

Sinonasal Outcomes After Endoscopic Sinus Surgery in Asthmatic Patients With Nasal Polyps: A Difference Between Aspirin-Tolerant and Aspirin-Induced Asthma?

Osama G. Awad, MD; John H. Lee, MD; Mary Beth Fasano, MD, MSPH; Scott M. Graham, MD

Objectives/Hypothesis: Aspirin-sensitivity, asthma, and nasal polyposis (NP) comprise the clinical entity of Samter's triad. The aim of this study is to report the sinonasal outcomes of endoscopic sinus surgery (ESS) in treating NP in asthmatic patients, comparing aspirin-induced asthmatic (AIA) patients with aspirin-tolerant asthmatics (ATA).

Study Design: Retrospective chart review.

Methods: The records of 66 patients with NP and asthma were retrospectively reviewed. Forty-one AIA patients were compared with 25 ATA patients. For each patient, a Lund-Mackay computed tomography (CT) score of the preoperative scans and the available postoperative CT scans in a period of 18 months were calculated and used as primary endpoint. Sinonasal improvement assessed by patients and reported with a symptoms scale was used as the secondary endpoint for the comparison immediately before surgery and 6 months and 12 months following ESS.

Results: Preoperative CT scores in AIA patients compared with ATA patients were significantly higher 19 (standard deviation, 4.82) vs. 14 (standard deviation, 6.8), respectively ($P = .006$). This difference was sustained for the available postoperative CT scans ($P < .0001$). During the period of 18 months follow-up, 63.4% of AIA patients vs. 96% of ATA patients had CT improvement with a statistically significant difference between the two groups ($P = .003$). At 6 months following ESS, 63.4% of

AIA patients vs. 56% of ATA patients had symptomatic improvement. At 12 months, 68.3% of AIA patients vs. 60% of ATA patients had symptomatic improvement, with no significant difference between the two groups.

Conclusion: AIA patients had more extensive sinonasal disease than ATA patients. Both groups showed statistically significant improvement in sinonasal outcomes after ESS. The difference between the two groups was statistically significant for patients' CT improvement with worse CT scores being seen in AIA patients.

Key Words: Nasal polyposis, endoscopic sinus surgery, asthma, aspirin-induced asthma, aspirin-tolerant asthma.

Laryngoscope, 118:●●●–●●●, 2008

INTRODUCTION

Sinonasal disease in asthmatic patients may be expressed as rhinosinusitis or nasal polyposis (NP). This is usually severe and more refractory to treatment than in nonasthmatic patients.¹ The mechanism by which sinus disease exacerbates asthma is not clearly understood; however, effective treatment of upper airways may improve and help to stabilize lower airway disease.²

In 1922, Widal et al.³ published the first article describing the association of aspirin-sensitivity, asthma, and NP. This observed association is usually known as Samter's triad.⁴ Many other terms have been used to describe this respiratory disease, with "aspirin-induced asthma (AIA)," commonly used in the literature.

The overall prevalence of AIA is uncertain; however, estimates suggest that 10 to 20% of asthmatic patients have AIA.⁵ The mechanism of the hypersensitivity reaction to aspirin may be related to interference with arachidonic acid metabolism with an end-result of formation of leukotrienes and other inflammatory mediators that promote bronchoconstriction and vasodilatation. This results in increased edema and secretions associated with the inflammatory process in AIA.⁶ Aspirin-tolerant asthmatic

From the Department of Otolaryngology–Head and Neck Surgery (O.G.A., J.H.L., S.M.G.), and the division of Allergy Immunology, Department of Internal Medicine (M.B.F.), University of Iowa, Iowa City, Iowa, U.S.A.

Editor's Note: This Manuscript was accepted for publication February 26, 2008.

Send correspondence to Scott M. Graham, MD, Department of Otolaryngology–Head and Neck Surgery, University of Iowa Hospitals and Clinics, 200 Hawkins Dr., PFP, Iowa City, IA 52242-1091, U.S.A. E-mail: scott-graham@uiowa.edu

DOI: 10.1097/MLG.0b013e318170af1e

(ATA) patients may also suffer from chronic rhinosinusitis (CRS) and NP.

Previous work has suggested that endoscopic sinus surgery (ESS) results in the improvement of asthma in AIA patients.⁷ However, the efficacy of ESS in improving sinonasal outcome in AIA patients who fail medical treatment is largely unstudied. In this current review, retrospective objective and subjective parameters were used to analyze the sinonasal outcome after ESS in asthmatic patients with NP. Further information is sought on potential differences in sinonasal outcomes in the aspirin-induced and aspirin-tolerant subgroups of asthmatic patients with NP.

MATERIALS AND METHODS

A retrospective chart review was performed of 91 adult asthmatic patients with NP who were classified into two groups. Group 1 included 56 patients with AIA. Group 2 included 35 patients with ATA. Fifteen AIA patients and 10 ATA patients were excluded from the study due to lack of sufficient postoperative data and computed tomography (CT) scans. A total of 66 patients (41 AIA patients and 25 ATA patients) form the basis of this study. The two groups of patients underwent ESS between January 2003 and April 2005 after failing medical treatment at a single tertiary referral institution.

Patient Criteria for Eligibility

Patients were selected using the following eligibility criteria: 1) Patients were diagnosed with asthma by an asthma specialist for at least 12 months before surgery in accordance with National Institutes of Health guidelines for diagnosis and management of asthma.⁸ 2) Patients were diagnosed as having NP based on the presence of bilateral polyps on endoscopic examination. 3) Confirmatory evidence of NP on CT scans supported the endoscopic findings. 4) Aspirin-intolerance was determined by the patient history of worsening upper and/or lower airway symptoms after ingesting aspirin or other nonsteroidal antiinflammatory drugs. 5) Postoperative follow-up by the patient's same otolaryngologist for at least 18 months. 6) Postoperative asthma management by the same patient's asthma specialist for at least 18 months.

Polyp size was not an inclusion criterion. Allergic status was defined as presence of at least one positive skin test on a panel of regionally relevant aeroallergens. The decision for surgical intervention was made when patient's symptoms had not improved after intensive medical therapy. Intensive medical therapy was offered to all patients before surgical intervention. This included nasal saline irrigations, topical nasal corticosteroid spray, a broad-spectrum antibiotic, and oral corticosteroid administration in the form of 40 mg prednisone per day for 5 consecutive days. Patients with any of the following conditions were excluded from the study: cystic fibrosis, Kartagener's syndrome, allergic fungal sinusitis, immune deficiency disorders, and lung diseases other than asthma.

National Institutes of Health-based guideline therapy⁸ for asthma management was used for all patients before and after surgical intervention and included bronchodilators, inhaled corticosteroids, leukotriene-modifying drugs, and, as needed, oral corticosteroids. No patients underwent aspirin desensitization before or after ESS. No patients had changes in the use of leukotriene-modifying drugs in the form of addition of these medications for the first time after surgery or change of the previously prescribed preoperative dose.

ESS was performed on all patients under general anesthesia. The extent of the surgery was determined by the extent of disease but always included polypectomy, uncinectomy, anterior ethmoidectomy, and exploration of the posterior ethmoids. If the

posterior cells were involved, surgery was continued posteriorly with posterior ethmoidectomy and, if necessary, a sphenoidotomy. When required, the ostium of the maxillary sinus was enlarged and the frontal recess opened. If there was a markedly pneumatized concha bullosa, the lateral mucosa and bone were usually removed. The operation was followed in all patients by continuing use of topical nasal corticosteroids and saline nasal washing for at least 6 months. Prednisone was universally used immediately pre- and postoperatively.

Patients' demographic data were obtained from their chart review. Sinonasal outcome was assessed using the following objective and subjective measures: 1) Objectively, the preoperative Lund-Mackay CT staging scores⁹ were determined in a blinded manner. The Lund-Mackay CT scoring system was selected for its simplicity and reproducibility.¹⁰ Available postoperative CT scans during a period of 18 months after surgery (either ordered through our institution or brought from outside facilities) were reviewed. The change of the CT scores was used as an objective parameter for sinonasal outcome. 2) Changes in patients' symptoms were assessed using a previously reported 5-level scale of measurement¹¹ (cured, much improved, improved, unchanged, or worse). This was determined from patients' evaluations at 6- and 12-month postoperative visits. The change in patients' symptoms was used as a secondary endpoint.

The study was approved by the Institutional Review Board at the University of Iowa. Because the study involved no deviation from existing standard therapy for these patients and no new drugs, individual consent was not required by the board.

Statistical analysis was done using statistical software SPSS (SPSS, Inc., Chicago, IL). The χ^2 test was used to analyze differences in categorical variables between the two groups. Mean differences between pre- and postoperative Lund-Mackay scores

TABLE I.
Patient Characteristics by Type of Illness.

Characteristic	AIA (n = 41)		ATA (n = 25)	
	No.	%	No.	%
Age*				
<20	0	0	1	4.0
20–50	28	86.3	18	72.0
51+	13	31.7	6	24.0
Sex				
Male	22	53.7	10	40.0
Female	19	46.3	25	60.0
Race				
White	29	70.7	19	76.0
Black	4	9.8	2	8.0
Other	8	19.5	4	16.0
Allergic status				
Yes	33	80.5	17	68.0
No	8	19.5	8	32.0
Asthma onset				
Childhood onset	12	29.3	16	64.0
Adult onset	29	70.7	9	36.0
Previous sinus surgery				
Yes	25	37.9	5	20.0
No	41	62.1	20	80.0

*The mean and range of ages was 43.76 (23–64 years) and 41.66 (15–70 years) for the AIA and ATA groups, respectively.

AIA = aspirin-induced asthmatic; ATA = aspirin-tolerant asthmatics.

were evaluated for statistical significance using the patient's *t* test. The level of significance was $P < .05$ for all tests.

RESULTS

The preoperative characteristics and comorbidities of AIA and ATA patients are presented in Table I. Twenty AIA patients had previous sinonasal surgeries (1–5 surgeries per patient, mean = 1.9) compared to five ATA patients (1–3 surgeries per patient, mean = 1.5). This difference in the rate of previous sinonasal surgeries did not reach statistical significance ($P = .514$).

1) Change in Lund-Mackay Computed Tomography Scores (Fig. 1)

AIA patients had significantly higher preoperative mean of CT scores compared to ATA patients (19 vs. 14, respectively, $P = .006$). Postoperative CT scores were obtained 4–18 months (mean = 9 months) following ESS in AIA patients compared to 4–18 months (mean = 10.7 months) in ATA patients. The period of getting follow-up CT scans was not significantly different between the two groups ($P = .261$). Mean CT scores in AIA patients improved to 14 ($P = .0009$), and in ATA patients improved to 5 ($P < .0001$). AIA patients had significantly higher postoperative CT scores ($P < .0001$) (Table II). A total of 63.4% of AIA patients had improvement of their CT scores vs. 96% of ATA. The difference in ratio of patients with postoperative improvement was statistically significant between the two groups ($P = .003$; Table III).

2) Change in Patients' Symptoms (Fig. 2)

At 6 months following surgery, 26 (63.4%) AIA patients recorded improvement of their symptoms. No patients reported complete cure, 12 patients reported much improved, and 14 patients reported that they had improved. Fourteen (56%) ATA patients recorded improvement of their symptoms. Three patients reported complete cure, five patients reported much improved, and six patients reported that they had improved. The difference between the ratio of improved patients in the two groups did not reach statistical significance ($P = .609$). At 12 months following surgery, 28 (68.3%) AIA patients recorded improvement of their symptoms. No patients reported complete cure, 12 patients reported much improved, and 16 patients reported that they had improved. Fifteen (60%) ATA patients recorded improvement of their

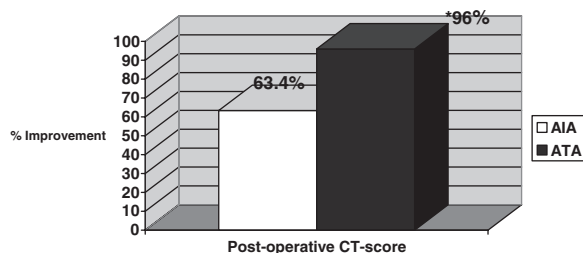


Fig. 1. Comparison of aspirin-induced asthmatic (AIA) patients and aspirin-tolerant asthmatics (ATA) patients with respect to postoperative improvement in their Lund-Mackay computed tomography (CT) scores. **P* values represent significant values $< .05$.

TABLE II.
Preoperative and Postoperative Mean of Lund-Mackay CT Scores (Mean $\pm$ Standard Deviation).

	AIA Patients (n = 41)	ATA Patients (n = 25)	<i>P</i> Value
Pretreatment	19 $\pm$ 4.82	14 $\pm$ 6.8	$P = .006$
Posttreatment	14 $\pm$ 7.4	5 $\pm$ 2.08	$P < .0001$

Higher scores represent worse functioning.
CT = computed tomography; AIA = aspirin-induced asthmatic; ATA = aspirin-tolerant asthmatics.

symptoms. Three patients reported complete cure, six patients reported much improved, and six patients reported that they had improved. The difference between the two groups did not reach statistical significance ($P = .597$; Table IV).

DISCUSSION

AIA is a well-recognized clinical entity. A positive history of aspirin hypersensitivity, which is the hallmark of this syndrome, is a significant and reliable indicator of chronic intractable sinonasal disease, persistent asthma of greater than average severity, and higher than ordinary medication requirements.¹² There is a general assumption in previous literature that sinonasal disease in AIA patients is more severe compared with ATA patients. Robinson et al.¹³ reported that patients with aspirin-intolerance had significantly worse preoperative sinus CT scans compared to other aspirin-tolerant patients.

Previous studies showing the beneficial effect of ESS on the sinonasal outcome in patients with AIA have been limited by the lack of inclusion of a comparison group as a control. Nakamura et al.¹⁴ evaluated the effect of sinus surgery (endoscopic or Caldwell-Luc surgery) on 22 patients with aspirin-sensitivity. Ninety percent of their patients reported symptomatic relief and 100% had normal nasal resistance after 1 year of postoperative follow-up.

Other studies comparing AIA patients and other asthmatic patients are sparse. Most of these studies compared AIA patients with NP to a heterogeneous group of asthmatic patients with either CRS, NP, or both. The presence of NP in patients with CRS has a significant negative impact (higher CT scores at presentation,

TABLE III.
Change of Lund-Mackay CT Scores Following ESS.

	AIA (n = 41)		ATA (n = 25)		<i>P</i> Value
	No.	%	No.	%	
CT score changes					.003
Improved	26	63.4	24	96.0	
The same	7	17.1	1	4	
Got worse	8	19.5	0	0	

A 2×2 χ^2 analysis compared the two patient groups: improved patients and non-improved patients (which represent a combination of the "no change" and "got worse" categories).

**P* values represent significant values $< .05$.

CT = computed tomography; ESS = endoscopic sinus surgery; AIA = aspirin-induced asthmatic; ATA = aspirin-tolerant asthmatics.

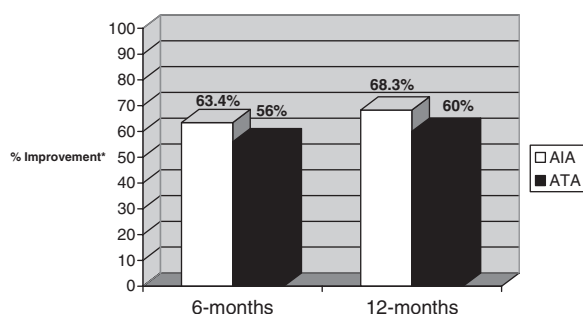


Fig. 2. Comparison of aspirin-induced asthmatic (AIA) patients and aspirin-tolerant asthmatics (ATA) patients with respect to improvement of patients' symptoms at 6- and 12-month follow-up. Improved patients include cured, much improved, and improved.

significantly higher need for revision surgery, and more severe symptoms with less improvement after operative intervention) compared with patients with CRS without NP.¹⁵ Bhattacharyya et al.¹⁶ recently reported that both nonpolyp and polyp patients derive similar clinically significant symptomatic improvement after ESS, and they suggested that polyp patients do not necessarily have a poorer symptomatic outcome after ESS. These investigators, however, did not look specifically at asthmatic patients with NP.

One study by Batra et al.¹¹ on 17 CRS patients with NP and steroid-dependent asthma (9 aspirin-intolerant, 8 aspirin-tolerant), found that preoperative CT scores were not statistically different between the aspirin-intolerant and aspirin-tolerant patients. Postoperative Lund-Mackay CT scores improved in both groups and sinonasal symptoms trended toward improvement in both groups, but only reached statistical significance in the aspirin-tolerant group. The authors concluded that effect of ESS was better in aspirin-tolerant patients than in aspirin-sensitive patients.

In our retrospective study on 66 patients with medically-resistant NP and asthma in a single tertiary referral institution, our AIA population displayed significantly higher mean CT scores. Importantly, the CT score improved significantly in both AIA and ATA patients after ESS. However, ATA patients demonstrated significantly superior degree of CT score improvement during a similar period of follow-up. Aspirin-intolerance, therefore, was a

factor influencing the "objective" results of sinus surgery in our asthmatic patients.

Of parenthetical interest is the number of CT scans performed after surgery in this patient group. Of the 66 scans ordered in the postoperative period of up to 18 months, only 2 were ordered by the senior author. Recent interest in both the lay and scientific press has focused on increasing levels of radiation from widespread use of CT scans tied to a potential for carcinogenesis.¹⁷ It is our practice to rely on endoscopic examination and patients' symptoms for following-up patients with NP after surgical intervention. CT scans are ordered sparingly after surgery unless a revision operation is being planned. How this recent publicity regarding scans might affect patterns of CT use remains to be seen.

Postoperative assessment of patients' symptoms was used in our study as a secondary endpoint for comparing AIA and ATA patients after ESS. Interestingly, a similar number of patients in each group reported improvement of their symptoms at 6 and 12 months after surgery. The difference in the ratio of patients who reported subjective improvement did not reach statistical significance between the two groups. Our results support studies that reported similar proportions of improvement in aspirin-tolerant and aspirin-intolerant patients after ESS utilizing a variety of quality of life measures.¹³ Previous studies had also reported that extensive sinus disease is a significant factor in the ultimate need for more revision sinus surgeries in AIA patients.¹⁸ In our study, AIA patients had a similar average number of previous sinus surgeries compared to ATA patients.

Although aspirin-intolerance was not a major factor influencing the subjective results in our patients, some clinical points can be highlighted: 1) Three ATA (12%) patients reported a complete cure at 12 months of follow-up. None of the AIA patients reported such improvement at any time of data collection ($P = .036$). 2) At 12 months following ESS, 12.2% of AIA patients believed their sinonasal symptoms relative to their preoperative condition were worse compared with only 4% of ATA patients. We believe that these important clinical points may provide some guide as to the potential impact of aspirin-intolerance on the degree of improvement and the expected long-term outcome in AIA patients after ESS.

TABLE IV.
Change of Patients' Symptoms During the First Year Following ESS.

	Pretreatment to 6 Months					Pretreatment to 12 Months				
	AIA (n = 41)		ATA (n = 25)		P Value	AIA (n = 41)		ATA (n = 25)		P Value
	No.	%	No.	%		No.	%	No.	%	
Patients' symptoms					.609					.597
Improved*	26	63.4	14	56.0		28	68.3	15	60.0	
The same	12	29.3	10	40.0		8	19.5	9	36.0	
Got worse	3	7.3	1	4.0		5	12.2	1	4.0	

*Improved patients include cured, much improved, and improved.

ESS = endoscopic sinus surgery; AIA = aspirin-induced asthmatic; ATA = aspirin-tolerant asthmatics.

The discrepancy between the objective and subjective outcomes in our patients can perhaps be explained by a reported lack of correlation between CT and symptoms scores. Stewart et al.¹⁹ compared different CT staging systems with sinus-specific health surveys. Despite multiple statistical modifications and permutations of CT staging scores, no relationship was found between CT scan findings and the patient's perception of sinonasal symptoms, either in their study population as a whole or in various subgroups within that population. It could be suggested that subjective and objective measures might be examining different aspects of disease.

The explanation of the significantly higher preoperative disease extension and the significantly lower CT score improvement in AIA patients is not clear. Understanding the difference in the pathophysiology of sinonasal disease in AIA and ATA patients may provide some insight. The number of eosinophils is significantly higher in NP and sinonasal mucosa from AIA patients compared with ATA patients, and the number of apoptotic eosinophils has been found to be significantly lower in AIA patients.²⁰ NP tissue from AIA patients was found to have lower expression of cyclooxygenase-2. This enzyme is responsible for the production of prostaglandin E₂, which has significant anti-inflammatory activity, including an inhibitory effect on eosinophil chemotaxis and activation.²¹ AIA patients also have an inherently greater capacity for the synthesis of inflammatory mediators.²² From all the above data, it is possible that the marked increase of the inflammatory cells and mediators in AIA patients' sinonasal mucosa and NP play an important role and may contribute to the extent of disease and postoperative outcome.

It is important to rule out the possibility of confounding variables which might account for the postoperative outcome improvement. Our patients did not have a significant postoperative change in leukotriene-modifying drugs or aspirin-desensitization, and both may have beneficial effect on airway inflammation in asthmatic patients, especially those with AIA.²³

Although this study is retrospective and limited by the flaws potentially inherent in all retrospective reviews, we believe that this examination of a large patient population with well defined objective outcome measures and selection criteria helps to clarify the value of ESS for this group of difficult-to-treat patients. Identification of aspirin-sensitivity in asthmatic patients with NP may provide useful prognostic information regarding potential sinonasal outcomes after surgical treatment.

CONCLUSION

Our results demonstrated that ESS after maximal medical management results in beneficial effect on the sinonasal outcome parameters in both AIA and ATA patients with NP. The postoperative Lund-Mackay scores were statistically lower, and the sinonasal symptoms were also statistically better. When the data are compared between the AIA and ATA subsets, the positive effect in the AIA patients was significantly less pronounced for CT score improvement.

BIBLIOGRAPHY

1. Uri N, Cohen-Kerem R, Barzilai G, Greenberg E, Doweck I, Weiler-Ravell D. Functional endoscopic sinus surgery in the treatment of massive polyposis in asthmatic patients. *J Laryngol Otol* 2002;116:185–189.
2. Minor MW, Lockey RF. Sinusitis and asthma. *South Med J* 1987;80:114–117.
3. Widall F, Abrami P, Lermoyez J. First complete description of the aspirin idiosyncrasy-asthma-nasal polyposis syndromes. *J Asthma* 1987;24:297–300.
4. Samter M, Beers RF. Intolerance to aspirin: clinical studies and consideration of its pathogenesis. *Ann Intern Med* 1968;68:875–883.
5. Spector SL, Wangaard CH, Farr RS. Aspirin and concomitant idiosyncrasies in adult asthmatic patients. *J Allergy Clin Immunol* 1979;64:500–506.
6. Smith WL, Borgeat P, Fitzpatrick FA. The eicosanoids: cyclooxygenase, lipoxygenase, and epoxigenase pathways. In: Vance DE, ed. *Biochemistry of Lipids, Lipoproteins, and Membranes*. Amsterdam, The Netherlands: Elsevier Science; 1991:283–308.
7. Awad OG, Fasano MB, Lee JH, Graham SM. Asthma outcomes after endoscopic sinus surgery in aspirin-tolerant versus aspirin-induced asthmatics. *Am J Rhinol* 2008;197–203.
8. Guidelines for the diagnosis and management of asthma. Highlights of the Expert Panel Report 2. *NIH Publication No. 97-4051A*. Bethesda, MD: National Institutes of Health; 1997.
9. Lund VJ, Mackay IS. Staging in rhinosinusitis. *Rhinology* 1993;31:183–184.
10. Wabnitz D, Nair S, Wormald P. Correlation between preoperative symptom scores, quality-of-life questionnaires, and staging with computed tomography in patients with chronic rhinosinusitis. *Am J Rhinol* 2005;19:91–96.
11. Batra P, Kern R, Tripathi A, et al. Outcome analysis of endoscopic sinus surgery in patients with nasal polyps and asthma. *Laryngoscope* 2003;113:1703–1706.
12. Kowalski M. Management of aspirin-sensitive rhinosinusitis asthma syndrome: what role for aspirin desensitization? *Allergy Proc* 1992;13:175–184.
13. Robinson JL, Griest S, James KE, Smith TL. Impact of aspirin intolerance on outcomes of sinus surgery. *Laryngoscope* 2007;117:825–830.
14. Nakamura H, Kawasaki M, Higuchi Y, Takahashi S. Effects of sinus surgery on asthma in aspirin triad patients. *Acta Otolaryngol* 1999;119:592–598.
15. Deal RT, Kountakis SE. Significance of nasal polyps in chronic rhinosinusitis: symptoms and surgical outcomes. *Laryngoscope* 2004;114:1932–1935.
16. Bhattacharyya N. Influence of polyps on outcomes after endoscopic sinus surgery. *Laryngoscope* 2007;117:1834–1838.
17. Brenner DJ, Hall EJ. Computed tomography—an increasing source of radiation exposure. *N Engl J Med* 2007;357:2277–2284.
18. Berges-Gimeno MP, Simon RA, Stevenson DD. The natural history and clinical characteristics of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 2002;89:474–478.
19. Stewart MG, Sicard MW, Piccirillo JF, Diaz-Marchan PJ. Severity staging in chronic sinusitis: are CT scan findings related to patient symptoms? *Am J Rhinol* 1999;13:161–167.
20. Kowalski ML, Pawliczak R, Wozniak J, et al. Differential metabolism of arachidonic acid in nasal polyp epithelial cells cultured from aspirin-sensitive and aspirin-tolerant patients. *Am J Respir Crit Care Med* 2000;161:391–398.
21. Picado C, Fernandez-Morata JC, Juan M, et al. Cyclooxygenase-2 mRNA is downexpressed in nasal polyps from aspirin-sensitive asthmatics. *Am J Respir Crit Care Med* 1999;160:291–296.
22. Adamjee J, Suh YJ, Park HS, et al. Expression of 5-lipoxygenase and cyclooxygenase pathway enzymes in nasal polyps of patients with aspirin-intolerant asthma. *J Pathol* 2006;209:392–399.
23. Szczeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis, diagnosis, and management. *J Allergy Clin Immunol* 2003;111:913–921.