

Endoscopic sinus surgery improves aspirin treatment response in aspirin-exacerbated respiratory disease patients

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Background: Aspirin desensitization and treatment benefits most patients with aspirin-exacerbated respiratory disease (AERD), although some patients fail therapy. Our objective was to assess whether recent endoscopic sinus surgery (ESS) improved aspirin treatment outcomes in AERD patients who initially failed aspirin therapy.

Methods: Outcomes of aspirin desensitization and treatment in AERD patients prospectively enrolled were assessed preoperatively and at 4, 12, and 24 weeks after ESS by determining changes in Asthma Control Test (ACT) and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores and respiratory function. Biomarkers, including fractional excretion of nitric oxide (FeNO), spirometry, nasal inspiratory peak flow (NPF), immunoglobulin E (IgE), and eosinophil count, were measured.

Results: Nineteen patients who benefited (responders) and 21 patients who failed (nonresponders) preoperative aspirin treatment with a distant history of ESS (mean, 48 months) were identified. Nonresponders were more likely to be African American (71%, $p < 0.01$) and have higher baseline IgE levels (252 kU/L vs 87 kU/L in responders, $p < 0.01$). 24 of the 40 patients (nine responders and 15 non-responders) required subsequent ESS and under-

went another aspirin desensitization 3-4 weeks after ESS. All 24 patients tolerated a second round of aspirin desensitization and treatment. The primary aspirin therapy was associated with a significant increase in IgE in nonresponders, but there was no significant increase in IgE after the second aspirin desensitization and treatment.

Conclusion: Antecedent ESS enhances aspirin treatment responses in AERD patients and may convert patients who failed aspirin treatment before surgery to a more responsive phenotype after ESS. Patients with higher baseline serum IgE levels may benefit from ESS performed shortly before aspirin desensitization and therapy. © 2019 ARS-AAOA, LLC.

Key Words:

aspirin-induced asthma; asthma; nasal polyps; AERD; paranasal sinus diseases; sinusitis; treatment outcome

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Aspirin-exacerbated respiratory disease (AERD), also known as Samter triad, is a chronic condition that manifests as asthma; chronic rhinosinusitis with nasal polyposis; and hypersensitivity reactions, such as bronchospasm, rhinorrhea, and conjunctivitis to aspirin and other nonsteroidal anti-inflammatory drugs. AERD affects 7% of patients with asthma and 15% of patients with severe asthma.¹

Although understanding of its pathogenesis is limited, AERD is associated with extensive eosinophilic airway

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inflammation and mast-cell degranulation mediated by a type 2 inflammatory response.^{2,3} Endoscopic sinus surgery (ESS) is typically performed 2-4 weeks before starting aspirin desensitization and therapy to minimize the risk of polyp regrowth during the interval period.⁴ However there is a paucity of data about which patients benefit from ESS prior to aspirin therapy. Regardless of ESS status and timing, aspirin desensitization followed by daily aspirin provides therapeutic benefits to most patients with AERD, including improved asthma control, decreased oral steroid use, and reduced nasal polyp recurrence.⁵ Swierczynska-Krepa et al found that patients with AERD who underwent aspirin desensitization reported improvements in smell and nasal blockade, lower doses of inhaled corticosteroids, and decreases in 22-item Sino-Nasal Outcome Test (SNOT-22) and Asthma Control Questionnaire scores.⁶ Aspirin desensitization followed by daily maintenance appears to be safe and effective in improving airway disease and quality of life even after 10 or more years of continuous use.⁷

Although ESS enhances aspirin treatment response in patients with AERD when performed 3-6 weeks before initiation of aspirin desensitization and treatment,⁸ there is insufficient research on aspirin desensitization outcomes with and without antecedent ESS. In addition, aspirin seems to benefit some patients, even if surgery timing was not accounted for or if ESS was performed >12 months before start of aspirin treatment.^{6,9,10}

The goal of this study was to further elucidate the role of ESS in AERD treatment and to characterize AERD those patients who are less likely to respond to aspirin treatment without preceding ESS.

Patients and methods

Study population

This study was evaluated and approved by the institutional review board at the Albert Einstein College of Medicine. Patients >18 years of age with physician-diagnosed AERD, defined as a hypersensitivity reaction to aspirin with stable asthma (baseline forced expiratory volume in 1 second [FEV₁] >70% of predicted or 1.5 L absolute volume, and no asthma exacerbations for at least 2 months before the first challenge) and evidence of nasal polyposis on nasal endoscopy, were prospectively enrolled into an ongoing observational cohort investigation between 2016 and 2018.

Aspirin desensitization and treatment protocol

Patients underwent aspirin desensitization according to a previously published protocol.¹¹ For the week before aspirin desensitization, patients were instructed to take montelukast to increase the safety of the aspirin challenge.¹² Hypersensitivity reactions during the challenge were treated according to the symptoms. The patients who completed the aspirin desensitization protocol were prescribed 650 mg of aspirin twice daily. After 4 weeks of aspirin treatment patients were re-evaluated and, if considered

appropriate, patients continued aspirin treatment at 650 mg in the morning and 325 mg in the evening for a total of 975 mg of aspirin daily for an additional 8 weeks.

Aspirin treatment response

Response to aspirin treatment was defined by the ability to complete the desensitization protocol and by the change in Asthma Control Test (ACT) score of at least 3 points¹³ and/or at least 0.5 point¹⁴ in the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score. Patients who were unable to tolerate aspirin desensitization due to persistent, nonresolving symptoms of the hypersensitivity reaction (eg, abdominal pain, unresolved bronchospasm, and/or a persistent skin rash); had a decline in ACT score; or had an increase in RQLQ score, indicating worsening of respiratory symptoms after 4 weeks of aspirin treatment, were defined as “nonresponders.” The remaining cohort of study patients were considered “responders.”

Endoscopic sinus surgery

Patients were considered endoscopic sinus surgery (ESS) candidates if they had medically refractory disease defined as unsuccessful symptom resolution after previous medical therapy with systemic, broad-spectrum, or culture-directed antibiotics (≥ 2 -week duration) and either topical nasal corticosteroid sprays (≥ 3 -week duration) or at least a 5-day trial of systemic corticosteroid therapy.^{15,16} As mentioned earlier, some of the “nonresponder” patients who failed an aspirin treatment attempt and patients who demonstrated an initial response with aspirin therapy, but then experienced a subsequent decline in symptom control also underwent ESS on the appropriate involved sinuses.

Surgical procedures consisted of either unilateral or bilateral maxillary antrostomy, partial or total ethmoidectomy, sphenoidotomy, frontal sinus procedures, inferior turbinate submucous resection, septoplasty, and the use of intraoperative stereotactic surgical navigation. All ESS patients had placement of bilateral steroid-releasing sinus implants (PropelTM; Intersect ENT, Palo Alto, CA) in the ethmoid sinuses and/or frontal recess during ESS.¹⁷ All patients were seen within 1-2 weeks after surgery for postoperative debridement. Postoperative medical therapy consisted of nasal saline irrigations, topical corticosteroid rinses or sprays, oral steroids, and, in some cases, antibiotics. Oral corticosteroid tapers were administered to all patients beginning on postoperative day 1 and starting at 30 mg/d before tapering off by 10 mg either every 3 or every 4 days. Thus, the total duration of the corticosteroid taper was either 9 or 12 days in duration.

Postoperative aspirin desensitization

Three to 4 weeks after ESS, patients underwent a second aspirin desensitization according to the same protocol.¹¹ Besides administering montelukast before this desensitization, patients who were unable to complete aspirin desensitization the first time due to the persistent

gastrointestinal (GI) symptoms (epigastric and abdominal pain and nausea/vomiting) were also premedicated with famotidine (40 mg) or ranitidine (150 mg), omeprazole (40 mg), and ondansetron (4-8 mg) 1 hour before start of the procedure.

Patients who tolerated the second desensitization attempt were started on 650 mg of aspirin twice daily. After 4 weeks of aspirin treatment, patients were re-evaluated and advised to continue aspirin treatment with 650 mg in the morning and 325 mg in the evening for a total of 975 mg/d aspirin for additional 8 weeks (until a total of 12 weeks of aspirin therapy), then 325 mg twice daily. Patients were followed prospectively for a total of 24 weeks of aspirin treatment.

Biomarkers measurement

All patients underwent measurement of exhaled fractional excretion of nitric oxide (FeNO; NIOX VERO, Aerocrine AB, Morrisville, NC), spirometry (Renaissance® II spirometer, Puritan Bennett, Pleasanton, CA), and determination of nasal inspiratory peak flow (NPF; In-Check™ nasal inspiratory flow device, Clement International, Essex, UK). The best of 3 efforts was recorded for spirometry and NPF. Blood was collected at baseline for measurement of the eosinophil count and total serum immunoglobulin E (IgE) levels.

Statistical analysis

All summary statistics were expressed as mean $\pm$ standard error of the mean (SEM) or as median and interquartile range (IQR). Paired data were analyzed using the paired Student *t* test or Wilcoxon signed-rank test, as appropriate. Categorical data were analyzed by chi-square test or the Fisher exact test, as appropriate. All statistical analyses were performed with Stata version 15.1 software (StataCorp, College Station, TX). Significant differences were identified at $p < 0.05$.

Results

Study cohort and response to aspirin treatment

We identified 40 patients with aspirin-challenge-confirmed AERD who were offered aspirin desensitization. Eight patients (8 of 40, 20%) were unable to complete the desensitization protocol due to persistent reactions (bronchospasm, GI symptoms, and/or skin rash) during the procedure. The remainder of the patients were started on high-dose aspirin treatment, which was continued for 4 weeks. Treatment outcomes after aspirin treatment in responders and nonresponders are summarized in Figure 1. Nineteen patients classified as “responders” had a significant increase in the ACT score after 4 weeks of treatment compared with baseline (23 [IQR, 21-25] vs 20.5 [IQR, 17-22], $p < 0.01$) and a significant decline in RQLQ score compared with baseline (2.5 [IQR, 1.5-3.0] vs 1.2 [IQR, 0.5-2.0], $p < 0.05$). Twenty-one patients classified as “nonresponders” had a decline in ACT score at 4 weeks compared with baseline

(15 [IQR, 12-18] vs 19 [IQR, 15-22], $p < 0.05$), but no significant change in RQLQ score at 4 weeks compared with baseline (2.9 [IQR, 2.2-3.7] vs 2.6 [IQR, 2.0-3.8], $p = 0.6$).

The baseline characteristics for responders ($n = 19$) and nonresponders ($n = 21$) are presented in Table 1. Compared with responders, nonresponders were more likely to be African American than Caucasian (71% vs 26%, $p < 0.01$), with a lower baseline NPF (94 ± 8.7 L/min vs 125 ± 12.2 L/min, $p < 0.05$), fewer sinus surgeries before aspirin desensitization (1 [IQR, 0-1] vs 1 [IQR, 1-2], $p < 0.01$), and higher total serum IgE levels (252 [IQR, 96-479] kU/L vs 87 [IQR, 53-193] kU/L, $p < 0.01$). In addition, the nonresponders had higher FeNO levels than responders (48 [IQR, 29-86] vs 32 [IQR, 18-43] parts per billion [ppb], $p = 0.05$), although this outcome was of borderline significance. After 4 weeks, all nonresponders discontinued aspirin treatment and most of the responders continued aspirin treatment for at least 12 weeks (Fig. 1).

Effect of subsequent ESS on aspirin treatment outcomes

Twenty-four of the 40 patients (9 from the responder group and 15 from the nonresponder group) required subsequent ESS. Of these 24 patients, 1 (4.2%) had no frontal sinus involvement. Thirteen patients (54.2%) had Draf IIA frontal sinusotomies, 8 patients (33.3%) had Draf IIB frontal sinusotomies, and 2 patients (8.3%) had modified Lothrop (Draf III) procedures. All 24 patients underwent total ethmoidectomy. Wide maxillary antrastomies were created in all patients and, of these, 8 (33.3%) had maxillary mega-antrastomies.

At 4 weeks after ESS, all 24 patients had a significant improvement in RQLQ score compared with baseline before ESS (0.7 [IQR, 0.3-1.9] vs 2.5 [IQR, 1.9-3.6], $p < 0.001$) (Fig. 2) as well as an improvement in NPF compared with baseline (140 [IQR, 100-175] L/min vs 100 [IQR, 80-140] L/min, $p = 0.01$) (Fig. 3). However, 4 weeks after ESS, there was no significant change in ACT score compared with baseline (22 [IQR, 19-24] vs 19.5 [IQR, 17-22], $p = 0.1$) (Fig. 2), or in percent FEV₁ (78% [IQR, 65-102%] vs 81% [IQR, 70-99%], $p = 0.8$) (Fig. 3).

Reinitiation of aspirin therapy post-ESS

Three to 4 weeks after surgery, all 24 patients were able to complete the aspirin desensitization protocol and start aspirin therapy. Of note, 3 of 5 patients who could not complete desensitization before ESS due to persistent GI symptoms had no such GI symptoms during the desensitization after ESS. The other 2 patients had mild GI symptoms. These symptoms were treated and did not preclude continuation of aspirin desensitization.

After 4 weeks of aspirin therapy post-ESS, there was continuous improvement in NPF (140 [IQR, 100-175] L/min vs 155 [IQR, 100-205] L/min, $p < 0.05$) (Fig. 4). ACT and RQLQ scores as well as percent FEV₁ remained unchanged

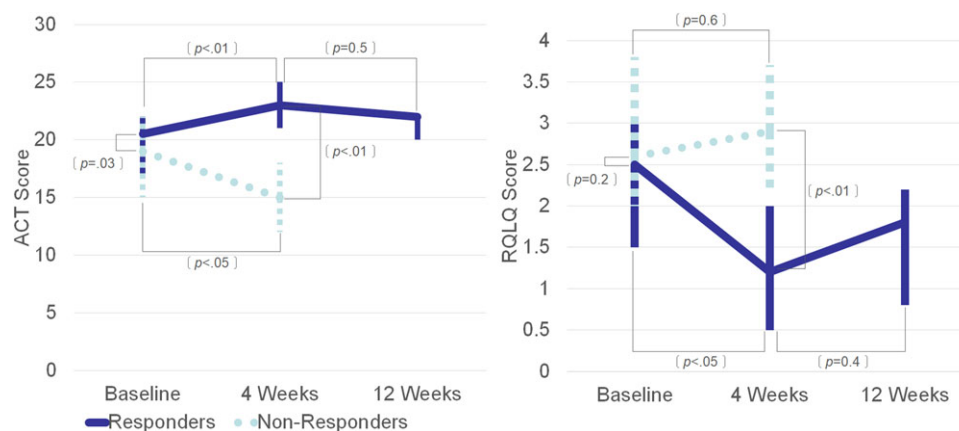


FIGURE 1. ACT (A) and RQLQ (B) outcomes in responders and nonresponders on primary aspirin desensitization and therapy before ESS. Vertical bars represent interquartile ranges. ACT = Asthma Control Test; ESS = endoscopic sinus surgery; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire.

at 4 weeks after ESS compared with values immediately post-ESS (Fig. 4). Long-term follow-up consistently showed stability in ACT score (Fig. 4A), RQLQ score (Fig. 4B),

NPF value (Fig. 4C), and percent FEV₁ (Fig. 4D) at the postoperative visit and at 12 and 24 weeks after initiation of maintenance therapy.

TABLE 1. Baseline comparison of responders and nonresponders

	Responders (n = 19)	Nonresponders (n = 21)	P value
Age, mean ± SE	43.6 ± 2.5 years	42.2 ± 2.5 years	0.7
Female patients, n (%)	9 (47)	15 (71)	0.1
Race, n (%)			<0.01 ^a
African American	5 (26)	15 (71)	
Latino	4 (22)	5 (24)	
White	9 (47)	1 (5)	
Asian	1 (5)	0	
Baseline percent predicted FEV ₁ ± SEM	81.3 ± 4.7%	84.6 ± 4.8%	0.6
ACT score at baseline, median (IQR)	20.5 (17-22)	19 (15-22)	0.3
Baseline nasal peak flow ± SEM	125 ± 12.2 L/min	94 ± 8.7 L/min	<0.05 ^a
FeNO, median (IQR)	32 (18-43) ppb	48 (29-86) ppb	0.05
Number of surgeries at baseline, median (IQR)	1 (1-2)	1 (0-1)	<0.01 ^a
SNOT-22 scores at baseline, median (IQR)	55 (43-58)	51 (38-66)	0.9
RQLQ scores at baseline, median (IQR)	2.5 (1.5-3.0)	2.6 (2-3.8)	0.2
High-dose ICS use	52%	48%	0.5
Systemic prednisone use	40%	60%	0.9
Time between preceding sinus surgery and desensitization to aspirin, median (IQR)	48 (24-72) months	48 (20-96) months	0.8
Lund-Mackay score presurgery, median (IQR)	19 (14-21)	19 (14-22)	0.8
Baseline peripheral blood eosinophil counts, median (IQR)	0.6 (0.4-0.8) K/μL	0.7 (0.5-0.9) K/μL	0.2
Baseline total serum immunoglobulin E level, median (IQR)	87 (53-193) kU/L	252 (96-479) kU/L	<0.01 ^a

^{aa}Statistically significant ($p < 0.05$).

ACT = Asthma Control Test; FEV₁ = forced expiratory volume in 1 second; FeNO = fractional excretion of nitric oxide; ICS = inhaled corticosteroids; IQR = interquartile range; ppb = parts per billion; SNOT-22 = 22-item Sino-Nasal Outcome Test; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; SEM, standard error of the mean.

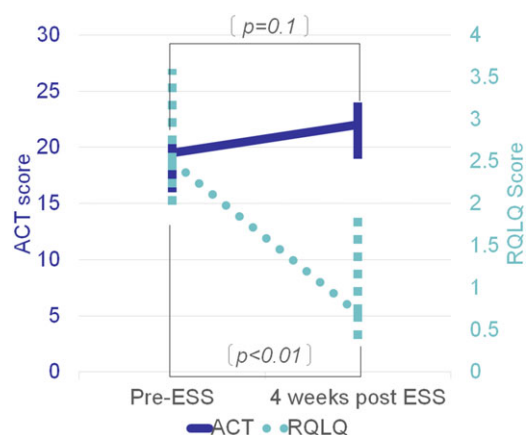


FIGURE 2. ACT and RQLQ changes in patients after ESS. Vertical bars represent interquartile ranges. ACT = Asthma Control Test; ESS= endoscopic sinus surgery; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire.

Changes in biomarkers after aspirin treatment pre-ESS

Peripheral blood eosinophil counts after the initial aspirin treatment increased from baseline to 4 weeks after treatment in both responders (0.6 [IQR, 0.4-0.8] K/ μ L vs 0.7 [IQR, 0.4-1.0] K/ μ L, $p < 0.01$) and nonresponders (0.7 [IQR, 0.5-0.9] K/ μ L vs 1.7 [IQR, 0.8-1.9] K/ μ L, $p < 0.001$) (Fig. 5A). Counts remained stable in responders over the course of 12 weeks of aspirin treatment (Fig. 5A).

Total serum IgE levels did not increase significantly in responders from baseline to 4 weeks of aspirin treatment (87 [IQR, 53-193] kU/L vs 91 [IQR, 32-122] kU/L, $p = 0.5$) (Fig. 5B), and remained stable after 12 weeks of aspirin treatment (113 [IQR, 29-125] kU/L, $p = 0.6$, vs IgE levels at 4 weeks of aspirin treatment). However, in nonresponders, total serum IgE levels increased significantly from baseline to after 4 weeks of aspirin therapy (252 [IQR, 96-479] kU/L vs 474 [IQR, 197-911] kU/L, $p = 0.02$) (Fig. 5B).

FeNO levels did not change significantly in responders from baseline to after 4 or 12 weeks of aspirin treatment (Fig. 5C). Similarly, in nonresponders, FeNO levels did not increase significantly from baseline to after 4 weeks of aspirin therapy (Fig. 5C).

Changes in biomarkers after aspirin treatment post-ESS

In the 24 patients who either failed initial desensitization or did not sustain an adequate response to aspirin therapy and had to undergo subsequent ESS, peripheral blood eosinophil counts dropped significantly from baseline to post-ESS (0.6 [IQR, 0.4-0.8] K/ μ L vs 0.3 [IQR, 0.1-0.5] K/ μ L, $p < 0.01$) (Fig. 6A). Eosinophil counts then increased significantly from post-ESS to after 4 weeks of aspirin treatment (0.3 [IQR, 0.1-0.5] K/ μ L vs 0.5 [IQR, 0.2-0.8] K/ μ L, $p < 0.05$) (Fig. 6A) and remained stable thereafter (Fig. 6A).

Serum IgE levels remained unchanged from pre-ESS baseline to any point post-ESS or after aspirin treatment (Fig. 6B).

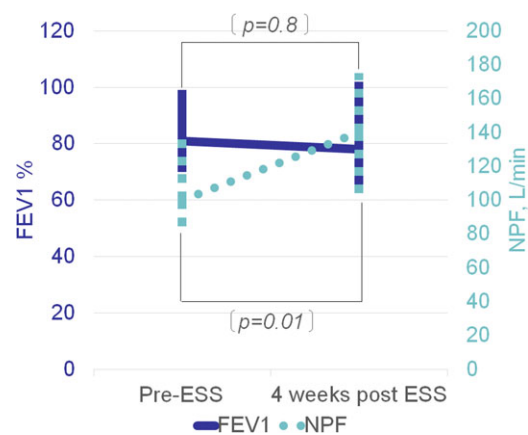


FIGURE 3. FEV₁ (%) and NPF changes in patients after ESS. Vertical bars represent interquartile ranges. ESS = endoscopic sinus surgery; FEV₁ = forced expiratory volume in 1 second.

FeNO levels decreased significantly from pre- to post-ESS (45 [IQR, 26-69] ppb vs 28 [15-41] ppb; $p < 0.01$) (Fig. 6C). However, FeNO levels increased significantly from a point post-ESS to after 4 weeks of aspirin therapy (28 [IQR, 15-41] ppb vs 38 [IQR, 24-77] ppb, $p < 0.05$) (Fig. 6C), but then remained stable at 12 and 24 weeks after aspirin therapy (Fig. 6C).

Discussion

Aspirin desensitization and daily maintenance therapy benefits many patients with AERD.^{3,7} Aspirin therapy has been shown to impart a long-term benefit of polyp regrowth reduction, improved sense of smell, and need for revision sinus surgery in prospective clinical trials.^{6,18-20} In addition to aspirin therapy, ESS has been shown to improve the disease process in both physician-reported (nasal endoscopy and Lund-Mackay [LM] computed tomography scores) and patient-reported (SNOT-22 score) measures.²¹ Although aspirin therapy may be beneficial, its impact does not appear to be universal. In previous studies, the response rates of aspirin desensitization and therapy varied from 77% and 93%.^{1,19,22} Cahill et al reported that 17% of AERD patients were unable to complete aspirin desensitization, with failures being due to gastrointestinal intolerance, persistent skin rash, or severe respiratory reactions.²³ Other patients showed worsening of respiratory symptoms during daily aspirin treatment.²⁴ There is currently a lack of data on the factors that can predict which patients respond well to desensitization. A confounder in the treatment protocol may be the length of time between preceding ESS, if one exists, and the initiation of aspirin therapy. Although some studies that showed response and benefit of aspirin therapy tested patients who had ESS 3-6 weeks before aspirin therapy,^{22,25} other studies showed no any correlation between preceding ESS time and initiation of aspirin therapy.^{6,18,24}

In our cohort, 20% of patients failed the initial desensitization protocol due to GI intolerance or persistent

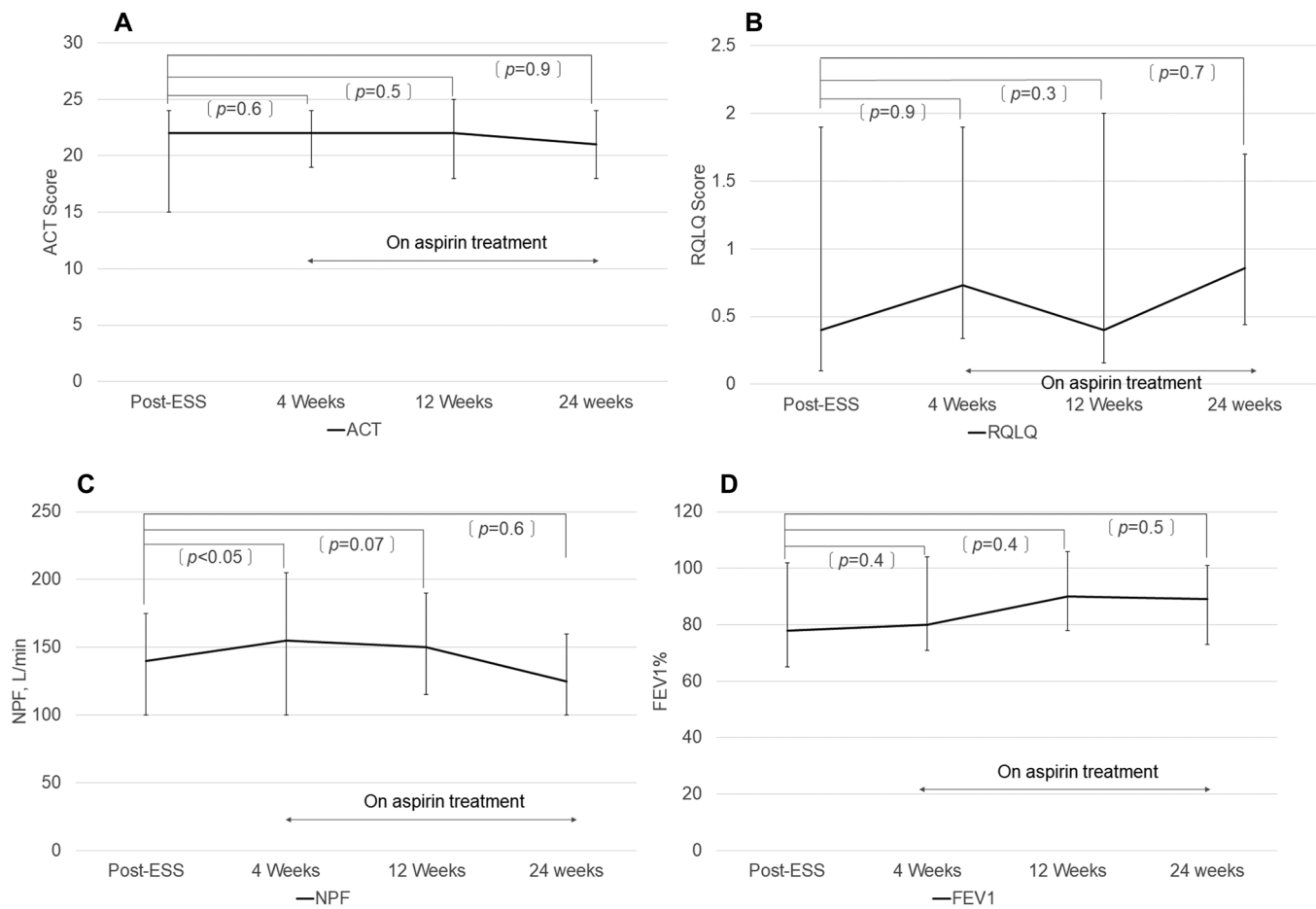


FIGURE 4. Post-ESS response of aspirin therapy as measured by ACT score (A), RQLQ score (B), NPF (C), and percent FEV₁ (D). Vertical bars represent interquartile ranges. ACT = Asthma Control Test; ESS = endoscopic sinus surgery; FEV₁ = forced expiratory volume in 1 second; NPF = nasal inspiratory peak flow; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire.

bronchospasm, similar to the 17% reported by Cahill et al.²³ A third of the patients were able to complete desensitization but reported no change or worsening of respiratory symptoms on aspirin maintenance therapy. Ultimately, this group of “nonresponders” were not able to benefit from

aspirin therapy for their AERD. They had lower NPF values and higher total serum IgE levels compared with the patients who were able to tolerate aspirin desensitization and therapy with symptomatic improvement. Interestingly, there was no difference in timing of the preceding ESS,

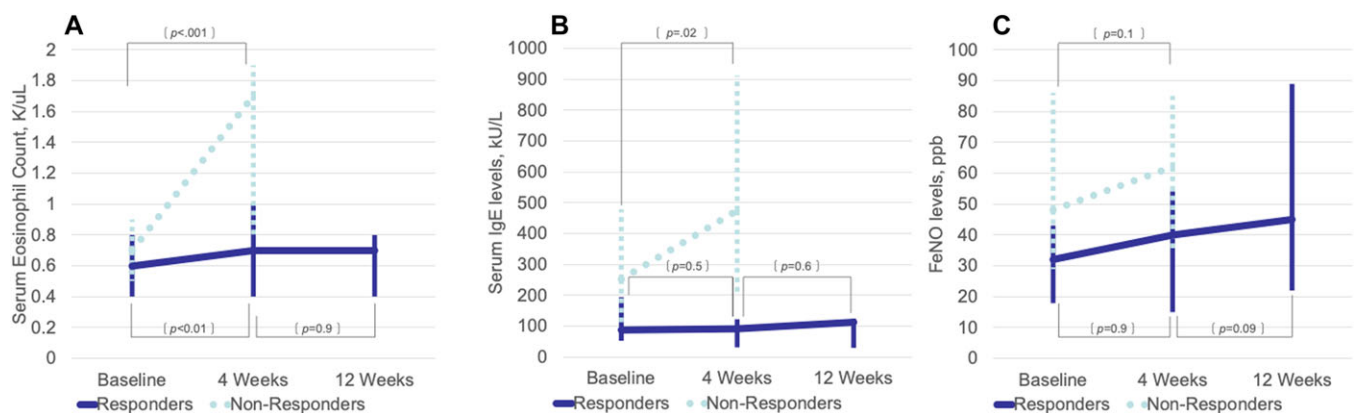


FIGURE 5. Serum eosinophil count (A) and IgE (B) and FeNO (C) changes in responders and nonresponders to aspirin desensitization and therapy before ESS. Vertical bars represent interquartile ranges. ESS = endoscopic sinus surgery; FeNO = fractional excretion of nitric oxide.

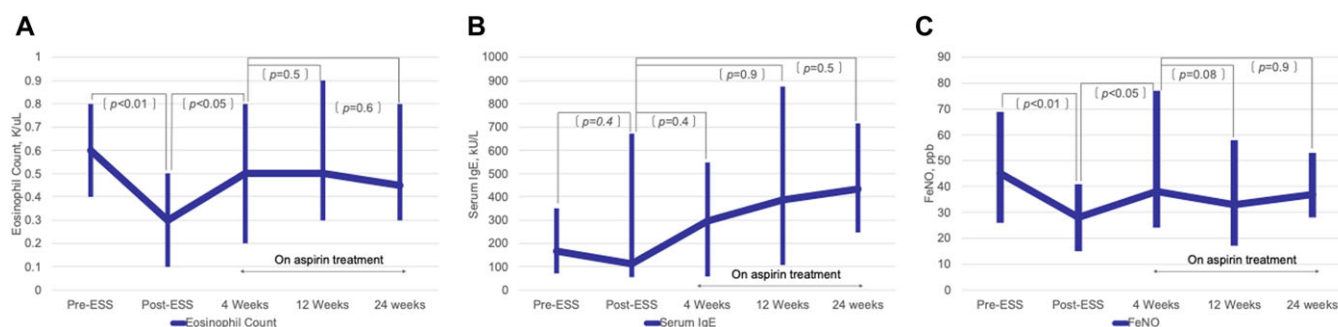


FIGURE 6. Post-ESS changes to aspirin therapy as measured by serum eosinophil count (A), IgE levels (B), and FeNO levels (C); vertical bars represent interquartile ranges. ESS = endoscopic sinus surgery; FeNO = fractional excretion of nitric oxide; IgE = immunoglobulin E.

LM scores, lung function, or medication use between the 2 groups. However, when nonresponders underwent ESS and then underwent aspirin desensitization, they were all able to tolerate the same desensitization protocol and aspirin maintenance therapy with symptomatic improvement.

In the present study we found that aspirin responders tended to have lower total serum IgE levels than nonresponders. Although the role of serum IgE is not well established in the natural progression of AERD, previous studies have reported high levels of IgE in patients with AERD in the absence of atopy²⁶ and also as a response to staphylococcal superantigens.²⁷ Interestingly, aspirin responders in this study—as well as in another study on aspirin treatment responders where IgE levels were reported—appeared to have lower IgE levels than aspirin nonresponders.¹⁰ Nonresponders were more likely to be African American. Several studies showed that African Americans tend to have higher IgE levels than Caucasians.^{28,29} In a presumably majority Caucasian AERD population from Poland, higher IgE levels were associated with more emergency department visits and hospitalizations for asthma exacerbations and poorer asthma control as measured through the ACT, further supporting the concept of IgE being a significant biomarker of worse disease in AERD.³⁰

Although serum IgE levels did not change over the course of treatment in aspirin responders in this study, as well as in another recent report,²⁰ IgE levels increased significantly in nonresponders during aspirin treatment. This is consistent with the recent observation that high-dose aspirin therapy increases markers of type 2 inflammation in AERD patients²⁰ and may make patients with higher baseline levels of IgE more prone to treatment failure. Interestingly, there was no change in IgE levels in our cohort after the second, post-ESS aspirin desensitization. This may indicate that the absence of nasal polyp burden, due to the recent ESS, before aspirin desensitization, suppressed the increase in type 2 inflammation in AERD patients treated with aspirin. We previously reported that aspirin challenges are more likely to be asymptomatic after recent ESS.³¹ In this study we also found that recent ESS was likely to improve aspirin desensitization and treatment outcomes, especially in patients with high baseline serum IgE levels. Of note, peripheral blood eosinophil counts were observed to decrease

significantly after ESS. It is possible that this decrease was due to the preceding corticosteroid taper that was administered to patients in the immediate postoperative period.

It is postulated that aspirin therapy can prevent the regrowth of polyps that have been recently surgically cleared, but has no effect on polyps already existing in the nasal cavity.^{32,33} However, there was no difference in LM scores between the responders and nonresponders in our cohort (score of 19 for both groups, $p = 0.8$), suggesting that anatomic burden of nasal polyps alone did not contribute to the outcome of response. Of note, nonresponders had a lower baseline NPF rate.

Although ESS seems to benefit outcomes of aspirin desensitization and therapy, some patients are reluctant to undergo surgery for various reasons. Our results may help to stratify patients, via serum biomarkers and other clinical characteristics, into groups that may gain clinical benefit from aspirin desensitization and therapy without preceding ESS and those who require ESS before desensitization to decrease disease burden and increase chances of success. Our study supports previous reports showing that some groups of patients may benefit from aspirin desensitization regardless of preceding ESS timing,^{6,10} and that other patients, possibly with serum biomarker characteristics of higher T2 inflammation, may require ESS to be able to tolerate desensitization and fully benefit from long-term aspirin therapy.

This study has several limitations. The patients in our study were not systematically tested for atopy, which could potentially explain some of the peripheral biomarker levels and subsequent difference in aspirin challenge response. In addition, although we analyzed prospectively collected data, not all confounders and systematic biases can be excluded without blinding and randomization. All patients who underwent ESS had mometasone-eluting implants placed at the time of surgery and received postoperative oral corticosteroid taper. Consequently, the potential impact of these treatments on the subsequent response to aspirin desensitization and therapy could not be evaluated. Furthermore, although we noted that aspirin therapy nonresponders were more likely to be African American, there was insufficient power to evaluate aspirin treatment outcomes by race or ethnic background due to the relatively modest sample size.

Conclusion

Antecedent ESS enhances aspirin treatment response in AERD patients and may convert patients who failed aspirin treatment before surgery to a more responsive

phenotype after ESS. Patients with higher baseline serum IgE levels may especially benefit from ESS performed shortly before aspirin desensitization and long-term treatment initiation. 

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