vitamin A and E, malondialdehyde (MDA) from oxidative stress product metabolites formed in the result of lipid peroxidation and total antioxidant status (which shows the oxidative stress balance) have been examined in blood tests of 40 patients diagnosed with allergic rhinitis, and results have been compared with control group consisting of 40 healthy individuals; and it was determined that MDA levels were significantly higher in allergic rhinitis patient group compared to control group, and that MPO, vitamin A and E levels and TAS were significantly lower. These results show that the level of oxygen radicals is increased in allergic rhinitis patients. The lack of balance between oxidative stress and antioxidant defense mechanism is considered to play a role in the pathogenesis of allergic rhinitis.¹⁷

While intranasal steroids are recommended as the first-line treatment for allergic rhinitis, oral antihistamines, leukotriene receptor antagonists and oral steroids are other alternative treatment options. According to current guidelines, nasal steroids is the treatment option that is recommended before antihistamines, leukotriene antagonists and nasal antihistamines in the treatment of allergic rhinitis.¹⁸ Intranasal corticosteroids, beclomethasone, flunisolide, budesonide, fluticasone and mometasone are the most efficient treatment options in the treatment of allergic rhinitis.^{19,20} They reach high concentrations in the receptor areas on nasal mucosa and have minimal systemic adverse effects. Their effect is observed 7–8 hours after administering the intranasal dose, however, it may be required to wait for about 2 weeks for maximum effect. They are effective on all symptoms of allergic rhinitis. They are well-tolerated, adverse effects are rare and similar to placebo. Their long term use is recognized to be far from concerns in long-term oral glucocorticoid use.²⁰ Antihistamines and H1 blockers are cornerstones of allergic rhinitis treatment. First generation antihistamines are not generally recommended at first-line.¹⁹ As opposed to first generation antihistamines, second generation antihistamines have minimal sedation effect and other adverse effects are observed lower. Oral antihistamines prevent rhinorrhea, sneezing, nasal itching and eye symptoms that are developed due to histamine while showing effect, and their effect of nasal congestion is lower. Long term use of oral antihistamines is safe (for years) and they may also be used in children.²⁰ New-generation antihistamines (levocetirizine, desloratadine, ebastine, etc.) are recommended for allergic rhinitis patients instead of old generation antihistamines since they do not cause sedation and do not interact with cytochrome P450 enzyme system.^{18,20} The use of oral antihistamines is more common on the foreground compared to nasal antihistamines.⁶ Antihistamines increase patient's quality of life by decreasing allergic rhinitis symptoms, and they provide a cost-effective treatment.¹⁹ A significant decrease was determined in post-treatment TOS value in our

study, and it suggests that inflammation is reduced with treatment. In our study, we have administered either only nasal steroids, or the combination of nasal steroids and oral antihistamines to our patients. In the result, we have determined that there was a more significant decrease in TOS level in the group receiving both nasal steroid and oral antihistamine treatment. Although this result first brings to mind that combination therapy is more effective in allergic rhinitis treatment and thus lowers the oxidative stress in the body, it should also be considered that used antihistamines may have reduced oxidative stress by showing a possible direct antioxidant effect (binding or removing free radicals). Since our study was the first study to investigate the effect of treatment on TAS TOS, we did not anticipate that the TOS values of the group that added antihistamines would decrease. Obviously, when we formed the idea of doing the study, we expected an increase in TAS values and a decrease in TOS values of both the nasal steroid group and the combined group (maybe more in the combined group). Because clinically, many patients can only be treated with nasal steroid use, while a group of patients with more severe symptoms improve with combination therapy. We predicted that TAS TOS values would change in parallel with this clinical situation. Considering that TAS and TOS measurements were performed on blood samples, the possibility of oral antihistamines to show effect on the oxidative stress in systemic circulation is much higher than local-effect topical steroids. Further interpretation of results reveals that some level of increase, albeit not statistically significant, was observed in TOS values in patients using only nasal steroids, and this result suggests that nasal steroids bring an extra, although low oxidative stress burden to the body. It has been shown in previous studies that steroids may increase oxidative stress by affecting the activity of free oxygen radicals.²¹

While there was no significant difference between genders with regard to TAS and TOS values, it was observed that there was a statistically significant decrease in post-treatment TOS levels of women compared to pre-treatment values. Although TOS values were decreased in men compared to pre-treatment values, this decrease was not determined to be statistically significant. The reason of this may be men are less willing to use their medicines regularly compared to women.

Upon evaluating treatment efficiency with regard to seasonal or year-round allergic rhinitis, it was observed that there was a statistically significantly decrease in TOS values of seasonal allergic rhinitis patients after treatment. The fact that allergy symptoms of seasonal allergic rhinitis patients are significantly more severe compared to year-round allergic rhinitis patients may be associated with oxidative stress. The reason of that is oxidative stress is significantly reduced following the

recovery of these severe symptoms with treatment. In adults with pollen allergy, a strong effect of ozone concentrations was determined on rhinitis symptoms.²² Another interesting point was that 77.8% of women had seasonal allergic rhinitis while 66.7% of men had seasonal allergic rhinitis. This rate may be one of the reasons why there was no statistically significant TOS value decrease in men.

Also significant improvements in VAS, NCV and NAR values can be seen in patients given combination therapy.²³ It is in line with our study that combination therapy showed a more significant improvement.

In the result, a significant increase was observed on literature in serum total oxidant and antioxidant levels of allergic rhinitis patients.^{9,10} In our study, we have observed that concomitant use of nasal steroids and antihistamines significantly reduces oxidative stress. While these results may show that combination therapy causes significant decrease in inflammation, it may also suggest that antihistamines may have antioxidant characteristics. Whatever the reason, it may be stated that the administration of antihistamines with nasal steroids has a positive effect on allergic rhinitis treatment.

Declaration of Conflicting Interests

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Ethical Approval

All procedures performed in this study were in accordance with the ethical standards of the Afyon Kocatepe University Ethical Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study before surgery.

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References

1. Valko M, Izakovic M, Mazur M, Rhodes CJ, Telser J. (2004). Role of oxygen radicals in DNA damage and cancer incidence. *Mol Cell Biochem.* 266: 37–56.
2. Castaner A, Roig E, Serra A, et al. (1990). Risk stratification and prognosis of patients with recent onset angina. *Eur Heart J.* 11: 868–875.
3. Uysal M. Serbest radikaller, lipid peroksidleri ve organizmada prooksidan-antioksidan dengeyi etkileyen koşullar. *Klinik Gelişim.* 1998;11:336–340.
4. Harman D. Aging: a theory based on free radical and radiation chemistry. *J Gerontol.* 1956;11(3):298–300.
5. Koch OR, Pani G, Borrello S, et al. (2004). Oxidative stress and antioxidant defenses in ethanol-induced cell injury. *Mol Aspects Med.* 25: 191–198.
6. Lalwani AK, eds. *Current Diagnosis & Treatment in Otolaryngology-Head and Neck Surgery.* New York: McGraw-Hill; 2004: 278.
7. Dykewicz MS, Fineman S, Skoner DP, et al. Diagnosis and management of rhinitis: Complete guidelines of the Joint Task Force on practice parameters in allergy, asthma and immunology. *Ann Allergy Asthma Immunol.* 1998; 81:478–518.
8. Bowler RP, Crapo JD. Oxidative stress in allergic respiratory diseases. *J Allergy Clin Immunol.* 2002;110(3): 349–356.
9. Emin O, Hasan A, Aysegül D, Rusen D. Total antioxidant status and oxidative stress and their relationship to total IgE levels and eosinophil counts in children with allergic rhinitis. *J Investig Allergol Clin Immunol.* 2012;22(3):188–192.
10. Sim CS, Lee JH, Kim SH, et al. Oxidative stress in school-children with allergic rhinitis: propensity score matching case-control study. *Ann Allergy Asthma Immunol.* 2015;115(5):391–395.
11. Bousquet J, Van Cauwenberge P, Khaltaev N. Aria Workshop Group; World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108(5 Suppl):147–334.
12. Serafini M, Del Rio D. Understanding the association between dietary antioxidants, redox status and disease: is the total antioxidant capacity the right tool? *Redox Rep.* 2004;9(3):145–152.
13. Berlett BS, Stadtman ER. Protein oxidation in aging, disease, and oxidative stress. *J Biol Chem.* 1997;272(33): 20313–20316.
14. Motor S, Ozturk S, Ozcan O, et al. Evaluation of total antioxidant status, total oxidant status and oxidative stress index in patients with alopecia areata. *Int J Clin Exp Med.* 2014;7:1089–1093.
15. Aydın M, Selçoki Y, Nazlı Y, et al. Relationship between total antioxidant capacity and the severity of coronary artery Disease. *J Clin Exp Invest.* 2012;3:22–28.
16. Şahin DY, Elbasan Z, Gür M, et al. Relationship between oxidative stress markers and cardiac syndrome X. *J Clin Exp Invest.* 2012;3:174–180.
17. Akbay E, Arbağ H, Uyar Y, Öztürk K. Oxidative stress and antioxidant factors in pathophysiology of allergic rhinitis. *Tr-ENT.* 2007;17(4):189–196.
18. Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol.* 2010;126(3):466–476.
19. Nathan RA. Management of patients with allergic rhinitis and asthma: literature review. *South Med J.* 2009;102(9):935–941.
20. Bousquet J, van Cauwenberge P, Ait Khaled N, et al. Pharmacologic and anti-IgE treatment of allergic rhinitis

- ARIA update (in collaboration with GA2LEN). *Allergy*. 2006;1(9):1086–1096.
21. Stanić D, Plećaš-Solarović B, Petrović J, et al. Hydrogen peroxide-induced oxidative damage in peripheral blood lymphocytes from rats chronically treated with corticosterone: The protective effect of oxytocin treatment. *Chem Biol Interact*. 2016;256:134–141.
22. Riediker M, Monn C, Koller T, Stahel WA, Wuthrich B. Air pollutants enhance rhinoconjunctivitis symptoms in pollen-allergic individuals. *Ann Allergy Asthma Immunol*. 2001;87:311–318.
23. Chen H, Zhang L, Lou H, Wang Y, Cao F, Wang C. A Randomized Trial of Comparing a Combination of Montelukast and Budesonide With Budesonide in Allergic Rhinitis [published online ahead of print, 2019 Nov 29]. *Laryngoscope*. 2019;10. doi:10.1002/lary.28433