

Complete endoscopic sinus surgery followed by aspirin desensitization is associated with decreased overall corticosteroid use

John V. Bosso, MD¹, Tran B. Locke, MD¹ , Edward C. Kuan, MD, MBA² , Siddhant H. Tripathi, BS¹, Kevin I. Ig-lzevbekhai, BA¹, Laila T. Kalaf, BSA¹, Michael A. Kohanski, MD, PhD¹ , James N. Palmer, MD¹ and Nithin D. Adappa, MD¹

Background: Aspirin-exacerbated respiratory disease (AERD) is an aggressive respiratory tract inflammatory disorder manifesting as asthma, chronic rhinosinusitis with nasal polyposis, and a respiratory sensitivity to aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs). Corticosteroids, both systemic and topical/inhaled, are used to treat inflammation of the upper and lower airways. Our objective was to examine the potential impact of complete endoscopic sinus surgery (ESS) and aspirin desensitization (AD) on short-term and long-term corticosteroid use.

Methods: For this pilot study, a retrospective chart review of all patients with AERD who underwent ESS followed by AD was performed. Daily prednisone use, average daily prednisone dose, and inhaled corticosteroid use were analyzed at the following time points: preoperative, postoperative/pre-AD, and 2 to 3 months, 4 to 6 months, 7 to 12 months, and 13 to 24 months following AD.

Results: A total of 125 patients underwent ESS followed by AD. Compared to preoperatively, patients who underwent ESS and AD were less likely to be on daily prednisone at all time points and upon long-term follow-up (32% preoperatively vs 10% at 13 to 24 months, McNemar's test = 9.00, $p = 0.009$). Average daily prednisone dose de-

creased from 10.6 ± 7.9 mg preoperatively to 3.8 ± 2.6 mg at 13 to 24 months following AD (Mann-Whitney U ; $W = 122$, $p = 0.01$). Similarly, high-dose and medium-dose inhaled corticosteroid use decreased from 18% to 7% and from 36% to 22% respectively (Pearson's chi-square = 8.06, $p = 0.05$).

Conclusion: In our AERD cohort who underwent ESS followed by AD, there was an observed decrease in overall systemic and topical/inhaled corticosteroid use. These findings can have implications for treatment given the potentially hazardous side effects of corticosteroid use. © 2020 ARS-AAOA, LLC.

Key Words:

aspirin-exacerbated respiratory disease; aspirin desensitization; corticosteroids; nasal polyps; endoscopic sinus surgery

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Aspirin-exacerbated respiratory disease (AERD), otherwise known as Samter's triad, is an aggressive inflammatory disease of the upper and lower respiratory tract,

characterized by nasal polyposis, adult-onset asthma, and hypersensitivity to acetylsalicylic acid (ASA, aspirin) and other cyclooxygenase-1 (COX-1) inhibitors.¹⁻³ The pathophysiology of AERD stems from an abnormal arachidonic acid metabolism, resulting in an overproduction of pro-inflammatory leukotrienes via the 5-lipoxygenase pathway due to the inhibition of COX-1. Overproduction and heightened sensitivity to cysteinyl leukotrienes, especially leukotriene E₄, leads to stimulation of the epithelial innate immune alarmins thymic stromal lymphopoietin (TSLP), interleukin 25 (IL-25), and IL-33, which in turn stimulate mast cell activation, prostaglandin D₂ (PGD₂) release, chemoattractant receptor-homologous molecule expressed on T-helper 2 (Th2) cells (CRTH2) receptor stimulation, type 2 innate lymphoid (ILC2) cell activation, eosinophilic inflammation, and an amplification of the type 2 adaptive

¹Department of Otolaryngology-Head and Neck Surgery, University of Pennsylvania, Philadelphia, PA; ²Department of Otolaryngology-Head and Neck Surgery, University of California, Irvine, Orange, CA

Correspondence to: Nithin Adappa, MD, University of Pennsylvania, 3400 Spruce Street, Ravdin 5, Philadelphia, PA 19104; e-mail: nithin.adappa@uphs.upenn.edu

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TABLE 1. Low-dose, medium-dose, and high-dose inhaled corticosteroid parameters based on the National Institutes of Health for individuals age ≥ 12 years¹⁶

Medication	Low-dose (μg)	Medium-dose (μg)	High-dose (μg)
Beclomethasone HFA	80–240	240–480	>480
Budesonide	180–600	600–1200	>1200
Flunisolide	320	320–640	>640
Fluticasone HFA/MDI	88–264	264–440	>440
Fluticasone DPI	100–300	300–500	>500
Mometasone DPI	200	400	>400

DPI = dry power inhaler; HFA = hydrofluoroalkane; MDI = metered-dose inhaler.

immune response.⁴ The prevalence of AERD ranges from 10% to 20% of asthmatic patients and upward of 30% of patients with chronic rhinosinusitis with nasal polypsis (CRSwNP).^{1,5,6} Chronic rhinosinusitis (CRS) patients with AERD have a higher severity of disease and are often recalcitrant to conventional medical and surgical therapies, with failure rates up to 90% after endoscopic sinus surgery (ESS).^{7,8} Approximately 24% to 51% of AERD patients are dependent on systemic corticosteroids for symptom management.^{9–11} Oral aspirin desensitization (AD) has been shown to be an effective tool for disease control.^{3,10–12} More recently, studies have shown that sinus surgery followed by AD and maintenance therapy leads to effective long-term control of sinus disease burden in AERD.^{7,13,14}

Despite the efficacy of corticosteroids in the treatment of AERD, little is known regarding the impact upon corticosteroid use of surgical treatment of inflammatory burden followed by AD. In this study, we aim to better understand the influence of complete ESS (ESS) and AD on short-term and long-term corticosteroid use in AERD patients. We hypothesized that ESS and AD will reduce oral and inhaled corticosteroid use within AERD patients. For this study, we examined the need for posttreatment oral or inhaled corticosteroids at various time points before ESS and after AD within our AERD cohort.

Patients and methods

This study was approved by the Institutional Review Board at the University of Pennsylvania. A retrospective review was performed of all patients with aspirin challenge–proven AERD who underwent ESS with subsequent AD at a tertiary academic medical center with a dedicated AERD center. Inclusion criteria for the study consisted of (1) oral aspirin challenge with subsequent worsening of upper and/or lower airway symptoms; (2) diagnosis of asthma; (3) CRS refractory to medical therapy; and (4) preoperative endoscopic evidence of CRSwNP. Exclusion criteria consisted of: age under 18 years, immunodeficiency, pregnancy, cystic fibrosis, initiation of a type 2 biological monoclonal antibody within 6 months, negative aspirin challenge, or

ASA intolerance after desensitization (eg, gastrointestinal issues, urticaria).

All patients underwent ESS, defined as removal of all polyp burden and bilateral wide maxillary antrostomy, sphenoethmoidectomy, and frontal sinusotomy with skeletonization of the skull base. A subset of patients underwent middle turbinate resection or Draf III due to increase disease severity. Regardless of surgical extent, all patients were given a similar postoperative taper starting with oral prednisone 20 mg daily based on endoscopic exam and started on topical corticosteroid irrigations that were continued post-AD long-term. Approximately 6 weeks after surgery, once systemic corticosteroids had been tapered off completely, patients underwent desensitization. Any patient with a questionable history of ASA-induced or nonsteroidal anti-inflammatory drug (NSAID)-induced respiratory reaction underwent aspirin challenge pre-operatively. Otherwise, patients had aspirin challenge performed post-operatively as part of the desensitization protocol. All AD was performed in an outpatient surgical center setting under continuous monitoring using the modified intranasal ketorolac and aspirin challenge/desensitization protocol.¹⁵ ASA maintenance therapy adhered to the following protocol: initial dosing of 650 mg twice daily with attempted titration after 3 to 6 months down to a minimum of 325 mg daily, depending on patient response and tolerance. About 6 months post-AD, patients were typically on a stable maintenance dose of 325 mg to 1300 mg of aspirin daily. Patients were given strict instructions to call the Penn Rhinology division for any acute or chronic corticosteroid needs.

Daily prednisone use, average daily prednisone dose, and inhaled corticosteroid use were analyzed preoperatively, postoperatively/pre-AD, and 2 to 3 months, 4 to 6 months, 7 to 12 months, and 13 to 24 months after AD. Patients were enrolled on a rolling basis during the study period. Daily prednisone use was defined as at least 1 month of consecutive daily prednisone. Oral corticosteroids were occasionally prescribed by the treating rhinologist or allergist based on sinus and asthma symptoms. High-dose, medium-dose, and low-dose inhaled corticosteroids were defined based on the National Institute of Health guidelines (Table 1).¹⁶ McNemar's test was used to compare bivariate

TABLE 2. Daily prednisone use before and after complete endoscopic sinus surgery and AD*

Time point	On daily prednisone n (%)	Not on daily prednisone n (%)	Test statistic (McNemar's test)	p
Preoperative	35 (32.1)	74 (67.9)		
Postoperative, pre-AD	94 (75.2)	31 (24.8)	36.00	<0.001
2–3 months postoperatively	20 (18.3)	89 (81.7)	4.84	0.03
4–6 months postoperatively	9 (10.3)	78 (89.7)	7.35	0.007
7–12 months postoperatively	7 (9.7)	65 (90.2)	11.6	<0.001
13–24 months postoperatively	4 (9.8)	37 (90.2)	9.00	0.003

*Chi-square analysis used preoperative data as baseline comparison against other time points. Bold values indicate statistical significance at 0.05 level.
AD = aspirin desensitization.

categorical variables, whereas Pearson's chi-square was used in such comparisons for multiple variables. The Mann-Whitney *U* test was used to compare continuous variables. The significance level was set to 0.05 and all reported *p* values are 2-tailed. All reported means are written with accompanying standard deviations (SDs). Statistical analysis utilized Stata Statistical Software, version 15.1 (StataCorp LP, College Station, TX).

Results

In our study, 132 patients with aspirin challenge-proven AERD from August 2016 to December 2018 met inclusion criteria. Patients who were unable to complete the initial AD and remain on maintenance therapy, failed to follow up, or did not undergo ESS were excluded. A total of 125 patients successfully underwent ESS followed by AD. The mean $\pm$ SD age at desensitization was 50.13 ± 12.8 years with a slight female predominance ($n = 74$). Patients were enrolled in the study on a rolling basis. As a result, there was variation in final follow-up duration based on the time of enrollment. The average follow-up time in the study was 15.4 months.

Compared to the preoperative time point, after ESS and AD, patients were less likely to be on daily prednisone at all time points (32.1% preoperatively; 18.4% at 2 to 3 months post-AD [McNemar's test = 4.84, $p = 0.03$]; 10.3% at 4 to 6 months post-AD [7.35, $p = 0.007$]; 9.7% at 7 to 12 months post-AD [11.6, $p < 0.001$], and 9.8% at 13 to 24 months post-AD [9.00, $p = 0.003$]; all $p < 0.05$) (Table 2, Fig. 1). Average daily prednisone dose decreased from 10.6 ± 7.9 mg preoperatively to 3.8 ± 2.6 mg at 13 to 24 months post-AD (Mann-Whitney *U*, $W = 122$, $p = 0.01$) (Table 3, Fig. 2). Similarly, high-dose inhaled corticosteroid use decreased from 18.3% preoperatively to 14.9% at 4 to 6 months post-AD, whereas the rate of low-dose inhaled corticosteroid use increased from 17% to 36%. Medium-dose inhaled corticosteroid use decreased from 35.8% to 29.9% during the same time frame (Pearson's chi-square = 8.59, $p = 0.03$) (Table 4). At 7 to 12-month follow-up, there was a further decrease

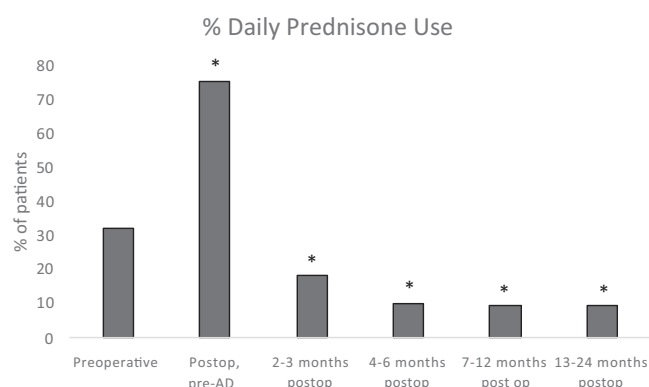


FIGURE 1. Proportion of patients with daily prednisone use before and after surgery and aspirin desensitization. Asterisks indicate statistical significance at the 0.05 level.

in the proportion of patients on high-dose steroids, from 18.3% to 12.5% (chi-square = 7.74, $p = 0.05$). At the 13 to 24-month follow-up, both high-dose and medium-dose steroid use decreased from 18.3% to 7.3%, and 35.8% to 22.0%, respectively (chi-square = 8.06, $p = 0.05$).

Discussion

AERD, manifesting as a triad of asthma, CRSwNP, and hypersensitivity to COX-1-inhibiting medications, is a challenging inflammatory disease to manage. AD and maintenance therapy plays an important role in the medical management of the disease and has been shown to be safe and well-tolerated among AERD patients.^{10,17} Studies have demonstrated significant improvement in symptom scores, corticosteroid use, revision surgery, and sinus infections after AD therapy.^{2,3} A study by Berges-Gimeno et al.¹¹ noted that medical therapy with AD alone resulted in a decrease in daily prednisone use and mean prednisone dose from 10.8 mg/day to 8.1 mg/day and 3.6 mg/day at 6 months and 12 months, respectively. This association was also seen in our postsurgical AERD patients who underwent AD. Furthermore, a unique observation in this study was a decrease

TABLE 3. Daily prednisone dose before and after complete endoscopic sinus surgery and AD*

Time point	n	Daily prednisone dose (mg) (mean $\pm$ SD)	Test statistic (W)	p (Mann-Whitney U)
Preoperative	35	10.6 $\pm$ 7.9		
Postoperative, pre-AD	94	11.0 $\pm$ 6.4	1501	0.43
2–3 months postoperatively	20	7.5 $\pm$ 6.7	469	0.03
4–6 months postoperatively	9	6.5 $\pm$ 5.7	227	0.03
7–12 months postoperatively	7	5.3 $\pm$ 2.7	186	0.02
13–24 months postoperatively	4	3.8 $\pm$ 2.6	122	0.01

*Mann-Whitney U tests used preoperative data as baseline comparison against other time points. Bold values indicate statistical significance at 0.05 level. AD = aspirin desensitization; SD = standard deviation.

in high-dose and medium-dose inhaled corticosteroid use after sinus surgery and AD.

Current recommendations advise complete ESS followed by AD for AERD patients with recalcitrant rhinosinusitis.¹⁸ Other studies have highlighted the added benefit of AD after ESS, including improvement in quality of life metrics.^{7,19} Our group previously evaluated 22-item Sino-Nasal Outcome Test (SNOT-22) scores after complete ESS and AD and found that SNOT-22 scores decreased immediately postoperatively and there were no significant increases in total SNOT-22 scores through the 30-month follow-up period after AD, thereby demonstrating preservation of the effects of ESS.¹³ In this current study, we observed a significant decrease in systemic corticosteroid usage and dose through the study period. We also noticed a significant decrease in high-dose and medium-dose inhaled corticosteroid usage. It is important to point out that pre-AD corticosteroid levels are elevated due to most postoperative plans requiring extended courses of prednisone as part of the

management. These results are consistent and strengthen previous studies showing a qualitative decrease in corticosteroid use after ESS in patients with AERD.^{20–23} To the best of our knowledge, this is the first study to show improvement in oral and inhaled steroid use after ESS with AD.

There is a high rate of corticosteroid dependence in AERD, with up to 50% of the AERD patients taking a mean equivalent of 8 mg of prednisone and almost one-quarter requiring intravenous (IV) steroids yearly.^{9,10} Short-term courses of corticosteroids have been effective in treating nasal polyps and asthma with maximal benefits not observed until 3 weeks of therapy are completed.²⁴ However, this therapy is not without risks. Adverse effects of corticosteroids include but are not limited to anxiety, hyperglycemia, insomnia, weight gain, abdominal striae, adrenal insufficiency, diabetes, cataracts, increased intraocular pressure, osteoporosis, and avascular necrosis of the femur.²⁵ The decreased dosage and use of corticosteroids

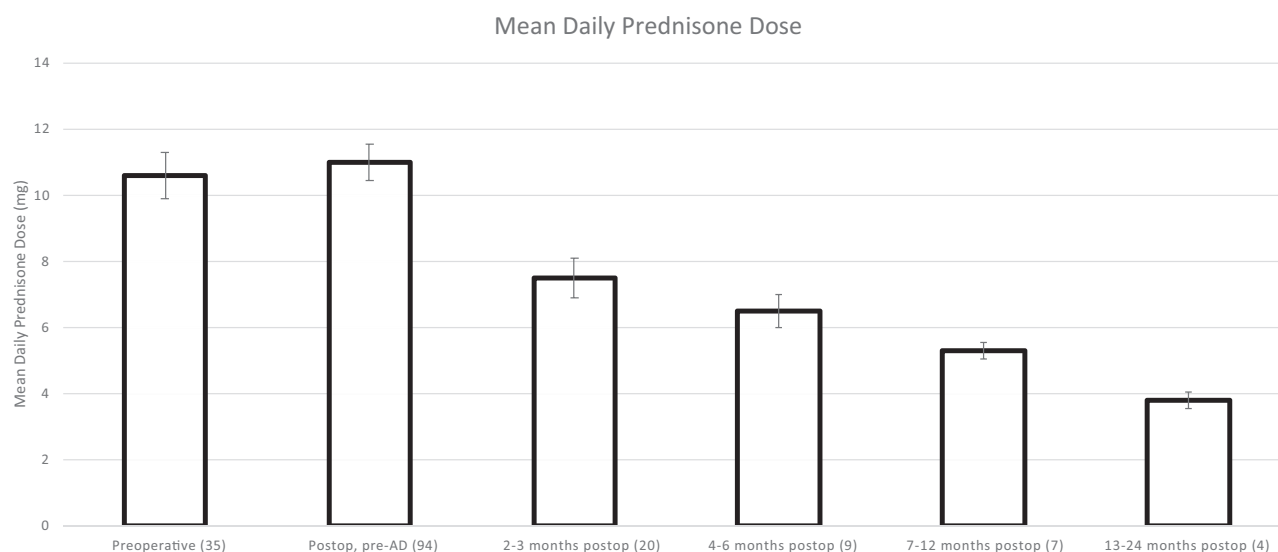

FIGURE 2. Mean $\pm$ standard error daily prednisone dose (in mg) before and after surgery and aspirin desensitization.

TABLE 4. Inhaled corticosteroid use before and after complete endoscopic sinus surgery and AD*

Time point	High-dose n (%)	Medium-dose n (%)	Low-dose n (%)	None n (%)	Test statistic (Pearson's χ^2)
Preoperative	20 (18.3)	39 (35.8)	19 (17.4)	31 (28.4)	
Postoperative, pre-AD	24 (19.2)	43 (34.4)	31 (24.8)	27 (21.6)	2.63, $p = 0.45$
2–3 months postoperatively	19 (17.4)	36 (33.0)	31 (28.4)	23 (21.1)	4.21, $p = 0.24$
4–6 months postoperatively	13 (14.9)	26 (29.9)	31 (35.6)	17 (19.5)	8.69, $p = 0.03$
7–12 months postoperatively	9 (12.5)	24 (33.3)	25 (36.1)	14 (19.4)	7.74, $p = 0.05$
13–24 months postoperatively	3 (7.3)	9 (22.0)	13 (31.7)	16 (39.0)	8.06, $p = 0.05$

*Chi-square analysis used preoperative data as baseline comparison against other time points. Bold values indicate statistical significance at 0.05 level.
AD = aspirin desensitization.

after ESS and AD in AERD patients may mitigate the aforementioned risks.

The significant decrease in usage and dose of systemic and inhaled corticosteroids after surgery and AD likely reflects a blunting of the inflammatory response, resulting in less required prednisone. In a study by Bobolea et al.,²⁶ AERD patients who underwent oral AD followed by maintenance therapy were found to have changes in arachidonic acid metabolites, including a decrease in proinflammatory prostaglandin D2 and an increase in anti-inflammatory prostaglandin E2 (PGE2). A double-blind, placebo-controlled trial by Świerczyńska-Krępa et al.²⁷ compared AD followed by 6 months of maintenance therapy in AERD patients vs those with aspirin-tolerant asthma (ATA). Only the AERD group showed improvement in quality of life measures for asthma and CRS as well as objective measures, including peak nasal inspiratory flow and inhaled corticosteroids.

Although our pilot study showed an association between sinus surgery and AD on oral and inhaled corticosteroid use, the study is limited by its retrospective nature. Due to our intent to analyze available data, patients had varying lengths of follow-up. The differences in the number of patients seen in Tables 1, 2, and 4 at each time point can also be attributed to other factors. First, there was an observed survey response bias preoperatively because not all patients completely filled out surveys or accurately recalled their medications. Analysis was performed on the data recorded in the electronic medical record. As a result, any discrepancy in the recorded data accounts for the difference in total patient numbers at various time points between

Tables 1 and 4. Second, a subset of patients extended out their follow-up appointments or were lost to follow-up due to potential improvement in symptoms, preference for local follow-up, or medication noncompliance. Although the number of patients decreased over time, the same subjects are compared at each time point. In addition, it is possible that patients lost to follow-up could have been prescribed higher doses of oral or inhaled corticosteroids by outside providers.

We also chose to not have a control arm because the standard of care at our AERD center is to have AD after ESS. In addition, although we did not have standardized endoscopic grading data collected for all patients, both primary surgeons perform similar corticosteroid tapers postoperatively. The time points used in our study reflect the progressively longer intervals of time between postoperative follow-up visits because the vast majority of patients had clinical improvement. Our study will benefit from a future prospective, randomized, double-blind study aimed to better quantify the effect of sinus surgery and AD on AERD patients and associated oral and inhaled corticosteroid use.

Conclusion

AERD patients benefit from a multidisciplinary approach to provide optimal care for this challenging disease. In our AERD population, complete ESS followed by AD is associated with a decrease in overall systemic and topical/inhaled corticosteroid use. This has potential implications for treatment in light of potentially hazardous adverse effects involved with chronic corticosteroid use. 

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