

Aspirin hypersensitivity in patients with chronic rhinosinusitis and nasal polyposis: Frequency and contributing factors

Mohammad Nabavi, Ph.D.,¹ Hossein Esmailzadeh, M.D.,^{1,2} Saba Arshi, Ph.D.,¹ Mohammad Hassan Bemanian, Ph.D.,¹ Morteza Fallahpour, Ph.D.,¹ Ahmad Bahrami, Ph.D.,¹ Negar Mortazavi, Ph.D.,³ Kamran Kamrava, Ph.D.,⁴ Mohammad Farhadi, Ph.D.,⁴ Reza Taghipour, Ph.D.,¹ and Nima Rezaei, Ph.D.^{2,5}

ABSTRACT

Background: Aspirin-exacerbated respiratory disease (AERD) is a syndrome frequently seen in patients with chronic rhinosinusitis and nasal polyposis (CRSwNP). However, there are few studies on evaluating the prevalence of aspirin (acetylsalicylic acid [ASA]) hypersensitivity in patients with CRSwNP using the oral aspirin challenge (OAC) test. This cross-sectional study was designed to determine the frequency of ASA hypersensitivity and factors associated with it in patients with CRSwNP in Tehran, Iran.

Methods: Adult patients with CRSwNP who were presented to the asthma and allergy clinic were recruited for the study. After confirming CRS and NP, OAC was performed to evaluate/confirm the diagnosis of ASA hypersensitivity. Atopic evaluation was performed using skin-prick test, nasal smear, blood eosinophil count, and serum total IgE.

Results: Eighty Iranian patients (43 women and 37 men) with CRSwNP were enrolled (mean age, 38.9 ± 10.7 years). OAC was performed in all of the patients and 39 patients (48.8%) had a positive reaction; among them, 14 (35.8%) had a self-reported history of ASA hypersensitivity. Concomitant asthma, previous polyp surgery, high polyp score, and ASA hypersensitivity history were all associated with positive OAC ($p < 0.05$). Presence of AERD was not associated with age, stage of asthma, blood eosinophilia, nasal smear eosinophilia, and atopy.

Conclusion: ASA hypersensitivity is common in patients with CRSwNP in Tehran, Iran. Patients at risk for AERD should be evaluated for the presence of ASA hypersensitivity with ASA provocation challenge test to confirm the diagnosis.

(Am J Rhinol Allergy 28, 239–243, 2014; doi: 10.2500/ajra.2014.28.4034)

Chronic rhinosinusitis (CRS) is an inflammatory disorder of the nose and paranasal sinuses of unknown cause, and it is defined based on characteristic symptoms and objective evidence of sinus disease *via* direct visualization or imaging studies.^{1–3} It has been reported that ~20% of patients with CRS also have nasal polyposis (NP).^{4,5}

CRS with NP (CRSwNP) is often associated with other respiratory diseases such as asthma, aspirin sensitivity, and idiopathic bronchiectasis.^{6,7} The prevalence of nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity seems to increase with increasing asthma severity and treatment resistance of underlying asthma and CRS.^{8–10}

Aspirin-exacerbated respiratory disease (AERD), previously known as Samter's syndrome, is a clinical tetrad of nasal polyps, chronic hypertrophic eosinophilic sinusitis, asthma, and sensitivity to any NSAIDs, specifically aspirin (acetylsalicylic acid [ASA]). AERD has been reported in 8–26% of patients with CRSwNP and in 10–20% of asthmatic patients.^{5,11,12} Ingestion of most NSAIDs results in a spectrum of upper and/or lower respiratory reactions, including rhinitis, conjunctivitis, and bronchospasm.^{11,13} AERD affects 0.3–0.9% of the

general population but the prevalence rises to 10–20% of asthmatic patients and up to 30–40% in those asthmatic patients with NPs.^{12–15} The average age of onset is 34 years, and it is more commonly reported in female patients.^{14,16}

There are no studies evaluating the ASA hypersensitivity in patients with CRSwNP in Iran. Therefore, this cross-sectional study was performed to assess the prevalence of AERD in adult patients with CRSwNP and to document the clinical features of the disease and risk factors.

METHODS

Patient Selection

This prospective study was conducted in the Department of Allergy and Clinical Immunology of Rasool-e-Akram Hospital, Tehran, Iran, in 2012. This study was approved by the Ethics Committee of Tehran University of Medical Sciences. According to the principles of the Helsinki Declaration, informed consent to the entire protocol was obtained from each patient. Consecutive patients with CRSwNP, who agreed to enroll to this study, were recruited for AERD evaluation.

Patients with diagnosis (or history of) of CRSwNP at the time of the visit to asthma and allergy clinic were recruited for AERD evaluation. CRS diagnosis was based on the European position paper on rhinosinusitis and nasal polyps (EPOS 2012)² and in all cases a diagnosis of NP was established by means of clinical criteria (ear, nose, and throat examination, including rhinoscopy, and computed tomographic scan of paranasal cavities) at the time of the visit. All of the patients had homogenous ethnicity from Persian origin. A single-blinded 2-day, oral aspirin challenge (OAC) was used to detect ASA hypersensitivity.

Evaluation of Predicting Outcomes

We collected clinical information including, age, gender, history of asthma diagnosed by physician, age of onset of asthma, nasal polyp,

From the ¹Department of Allergy and Immunology, Rasool-e-Akram Hospital, Iran University of Medical Sciences, Tehran, Iran, ²Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran, ³Department of Clinical Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran, ⁴Ear, Nose, and Throat–Head and Neck Surgery Research Center, Iran University of Medical Sciences, Tehran, Iran, and ⁵Molecular Immunology Research Center, and Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
The authors have no conflicts of interest to declare pertaining to this article
Address correspondence to Hossein Esmailzadeh, M.D., Department of Allergy and Immunology, Rasool-e-Akram Hospital, Iran University of Medical Sciences, PO Box 1993663194, Mollasadra Ave., Saeb Tabrizi Gharbi St. No. 22, Tehran, Iran
E-mail address: esmailzadeh_ho@yahoo.com
Copyright © 2014, OceanSide Publications, Inc., U.S.A.

Table 1 Demographic data in CRS patients with and without ASA sensitivity

Data	Total	With ASA Sensitivity	Without ASA Sensitivity
Male	37	14	23
Female	43	25	18
Mean age (yr; range, 19–65 yr)	38.88 ± 10.7	38.54 ± 11.8	39.20 ± 9.6
Mean age of polyp presentation (yr; range 15–60 yr)	38.28 ± 10.034	30.97 ± 10.310	33.51 ± 9.729
Mean age gap between asthma and polyp (yr)	5.61 ± 4.742 (0–15)	8.00 ± 5.933	4.42 ± 3.753

ASA = aspirin; CRS = chronic rhinosinusitis.

Table 2 The OAC outcome in symptomatic patients

Challenge Outcome	Frequency of Symptomatic Patients (n = 39)	Percent of Symptomatic Patients
Extrabronchial reactions	5	12.8
Mild bronchial reaction	13	33.3
Moderate bronchial reaction	12	30.7
Severe bronchial reaction	9	23.1

OAC = oral aspirin challenge.

rhinosinusitis/rhinitis, medications, and emergency room visit or hospitalization according to respiratory problem for the preceding year. We also collected information regarding the number of nasal polypectomies and history of reactions to ASA or other NSAIDs.

All subjects underwent a complete allergological evaluation including skin-prick tests with the most common inhaled allergens in Iran (Chenopodiaceae, Russian thistle, dust mites, rye grass, cockroach, *Aspergillus*, and Timothy grass), serum total IgE, nasal smear, and blood eosinophil determinations.

Polyposis staging was established by endoscopic evaluation of each patient.¹⁷ Asthma stage was classified as 1–4 as defined by the Global Initiative for Asthma guidelines at the time of the initial visit.¹⁸

Oral Aspirin Challenge

An OAC was performed as described by Macy and Nizankowska-Monilnicka.^{19,20} All challenges were performed in the outpatient Asthma and Allergy Clinic. The use of oral and intranasal antihistamines, decongestants, short-acting and long-acting β -agonists, and cromolyn were discontinued 48 hours before challenges and leukotriene modifiers and oral steroids 1 week before challenges but patients were allowed to take their other usual controller medications.^{19,21} Patients had to be clinically stable and have a forced expiratory volume in 1 second (FEV₁) at least 70% of the best predicted value before the challenge. Patients were asked to withhold use of mentioned drugs before challenge.

The challenge was performed in 2 consecutive days. On the 1st day, the challenge was started if the baseline FEV₁ was at least 70% of the best predicted value. Then, placebo ASA capsules were administered every 90 minutes for four doses and spirometry was performed every 60 minutes. The patient was not clinically stable at the end of the challenge on day 1 if FEV₁ was <70% of best predicted value, so the patient was excluded from the study. On the 2nd day of the challenge, baseline spirometry was performed and increasing doses of ASA (20, 40, 80, and 160 mg) were administered every 90 minutes until a cumulative dose of 325 mg was reached. Patients were discharged from the clinic 3 hours after the final dose. The dosing is based on using 80, 320-mg ASA tablets, and using a pill cutter to obtain the lower doses put inside placebo capsules. The dosing interval was extended to 3 hours in patients with history of emergency department visits or use of systemic corticosteroid for asthma exacerbations at least once in the last 6 months (not including NSAID-induced asthma

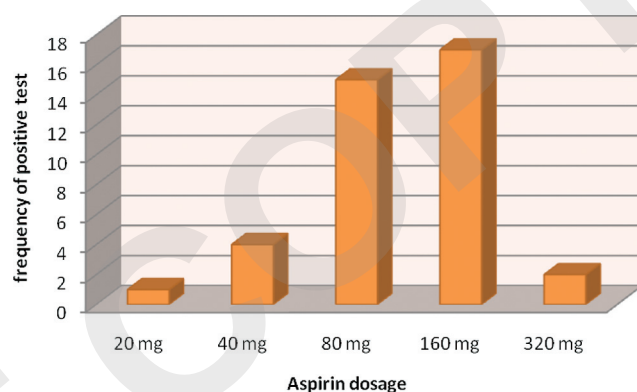


Figure 1. Aspirin (ASA) challenge test in chronic rhinosinusitis with nasal polyposis (CRSwNP) patients according to ASA dosage.

exacerbation), baseline FEV₁ of 70–80%, and self-reported history of severe reactions to NSAIDs. FEV₁ was measured and patients were evaluated every 60 minutes and before each ASA dose or more frequently if any sign of ASA-induced reactivity occurred. Reactions were confirmed by physician examination and challenge was interrupted and patients were treated with montelukast and other asthma attack managements. A positive reaction was defined as a decline in FEV₁ of at least 15% combined with naso-ocular reaction, pure lower respiratory tract reactions (related symptoms with 20% decline in FEV₁) or naso-ocular reactions only (severe nasal congestion, pronounced rhinorrhea, or tearing according to judgment of physician).

Statistics

Data were analyzed using SPSS software (Version 18; SPSS, Inc., Chicago, IL). Numerical values are given as mean ± SEM and categorical/ordinal values as n (%). Numerical values and ordinal/categorical values of patients with AERD and patients with ASA-tolerant asthma were compared, using unpaired samples *t*-test and chi-square tests, respectively. A value of *p* < 0.05 was considered as statistically significant.

RESULTS

A total of 80 patients with CRSwNP were enrolled in the study (53.7% female and 46.3% male patients) with a mean age of 38.88 ± 10.7 years. OAC was positive in 39 patients (48.8%), 25 female and 14 male patients. Demographic data of patients with and without ASA sensitivity is presented in Table 1. There was no statistically significant difference in patients with positive and negative OAC with regard to gender, age, age of nasal polyposis, and the time between diagnoses of asthma and polyp presentation (*p* > 0.05).

The mean ASA provoking dose was 121.5 mg. Bronchial reactions during OAC were classified as severe (FEV₁ decrease, >30%), moderate (FEV₁ decrease, 21–30%), or mild (FEV₁ decrease, 10–20%). occurred with no or minimal bronchospasm (Table 2).

Table 3 Clinical characteristics in patients with CRSwNP with and without ASA sensitivity

Clinical Characteristics	With ASA Sensitivity (n = 39)	Without ASA Sensitivity (n = 41)	p Value
Concomitant asthma (positive/negative)	87.1% (34)/12.8% (5)	68.2% (28)/31.7% (13)	0.043
History of previous surgery (positive/negative)	79.4% (31)/20.5% (8)	48.7% (20)/51.2% (21)	0.004
Frequency of surgeries (first time/≥2)	53.8% (21)/25.6% (10)	31.7% (13)/17% (7)	0.839
IgE level (≥100/<100)	66.6% (26)/33.3% (13)	70.7% (29)/29.2% (12)	0.695
Prick test (positive/negative)	56.4% (22)/43.5% (17)	53.6% (22)/46.3% (19)	0.805
History of immunotherapy (positive/negative)	41% (16)/58.9% (23)	7.3% (3)/92.6% (38)	0.236
Blood eosinophilia (≥450/<450)	12.8% (5)/87.1% (34)	12.1% (5)/87.8% (36)	0.933
Nasal smear eosinophilia (≥10%/<10%)	12.8% (5)/87.1% (34)	12.1% (5)/87.8% (36)	0.933
Asthma stage (mean ± SD)	3.06 ± 0.851	3.16 ± 0.746	0.637
Polyp score (mean ± SD)	4.33 ± 0.869	3.49 ± 1.247	0.001
History of NSAID hypersensitivity (positive/negative)	35.8%(14)/64.1% (25)	4.8% (2)/95.1% (39)	0.001

ASA = aspirin; CRSwNP = chronic rhinosinusitis with nasal polyposis; NSAID = nonsteroidal anti-inflammatory drug.

Table 4 Prick test in patients with CRSwNP with and without ASA sensitivity according to allergen type

Allergen Type	With ASA Sensitivity (n = 39)	Without ASA Sensitivity (n = 41)	p Value
Chenopodiaceae (positive/negative)	7/32	2/39	0.064
Russian thistle (positive/negative)	5/34	7/34	0.594
Dust mite (positive/negative)	2/37	5/36	0.264
Rye grass (positive/negative)	6/33	4/37	0.447
Cockroach (positive/negative)	2/37	1/40	0.527
<i>Aspergillus</i> (positive/negative)	4/35	5/36	0.784
Timothy grass (positive/negative)	0/39	0/41	—

ASA = aspirin; CRSwNP = chronic rhinosinusitis with nasal polyposis.

The mean elapsed time from ASA administration to the onset of reaction was 53 ± 28 minutes. No statistically significant correlation was observed between the baseline FEV₁ and change in FEV₁ in ASA-sensitive patients. Most of the positive reactions were observed at 80 and 160 mg of ASA.

The number of positive OAC for each dose of ASA is summarized in the Fig. 1. Compared with patients with negative OAC, patients with positive OAC had a statistically significant higher rate of concomitant asthma, previous surgery of nasal polyps, and polyp score (Table 3). Multiple operations of nasal polyps were higher in patients with positive OAC but the difference was not statistically significant. The positive prick test for individual allergens did not differ between the two groups of patients (Table 4). Sixteen patients (20%) had history of asthma or naso-ocular exacerbation after ingestion of NSAIDs and only two had a negative OAC. Statistically significant correlation was observed between NSAIDs hypersensitivity history and positive OAC ($p < 0.05$).

DISCUSSION

In this cross-sectional study, 48.8% of the patients with CRSwNP had AERD. Concomitant asthma, previous polyp surgery, high polyp score, and self-reported history of ASA hypersensitivity had a statistically significant higher rate of positive OAC. The exact prevalence of AERD is unknown. A limited number of epidemiological studies reported that the prevalence of AERD ranges from 4 to 44%.^{14,15} This

difference seems to be related with the heterogeneity of the population studied as well as the methods and criteria used for determining ASA hypersensitivity. A recent systematic review reported that the pooled incidence of AERD is 21% in adults.¹⁴

Most studies about the prevalence of AERD are performed in patients with asthma.^{22–24} In a large survey of a population-based random sample in Finland, the prevalence of AERD was 1.2%, using a postal questionnaire, and it was higher in patients with doctor-diagnosed asthma (8.8%).²² In Poland, hypersensitivity to ASA/NSAIDs was reported 12.9% in asthmatic patients *via* interview of subjects by medical students and nurses.²³ Similarly, in Turkey, 13.6% of the patients with asthma were reported to have hypersensitivity to ASA when interviewed by a specialist.²⁴

There are limited data on the frequency of ASA hypersensitivity in CRSwNP patients. Bevbek *et al.* conducted OACs in 53 adult patients with CRSwNP in Turkey and found that 22.6% had ASA sensitivity¹⁵ while Fan *et al.* reported a rate of 0.57% in 351 patients with CRS (309 with nasal polyps) in China.²⁵ Among glucocorticoid-dependent asthmatic patients and asthmatic patients with CRSwNP, NSAID sensitivity prevalence is up to 20–40%^{6,14}; this variability may be caused by geography and genetics differences.

In our cross-sectional study, the rate of AERD in patients with CRSwNP was 48.8%, which is slightly higher than what has been reported in the literature. This high rate may be caused by genetic and epigenetic factors. Among 39 patients with positive reaction to OAC, 25 (64.1%) did not report a history of ASA hypersensitivity and they had taken NSAIDs occasionally for pains and inflammations. In this study, we evaluated two patients with a reported history of AERD who had a negative OAC. The use of history alone in the assessment of ASA hypersensitivity among asthma patients has resulted in underestimation or overestimation of the real prevalence of AERD.^{7,14} Dursun *et al.* reported that history alone resulted in a much lower prevalence of AERD (16%) when compared with the pooled incidence of AERD.²⁶ Low rate of self-reporting of AERD may be explained by the lack of awareness of the patients, avoidance of NSAIDs by patients with asthma, or misunderstanding of the cause of asthma exacerbation by patients or even physicians. The rates of NSAID usages are different among patients and some of them just taking occasional acetaminophen. Our data show the value of ASA provocation challenge in the diagnosis of AERD. Thus, confirmatory OAC should be performed in the absence of a compatible history.

The European Network on Aspirin-Induced Asthma cohort study⁷ reported a typical pattern of persistent rhinitis/rhinosinusitis appearing first at the mean age of 30 years followed by asthma after 2 years and development of ASA-induced respiratory reactions and NP in the following 4 years (mean age of 34 years). In women who outnumbered men by a ratio of 2.3:1, the onset of symptoms occurred signifi-

cantly earlier, and the disease was more severe than in men. Once AERD developed, rhinosinusitis and asthma followed a course that is usually independent of the ASA and NSAID avoidance.¹⁶ In our report, the mean age of AERD onsets was during the third decade and natural course of developing AERD was similar to that previously reported but with slightly prolonged course of development (8.00 ± 5.9 years), which may increase the chance of AERD in CRSwNP.¹⁵ The female/male ratio in our study was 1.8:1, which is similar to other studies.^{2,14}

Hope *et al.* reported that most positive OAC reactions occurred at 45–100 mg of ASA, and the average time to reaction was 102 minutes after the last ASA dose.²¹ In our study, the most positive provocation reaction happened at 80- and 160-mg doses of ASA and, the mean elapsed time from the last ASA dose was 52 ± 28 minutes. A shorter time for the reaction may be because of different dosing intervals as we administered the dose every 90 minutes compared with Hope and colleagues who administered the dose every 3 hours.

It is well known that AERD patients suffer from a more severe persistent asthma.²⁷ However, our patients with AERD did not have a higher stage of asthma, which was similar to a report by Vaidyanathan *et al.*²⁸ Several risk factors have been identified for AERD including atopy, blood eosinophilia, and IgE; however, the role of these factors remains controversial.^{9,29,30} In this study, the atopy rate of all of the patients was higher than that of the general adult population but it seems to be related to the presence of asthma rather than ASA hypersensitivity because the atopy ratio was no more different in AERD than in ASA-tolerant asthma. In our study, positive skin-prick test, level of IgE, and blood eosinophil count was not associated with AERD.

AERD is a disease of intense eosinophilic inflammation that can produce fibrosis, hyperplasia, and remodeling. Chronic hyperplastic eosinophilic sinusitis is a predictor of AERD.³¹ Eosinophils are the main inflammatory cells found in the tissue specimens of nasal polyps³² but nasal smear did not show higher eosinophils in AERD patients in our study. We can not exclude the possibility that the high number of patients had a false negative eosinophil count because they were taking nasal steroids at the time of provocation challenge. On other hand, dominant inflammatory cell can vary according to the racial characteristics of the population.^{6,33}

The limitation of our study is the small sample size. To further obtain valid data on prevalence and comorbidities of AERD, a large prospective trial and multicenter study would be necessary on an unselected population from different geographic areas in Iran to show possible differences. According to routine use of ASA and other NSAIDs, this information could be useful in giving clinicians the data about the likelihood of having AERD and thus having the potential option of undergoing ASA provocation challenges.

CONCLUSION

ASA hypersensitivity is common in patients with CRSwNP. In patients with concomitant asthma, previous nasal polyp surgery, extensive nasal polyps, and prolonged course of development, AERD requires evaluation for the presence of ASA hypersensitivity with oral ASA provocation challenge tests to assess and appropriately manage the disease. Patients' self-report of hypersensitivity reactions to NSAIDs may underestimate the diagnosis of AERD.

ACKNOWLEDGMENTS

The authors express their sincere gratitude to the Ear, Nose, and Throat-Head and Neck Surgery Research Center. Their sincere thanks go to Dr. Hengameh H. Raissy, Research Associated Professor of Pediatric, University of New Mexico, and Dr. Roya Shahrivar, Dr. Babak Ghalebaghi, Dr. Mahsa Rekabi, Dr. Rasoul Molatefi, and Dr. Gila Mohammady Azar.

REFERENCES

1. Hamilos DL. Chronic rhinosinusitis: Epidemiology and medical management. *J Allergy Clin Immunol* 128:693–707, 2011.

2. Fokkens WJ, Lund VJ, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps. *Rhinol Suppl* 23:1–298, 2012.
3. Benninger MS, Ferguson BJ, Hadley JA, et al. Adult chronic rhinosinusitis: Definitions, diagnosis, epidemiology, and pathophysiology. *Otolaryngol Head Neck Surg* 129(suppl):S1–S32, 2003.
4. Tan BK, Chandra RK, Pollak J, et al. Incidence and associated pre-morbid diagnoses of patients with chronic rhinosinusitis. *J Allergy Clin Immunol* 131:1350–1360, 2013.
5. Chang JE, White A, Simon RA, and Stevenson DD. Aspirin-exacerbated respiratory disease: Burden of disease. *Allergy Asthma Proc* 33:117–121, 2012.
6. Mullol J, and Picado C. Rhinosinusitis and nasal polyps in aspirin-exacerbated respiratory disease. *Immunol Allergy Clin North Am* 33:163–176, 2013.
7. Szczeklik A, Nizankowska E, and Duplaga M. Natural history of aspirin-induced asthma. AIANE Investigators. European Network on Aspirin-Induced Asthma. *Eur Respir J* 16:432–436, 2000.
8. Samter M, and Beers RF Jr. Intolerance to aspirin. Clinical studies and consideration of its pathogenesis. *Ann Intern Med* 68:975–983, 1968.
9. Stevenson DD, and Szczeklik A. Clinical and pathologic perspectives on aspirin sensitivity and asthma. *J Allergy Clin Immunol* 118:773–786, 2006.
10. Graefe H, Roebke C, Dirk Schäfer D, and Meyer JE. Aspirin sensitivity and chronic rhinosinusitis with polyps: A fatal combination. *J Allergy* 81:7910, 2012.
11. Szczeklik A, Nizankowska-Mogilnicka E, and Sanak M. Hypersensitivity to aspirin and non-steroidal anti-inflammatory drugs. In *Middleton's allergy: Principles and practice*, 7th ed. Adkinson NF Jr, Bochner BS, Busse WW, et al. (Eds). New York NY: Mosby, 227–240, 2009.
12. Lee RU, and Stevenson DD. Aspirin-exacerbated respiratory disease: Evaluation and management. *Allergy Asthma Immunol Res* 3:3–10, 2011.
13. Stevenson DD. Aspirin sensitivity and desensitization for asthma and sinusitis. *Curr Allergy Asthma Rep* 9:155–163, 2009.
14. Jenkins C, Costello J, and Hodge L. Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. *BMJ* 328:434, 2004.
15. Bavybek S, Dursun B, Dursun E, et al. The prevalence of aspirin hypersensitivity in patients with nasal polyposis and contributing factors. *Am J Rhinol Allergy* 25:411–415, 2011.
16. Berges-Gimeno MP, Simon RA, and Stevenson DD. The natural history and clinical characteristics of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 89:474–478, 2002.
17. Lund VJ, and Kennedy DW. Quantification for staging sinusitis. The Staging and Therapy Group. *Ann Otol Rhinol Laryngol* 167:17–21, 1995.
18. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. National Heart and Blood Institute/World Health Organization (NHLBI/WHO) workshop report. NIH Publication 02-3659, Bethesda, MD, issued 1995, updated 2007.
19. Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, et al. EAACI/GA2LEN guideline: Aspirin provocation tests for diagnosis of aspirin hypersensitivity. *Allergy* 62:1111–1118, 2007.
20. Macy E, Bernstein JA, Castells MC, et al. Aspirin challenge and desensitization for aspirin-exacerbated respiratory disease: A practice paper. *Ann Allergy Asthma Immunol* 98:172–174, 2007.
21. Hope AP, Woessner KA, Simon RA, and Stevenson DD. Rational approach to aspirin dosing during oral challenges and desensitization of patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 123:406–410, 2009.
22. Hedman J, Kaprio J, Poussa T, and Nieminen MM. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. *Int J Epidemiol* 28:717–722, 1999.
23. Kasper L, Śladek K, Bochenek G, et al. The frequency of hypersensitivity to non-steroidal antiinflammatory drugs (NSAIDs) in the population of adult asthmatics in Poland based on an epidemiological questionnaire. *Pneumonol Alergol Pol* 77:431–439, 2009.
24. Bavybek S, Yilmaz I, Celik G, Aydin O, et al. Prevalence of aspirin-exacerbated respiratory disease in patients with asthma in Turkey: A cross-sectional survey. *Allergol Immunopathol (Madr)* 40:225–230, 2012.

25. Fan Y, Feng S, Xia W, et al. Aspirin-exacerbated respiratory disease in China: A cohort investigation and literature review. *Am J Rhinol Allergy* 26:e20–e22, 2012.
26. Dursun AB, Woessner KA, Simon RA, et al. Predicting outcomes of oral aspirin challenges in patients with asthma, nasal polyps, and chronic sinusitis. *Ann Allergy Asthma Immunol* 100:420–425, 2008.
27. Kowalski ML, and Makowska JS. Aspirin-exacerbated respiratory disease: An update on diagnosis and management. *Allergy Clin Immunol* 18:140–149, 2006.
28. Vaidyanathan S, Williamson PA, and Lipworth BJ. Is a positive nasal lysine-aspirin challenge test associated with a more severe phenotype of chronic rhinosinusitis and asthma? *Am J Rhinol Allergy* 26:e89–e93, 2012.
29. Bochenek G, Nizankowska E, and Szczeklik A. The atopy trait in hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy* 51:16–23, 1996.
30. Mitsui C, Taniguchi M, Higashi N, et al. Relationship between aeroallergen sensitization and asthma severity in patients with aspirin-exacerbated respiratory disease. *World Allergy Organ J* 5(suppl 2): S109, 2012.
31. Mascia K, Borish L, Patrie J, et al. Chronic hyperplastic eosinophilic sinusitis as a predictor of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 94:652–657, 2005.
32. Fahrenholz JM. Natural history and clinical features of aspirin-exacerbated respiratory disease. *Clin Rev Allergy Immunol* 24:113–124, 2003.
33. Chang JE, Chin W, and Simon R. Aspirin-sensitive asthma and upper airway diseases. *Am J Rhinol Allergy* 26:27–30, 2012. □

Copyright of American Journal of Rhinology & Allergy is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.