

State of the art: A systematic review of the surgical management of aspirin exacerbated respiratory disease

Jonathan Yip, M.D., Christopher M. Yao, M.D., and John M. Lee, M.D., F.R.C.S.C.

ABSTRACT

Background: Endoscopic sinus surgery is an important modality to the armamentarium of the otolaryngologist managing chronic rhinosinusitis (CRS). Within the spectrum of CRS, there exists a subset of patients who are recalcitrant to conventional treatment strategies, including those with aspirin-exacerbated respiratory disease (AERD). Although surgery is frequently undertaken in this group, there has been no general consensus on the efficacy or optimal extent of surgery.

Methods: Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a systematic review of published studies was conducted. Inclusion criteria included original publications of adult patients with AERD undergoing surgery, cohorts of greater than five subjects, a minimum follow-up of 3 months, and measurable clinical outcomes. An electronic search was performed using OVID MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Web of Science.

Results: Sixteen studies met the criteria for analysis. For our primary objective, sinus surgery appeared to improve patient-reported quality of life (QoL) and symptom profile in AERD. Overall, most studies reported a decrease in radiographic grading, endoscopy scores, and asthma severity. Compared with aspirin-tolerant asthmatic patients, AERD patients may have worse objective measures of disease severity both pre- and postoperatively; however, patient-reported QoL and symptom improvement may be similar after sinus surgery. Finally, this review showed that patients with AERD required revision surgeries sooner and more frequently compared with other subtypes of CRS. We also discussed the role of maximal surgical techniques and additional benefit of postoperative adjunctive therapies in the management of this disease entity.

Conclusion: The state of the art in the management of AERD patients suggests that surgery does play an important role in helping establish symptomatic control. In the future, more rigorous studies evaluating the comprehensiveness of surgery and postoperative adjuncts are required to understand their impact on long-term patient outcomes.

(Am J Rhinol Allergy 28, 493–501, 2014; doi: 10.2500/ajra.2014.28.4103)

Endoscopic sinus surgery (ESS) has evolved as an important adjunct to the medical management of chronic rhinosinusitis (CRS), with reported success rates ranging from 69.8 to 97%.^{1–6} However, the subset of patients who fail ESS and subsequently require multiple revision surgeries remain significant. Although the reasons are multifactorial, prognostic studies suggest that extensive sinonasal disease and high inflammatory load (*i.e.*, eosinophilia) are prominent contributors.^{1,7,8} Aspirin-exacerbated respiratory disease (AERD) represents a severe form of chronic hypertrophic eosinophilic rhinosinusitis, and is a syndrome of airway inflammation characterized by nasal polyposis, asthma, and sensitivity to acetylsalicylic acid (ASA) or other cyclooxygenase-1 inhibitors.^{9,10} The pathogenesis of AERD is postulated to involve dysregulated eicosanoid synthesis, resulting in baseline overproduction of proinflammatory leukotrienes *via* the 5-lipoxygenase (5-LO) pathway.⁹ Consequently, the ensuing up-regulated inflammatory response leads to bronchoconstriction, vasodilatation, submucosal edema, mucus hypersecretion, and further recruitment of eosinophils into the airway.¹¹ Inhibition of cyclooxygenase 1 by ASA results in acute exacerbations by decreasing prostaglandin E₂ (PGE₂), an inhibitor of leukotriene synthesis, and shifting substrates to the 5-LO pathway.^{9,10,12}

Compared with aspirin-tolerant patients, nasal polyps in AERD produce significantly lower amounts of PGE₂, possess a higher eosinophilic load, and are generally more refractory to conventional treatment strategies.^{13–15} Although surgery is frequently undertaken in this group, there has been no attempt to systematically combine outcome data to provide a general consensus on the efficacy or

optimal extent of surgery. The lack of evidence in guiding surgical treatment has led to conflicting philosophies on management and variation in approaches.

The primary research objective of this article was to systematically characterize the impact of surgery on AERD patients, specifically by comparing preoperative and postoperative measures. The main outcomes evaluated were patient-reported subjective measures, and secondary outcomes were objective measures, including radiographic grading, endoscopy scores, surgical revision rates, and asthma outcomes.

METHODS

Eligibility Criteria

Eligibility criteria for this study required published and unpublished studies conducted between 1946 and 2014 of adult patients (aged ≥ 18 years) who underwent sinus surgery for AERD and were followed postoperatively for a minimum of 3 months. AERD was defined as the presence of chronic eosinophilic rhinosinusitis, nasal polyposis, asthma, and sensitivity to aspirin. This article chose to categorize aspirin-intolerant asthmatic (AIA) patients to be synonymous with AERD. In all studies, surgery had to be a primary intervention, and all types of surgical approaches were permitted for this review. For studies comparing surgical approaches, two or more treatment groups with explicit details regarding each procedure were required. Included studies had to have a published series of at least five patients and a clear description of outcome measures. The primary outcomes were patient-reported subjective measures: Sino-Nasal Outcome Test (SNOT), Rhinosinusitis Disability Index (RSDI), Chronic Sinusitis Survey (CSS), symptom score scale (*i.e.*, visual analog scale [VAS]), and other nonvalidated scales. Secondary outcomes included objective measures: endoscopy score, computed tomography (CT) grading, revision surgery rates, asthma severity, and asthma-related physician visits. Preoperative and postoperative care was not specified in the eligibility criteria because of the diversity across the literature. Articles in any language were considered as long as a translated English version was attainable. Data on surgical cohorts

From the Department of Otolaryngology–Head and Neck Surgery, University of Toronto, St. Michael's Hospital, Toronto, Ontario, Canada

Presented at the North American Rhinology and Allergy Conference, January 23, 2014, Puerto Rico

The authors have no conflicts of interest to declare pertaining to this article

Address correspondence to John Lee, M.D., F.R.C.S.C., University of Toronto, St. Michael's Hospital, 30 Bond Street, 8 Cardinal Carter, Toronto, Canada ON M5B 1W8
E-mail address: leejo@smh.ca

Copyright © 2014, OceanSide Publications, Inc., U.S.A.

with concomitant therapies were excluded, because it obscured the impact of surgery on outcomes.

Information Sources

Electronic searches of OVID MEDLINE (1948 to January 2 2014), EMBASE (1980 to January 2014), and The Cochrane Central Register of Controlled Trials (CENTRAL; Wiley Online Library) were performed on January 19, 2014. The following search strategy was used: (Sinusitis OR Nasal Polyps) AND (Samter's Triad OR Aspirin Exacerbated Respiratory Disease OR ASA Triad OR Aspirin Triad OR Aspirin Intolerant Asthma) AND (Surgery OR Sinus Surgery OR Endoscopic Sinus Surgery OR Nasalisation OR Nasalization OR Polypectomy OR Turbinectomy OR Antrostomy). Abstracts and conference proceedings published between 2005 and 2013 were searched using the Web of Science. Reference lists of retrieved articles were screened to identify other potential studies for inclusion. We also attempted to contact experts and researchers in this field to extract unpublished data if available. Only human studies were included in the study.

Study Selection

Two independent reviewers (J.Y. and C.M.Y.) screened the titles and abstracts of studies retrieved from the systematic search. After collaboration, relevant abstracts were selected for full-article review. Each independent reviewer selected articles based on previously defined eligibility criteria to be included in this systematic review. Relevant data were also extracted independently using a data collection form. Any disagreement regarding the inclusion or exclusion of a study was resolved through discussion and consensus agreement. If disagreement persisted, an arbitrator (J.M.L.) was consulted for a final decision. Interobserver agreement was calculated using a Cohen's unweighted κ -statistic at both the abstract and the full-text screening stages.

Data Abstraction

A data collection form established by Lee and Grewal¹⁶ was modified to reflect the objectives of this study and was subsequently pilot tested by both reviewers. Characteristics such as inclusion/exclusion criteria, patient information, intervention, study design, follow-up duration, and relevant outcome measures were recorded. Both reviewers entered data independently and analysis was performed with Review Manager, Version 5.2 (The Cochrane Collaboration, Oxford, U.K.). In general, there was a lack in consistent reporting of results because of the heterogeneity of outcome measures and the methodologies used by studies.

Methodological Assessment and Data Synthesis

The Preferred Reporting of Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used for reporting of this study. Each reviewer used the Cochrane Handbook of Systematic Reviews (Version 5.1.0) to determine the methodological assessment. Each study was assigned a level of evidence based on guidelines published by the Oxford Center for Evidence-based Medicine—Levels of Evidence.¹⁷ Articles were also graded using the National Institute for Health (NIH) and Clinical Excellence scoring scale for case series, which has been previously applied in other systematic reviews in otolaryngology.^{18,19} Scores ≤ 3 indicate poor quality, 4 and 5 indicate fair, and ≥ 6 indicate good quality. Outcome data were pooled from included studies when appropriate and a meta-analysis was conducted using the random effects model. We chose this model because of the anticipated high interstudy variability and heterogeneity in outcome measures. Pooled estimates included a 95% CI and p value (two sided).

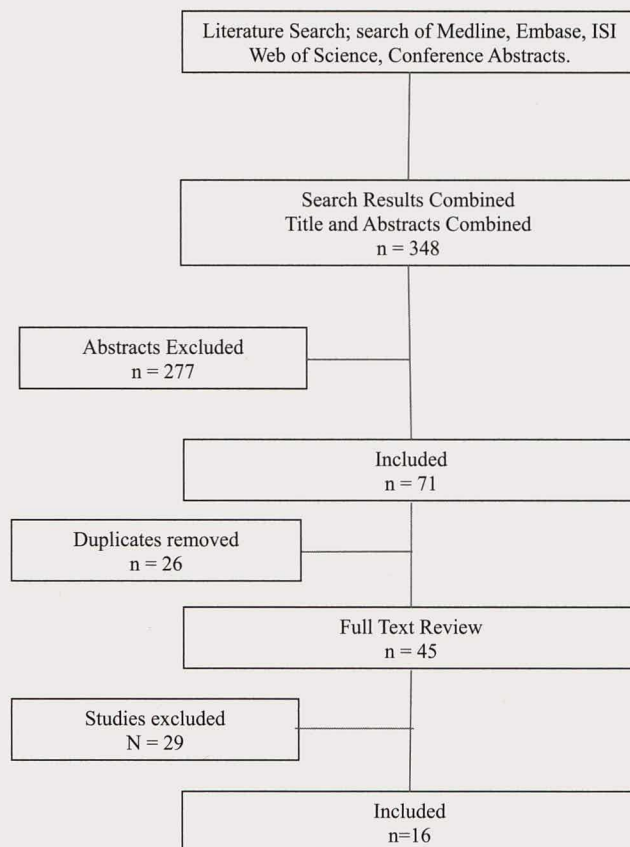


Figure 1. Flowchart of search results for systematic review.

RESULTS

Search Results

The systematic search of MEDLINE, EMBASE, CENTRAL, and Web of Science databases led to a total of 348 potential abstracts (citations) for review (Fig. 1). During the screening of abstracts, 71 studies were selected for full text review. The κ -agreement (unweighted) between the two reviewers was 0.839, which indicated "very good" strength of agreement. After the examination of full text, 55 studies were excluded, because they did not meet the inclusion criteria. The κ -agreement at this stage was 1.00. No additional study was found after reviewing the reference lists of included studies. There were no unpublished articles retrieved. In total, 16 studies met the inclusion criteria for this article, which are outlined in Table 1.

Methodological Quality of Included Studies

The level of evidence for each study is shown in Table 1. One study was considered level I evidence and five were deemed to be level II evidence. Among the studies with level II evidence, four were cohort studies and one was a low-quality randomized control trial because of $<80\%$ follow-up. The remainder were retrospective case-control studies labeled as level III or IV. Using the NIH and Clinical Excellence scale as a guide, the included studies were generally fair to good in quality. Reasons for this included: primarily single center studies, inadequate inclusion or exclusion criteria, incompletely defined outcomes, lack of consecutive patients, and absence of stratified outcomes.

Subjective Outcomes

For our primary research question, we aimed to determine whether sinus surgery would change the subjective quality of life (QoL) and symptom profile of patients with AERD.

Table 1 Study characteristics of included studies

Source	Study Design	Study Population	Objective(s)	Outcomes	Surgical Technique	Comments	Level of Evidence
Amar <i>et al.</i> ²⁸	Retrospective chart review	18 Patients with AERD, 22 patients with CRS	AERD vs CRS	Prevalence of postoperative symptoms, and revision rates at 1 mo and a minimum follow-up of 18 mo	Surgery was limited to disease indicated on preoperative imaging, and findings at time of surgery	No commercial funding reported	4
Awad <i>et al.</i> ³³	Retrospective chart review	41 AIA patients, 25 ATA patients	AIA vs ATA	CT scores (Lund-Mackay), patient-reported symptoms (Likert scale, non-validated) at 6 and 12 mo follow-up	The extent of the surgery was determined by the extent of disease but always included polypectomy, uncinctomy, anterior ethmoidectomy, and exploration of the posterior ethmoids	No commercial funding reported; postoperative scans occurred during a period of 18 mo after surgery	3b
Awad <i>et al.</i> ³⁶	Retrospective chart review	41 AIA patients, 50 ATA patients	AIA vs ATA	NIH asthma severity score, FEV ₁ , intranasal corticosteroid dose, oral corticosteroid use, number of asthma-related ER visits at 6 and 12 mo postoperatively	Endoscopic approach but surgical extent not specified	No commercial funding reported	3b
Batra <i>et al.</i> ³²	Retrospective chart review	9 AIA patients, 8 ATA patients	AIA vs ATA	CT scores (Lund-Mackay), FEV ₁ , patient-reported symptoms, oral corticosteroid use at minimum of 1-yr follow-up	Nasal polypectomy and ESS as described in the Messerklinger technique	All patients were steroid-dependent asthmatics; postoperative scans between 12 and 18 mo; no commercial funding reported	3b
Fruth <i>et al.</i> ²⁶	Prospective double-blind placebo-controlled randomized control trial	18 AERD patients in therapy group, 13 AERD patients in placebo group	AD versus placebo in context of AERD	QoL (RSDI), symptom score (nonvalidated), olfactory function (Sniffin sticks), and endoscopy scores at 6, 9, 12, 24, and 36 mo post-operatively	Not specified	No conflicts of interests declared; high dropout rate (39/70 patients) in both groups	2b
Havel <i>et al.</i> ²⁵	Retrospective chart review	65 AERD patients in therapy group, 81 AERD patients in control group	AD vs control group	QoL (VAS), symptom score (nonvalidated), endoscopy score (Rasp polyp grading), and revision surgery rates at 12 mo and minimum of 18 mo postoperatively	Endoscopic approach; surgical extent determined by extent of disease; procedure always included polypectomy, uncinctomy, and exploration of posterior ethmoid according to the criteria of the Messerklinger technique; septoplasty when necessary	No conflicts of interests declared; all patients were AIA	3b
Katoto-michelakis <i>et al.</i> ³⁰	Retrospective study	18 patients with AERD, 98 patients without AERD	Compare postoperative olfactory function between patients with and without AERD	Olfactory function (Sniffin sticks) at 1, 3, and 6 mo postoperatively	All operations followed the Messerklinger technique to the same extent (antrostomy, ethmoidectomy, sphenoidotomy, and opening of frontal sinus)	No conflicts of interests declared; all patients had CRSwNP (at least grade III by Malm classification)	3b
Loehrl <i>et al.</i> ³⁸	Retrospective chart review	34 patients with AERD	Asthma outcomes after surgery in AERD patients	FEV ₁ , oral corticosteroid use, inhaled corticosteroid use, and asthma-related physician visits, emergency room visits, and hospitalizations at 1 yr and long-term (mean 10 yr) follow-up	Endoscopic approach but surgical extent not specified	No conflicts of interests declared; response rate of study was 52.3%	4

Table 1 Continued

Source	Study Design	Study Population	Objective(s)	Outcomes	Surgical Technique	Comments	Level of Evidence
Mendelsohn <i>et al.</i> ³⁵	Retrospective cohort study	63 patients with AERD, 191 patients with CRSwNP and AERD, 295 patients with CRSwNP (control)	Compare recurrence and revision surgery rates among CRSwNP subgroups	Nasal polyp recurrence and revision rates at 5 and 10 yr postoperatively.	All patients underwent initial primary surgery, including polypectomy, maxillary antrostomy, ethmoidectomy, sphenoidectomy, or frontal sinusotomy	Kaplan–Meier analyses using survival analysis technique; no conflicts of interests declared	2b
McMains <i>et al.</i> ²²	Retrospective chart review	5 AERD patients who underwent AD (DS), 10 AERD patients who did not undergo DS (non-DS)	Compare objective and subjective outcomes among AERD and non-AERD patients after revision ESS. Secondary objective compared AERD patients undergoing DS and non-DS after revision ESS.	QoL (SNOT), endoscopy score (based on Rhinosinusitis Task Force Methodology), revision surgery rates up to 24 mo after surgery	ESS but surgical extent was not specified	No commercial funding reported	3b
Nakamura <i>et al.</i> ²⁷	Retrospective chart review	22 AIA patients (10 ESS, 12 patients underwent Caldwell–Luc	Determine effectiveness of sinus surgery in AIA patients, and to compare efficacy of ESS against Caldwell–Luc technique	Symptom score, NIH asthma severity score, CT score (Kennedy classification), FEV ₁ , topical steroid use, oral steroid use, and asthma-related physician visits, emergency room visits, and hospitalizations at 12 mo postoperatively.	ESS was based on Messerklinger technique, Caldwell–Luc with ethmoidectomy or sphenoidectomy	No discussion on selection criteria for ESS or Caldwell–Luc; no commercial funding reported	3b
Robinson <i>et al.</i> ²³	Prospective cohort study	19 Patients who were ASA intolerant, 104 patients who were ASA tolerant	ASA intolerant vs ASA tolerant	QoL (RSDI and CSS), endoscopy score, revision surgery rates at 3, 6, 12, and 18 mo postoperatively	Endoscopic approach but surgical extent not specified	74 and 79% of ASA-intolerant patients had nasal polyps and asthma, respectively; 30% and 40% of ASA-tolerant patients had nasal polyps and asthma, respectively. Supported by NIH.	2b
Rottenberg <i>et al.</i> ²¹	Three-arm, randomized, double-blinded, controlled trial	21 Patients who received saline irrigation alone (control), 19 patients with saline irrigation and budesonide nasal spray, and 20 patients with saline irrigation mixed with budesonide	Compare three different standardized medication regimens prescribed to AERD patients after ESS	QoL (SNOT), CT score (Lund–Mackay), and endoscopy score (Lund–Kennedy) at 6 mo and 1 yr postoperatively	Endoscopic approach; surgical extent based on extent of disease, but always included polypectomy, maxillary antrostomy, and ethmoidectomy	Four patients dropped out of study because of relocation, epistaxis and early disease exacerbation requiring prednisone; no conflicts of interests declared	1b
Seiberling <i>et al.</i> ³⁴	Prospective cohort study	6 AERD patients with CFT, 6 AERD patients with MMA (control group)	Compare the surgical outcome of CFT to standard MMA matched patients with the severely diseased maxillary sinus	Endoscopy score (of maxillary disease) and revision surgery rate at 6 and 12 mo postoperatively	All patients underwent either unilateral or bilateral CFT or MMA as part of their endoscopic sinus surgery	24/28 patients in treatment group, and 22/26 patients in control group completed study; all patients in both groups had nasal polyps, maxillary sinus grade 3 disease, and a predominance of eosinophils noted on pathology; no commercial funding reported	2b
Sobel <i>et al.</i> ³¹	Retrospective chart review	43 Patients with AERD, 350 patients without AERD	Assess treatment outcomes in patients undergoing ESS for CRS, with evaluation of prognostic indicators for success and failure	Symptom score (non-validated) at 6 and 12 mo postoperatively	Endoscopic approach based on extent of disease; all surgeries included middle meatal antrostomies, anterior and posterior ethmoidectomies, and removal of disease in the frontal recess; septoplasty and inferior turbinatectomy when necessary	No commercial funding reported	3b
Young <i>et al.</i> ²⁹	Prospective study	11 Patients with AERD, 7 patients with CRSwNP	Determine long-term subjective outcome of ESS between patients with and without AERD	Symptom score (validated; VAS) at 3, 6, 12, 24, and 36 mo postoperatively	Endoscopic approach but extent not specified	No commercial funding reported	2b

AERD = aspirin-exacerbated respiratory disease; AD = aspirin desensitization; AIA = aspirin-intolerant asthma; ATA = quality of life; ESS = endoscopic sinus surgery; CT = computed tomography; CSS = Chronic Sinusitis Survey; RSDI = Rhinosinusitis Disability Index; VAS = visual analog scale; NIH = National Institutes of Health; FEV₁ = forced expiratory volume in 1 s; SNOT = Sino-Nasal Outcome Test; CFT = canine fossa trephines; MMA = maxillary antrostomies; DS = desensitized; CRSwNP = chronic rhinosinusitis with nasal polyps.

Quality of Life

SNOT is a reliable, valid, and responsive disease-specific QoL-related measure of sinonasal function in the context of rhinosinusitis, with larger scores correlating with greater rhinosinusitis-related health burden.²⁰ Two studies assessed the impact of ESS on SNOT scores. The first was a double-blinded, randomized control trial on postoperative care of AERD patients with three treatment arms: saline irrigation (group A), budesonide nasal spray (group B), and budesonide mixed in saline irrigation (group C).²¹ Among all groups, SNOT-21 scores significantly improved at 6 months (group A, 29.7 [SD, 8.3] from baseline of 79.2 [SD, 10.4]; group B, 27.4 [SD, 11.9] from 82.4 [SD, 8.1]; group C, 28.2 [SD, 9.1] from 84.6 [SD, 12.6]; $p < 0.0167$ for all groups) and at 1-year postoperatively (group A, 42.5 [SD, 14.3]; group B, 47.9 [SD, 15.1]; group C, 42.2 [SD, 13.7]; $p < 0.0167$ among all groups) compared with preoperative baseline, but there was no statistical difference between groups. The weighted mean reduction in SNOT scores was 65.2% at 6 months and 46.2% at 1 year. McMains *et al.*²² compared SNOT-20 scores between non-AERD and AERD patients who were scheduled to undergo revision surgery. At 24 months postoperatively, SNOT-20 scores improved to 8.3 (SE, 1.9) from 31.9 (SE, 3.8) preoperatively for the AERD group ($p = 0.0000$), representing an average improvement of 74.0%. Although SNOT-20 scores also improved within the non-AERD ($p = 0.0000$), which had an SNOT-20 score of 30.5 (SE, 1.4) before surgery and 7.7 (SE, 0.7) at 24 months after intervention, the AERD group did not significantly differ from the non-AERD cohort at 24 months postoperatively ($p = 0.742$).

Robinson *et al.*²³ discussed the impact of surgery on RSDI, which is a broad-based, validated outcomes tool that uses three subscales (emotional, physical, and function) to combine measurements of rhinosinusitis disease-specific and general QoL measurements. They showed that RSDI scores declined after ESS in both aspirin-tolerant asthmatic (ATA) and AIA (or AERD) patients, which indicated an improvement in QoL. Within the AIA group, the mean preoperative, intermediate postoperative (mean follow-up of 11.3 [SD, 4.5] months), and long-term postoperative (mean follow-up of 17.7 [SD, 4.5] months) RSDI scores were 51.7 (SE, 4.6), 32.6 (SE, 4.5), and 38.7 (SE, 4.8), respectively. In comparison, the respective RSDI scores for the ATA group were 48.7 (SE, 2.0), 26.8 (SE, 1.9), and 27.2 (SE, 2.0). Although there appeared to be a trend toward worsening RSDI scores in the AIA group, the proportion of patients who reported improvement were similar between groups at both intermediate and long-term follow-up (AIA, 71% of patients; ATA, 63%; $p = 0.49$ at both time points). The lack of significance, however, may be the small sample size. It is also important to point out that not all patients in both groups had nasal polyposis (AIA, 74% of cohort; ATA, 30%).

The same study also evaluated the CSS score as an outcome measure, which is derived from a duration-based, sinus-specific questionnaire with a symptom and medication subscale.²⁴ For this scoring system, higher scores implied poorer QoL. Total CSS scores significantly improved after surgery compared with baseline in AIA and ATA patients. Among the AIA group, the mean preoperative, immediate postoperative, and long-term postoperative CSS scores were 36.6 (SE, 4.4), 53.9 (SE, 4.8), and 51.8 (SE, 5.1), respectively. As for the ATA group, their respective postoperative CSS scores were 31.4 (SE, 1.9), 54.0 (SE, 2.0), and 54.9 (SE, 2.2). The proportion of patients that improved by one-half of the SD did not differ between groups at the intermediate (AIA, 58% of patients; ATA, 73% of patients; $p = 0.18$) and long-term follow-up (AIA, 63%; ATA, 69%; $p = 0.60$).

Additionally, three studies investigated the impact of aspirin desensitization (AD) after ESS on QoL measures. After initially showing similar VAS ratings at baseline, Havel *et al.*²⁵ reported that the desensitized group, who received 500 mg of ASA daily, had significantly better overall sinonasal function at 1-year follow-up compared with controls treated with topical mometasone exclusively (no VAS values reported; $p < 0.001$). This effect was sustained at a mean follow-up duration of 31 and 35 months for the control and desensitization

group, respectively (no VAS values reported; $p < 0.001$). In another trial, AERD patients subjected to a postoperative AD protocol of 100 mg daily had significantly higher QoL by RSDI scores compared with placebo at 36 months postoperatively (AD, median = 46.0 [interquartile range [IQR], 40.0–55.5]; placebo, median = 68.6 [IQR, 48.5–84.5]; $p < 0.0324$).²⁶ Conversely, although McMains *et al.*²² found that surgery resulted in improved QoL within both desensitized (32.0 [SE, 3.6] preoperatively to 7.7 [SE, 1.3] postoperatively) and nondesensitized patients (31.8 [SE, 3.9] preoperatively to 8.8 [SE, 1.7] postoperatively), there was no significant difference in scores between groups (p value was not reported).

Symptom Profile

Nine studies described patient-reported symptom severity and frequency. Nasal symptom (*i.e.*, nasal blockage, rhinorrhea, and hyposmia) frequency and severity were generally less after surgery according to Nakamura *et al.* (no reported p value).²⁷ Amar *et al.*²⁸ found that patients with AERD more frequently reported the presence of sinonasal symptoms (*i.e.*, anosmia and anterior nasal discharge) at 1 and 46.5 months after ESS compared with CRS with nasal polyps (CRSwNP; proportions and p values were not explicitly provided). Young *et al.*²⁹ indicated that patients with AERD had a statistically significant return of nasal obstruction (preoperative VAS: 7.66 [SD, 2.54]; 24-month postoperative VAS: 4.13 [SD, 3.57]; $p = 0.04$) at 2 years, and anterior nasal discharge (preoperative VAS: 5.98 [SD, 3.72]; 36-month postoperative VAS: 5.00 [SD, 1.41]; $p = 0.001$) and anosmia at 3 years (preoperative VAS: 9.32 [SD, 1.38]; 36-month postoperative VAS: 8.00 [SD, 2.83]; $p = 0.006$) follow-up compared with those without AERD. A study examining the impact of olfactory function showed a greater degree of improvement in composite threshold-discrimination-identification score at 1 month (AERD, 9.72 [SD, 10.94] from 3.33 [SD, 4.03] preoperatively; non-AERD, 24.77 [SD, 9.62] from 11.78 [SD, 7.09] preoperatively; no p value reported) and at 3 months postoperatively (AERD, 14.67 [SD, 12.55]; non-AERD, 28.90 [SD, 8.22]; no p value reported) in the AERD group compared with non-AERD, but smaller improvement at 6 months postoperatively (AERD, 16.14 [SD, 12.34]; non-AERD, 32.18 [SD, 7.69]; no p value reported).³⁰ Interestingly, Sobol *et al.*³¹ reported that the presence of AERD did not change the frequency of patients who experienced a positive outcome after surgery (no proportions or p value reported).

Two studies reported on comparisons between steroid-dependent AIA and ATA patients. Batra *et al.*³² showed that there was a trend toward surgery reducing sinonasal symptoms among AIA patients (66.7% of patients reported reduced symptoms) at 1 year after surgery. However, this did not reach statistical significance ($p = 0.16$), which was in stark contrast to the ATA group (82.5% of patients; $p < 0.031$). Awad *et al.*³³ also found a similar proportion of patients who reported symptomatic improvement between both groups at 6 months (AIA, 63.4% of patients; ATA, 56%; $p = 0.609$) and 12 months postoperatively (AIA, 68.3% of patients; ATA, 60%; $p = 0.597$).

Two other studies compared symptomatic improvement among AERD patients with and without postoperative AD. Fruth *et al.*²⁶ used a composite symptom score out of 20 to characterize the severity of sinonasal symptoms, with higher scores indicative of major severity. They found that AD contributed to a greater reduction in composite symptom score after 36 months compared with placebo (AD, median 5.0 [IQR, 3.0–7.0]; placebo, median 11.0 [IQR, 9.0–12.8]; $p < 0.0001$); however, baseline values were not provided. There was a larger improvement in olfactory function by Sniffin Sticks' identification score in the treatment group than in the control group in the same postoperative period, but the difference was nonsignificant (AD, median 1.0 [IQR, 0.0–6.0]; placebo, median 5.0 [IQR, 0.5–7.0]; $p = 0.3191$). Likewise, Havel *et al.*²⁵ showed that the aspirin desensitized group had significantly better symptom ratings compared with controls for the following symptoms: nasal obstruction, postnasal drip, sense of smell, facial pain, sleep disturbance, and dry mouth at a minimum of 18-months postoperatively (all, $p < 0.05$).

Objective Outcomes

CT Scores. Four studies investigated the change in CT scores after surgery, of which three used the Lund–Mackay system and the other used the Kennedy classification. In one study, Awad *et al.*³³ found that Lund–Mackay scores significantly improved at a mean of 9 months after ESS in the AIA group (19 [SD, 4.82] to 14 [SD, 7.4]; $p = 0.006$). Batra *et al.*³² also showed that AIA patients improved (22 to 14; no measures of variance reported; $p < 0.006$) at 12–18 months after surgery. Likewise, Rottenberg *et al.*²¹ showed Lund–Mackay improvement at 1 year after ESS (20.3 [SD, 2.7] to 12.6 [SD, 3.1]; $p < 0.0167$). Nakamura *et al.*²⁷ reported a general improvement in Kennedy scores after surgery but no statistical analyses were performed.

It is interesting and important to note that in comparison, ATA cohorts had significantly lower pre- and postoperative CT scores. Batra *et al.*³² discovered that ATA patients improved after surgery (19 to 9; no measures of variance; $p < 0.001$). Awad *et al.*³³ showed that the ATA group improved (from 14 [SD] 6.8 to 5 [SD, 2.08]; $p < 0.0001$) after surgery, which represented a significantly greater improvement than the AIA cohort ($p < 0.0001$). The same study reported that the proportion of patients who improved on Lund–Mackay CT score was significantly higher for the ATA group compared with the AIA group (96 and 63.4%, respectively; $p = 0.003$).

Endoscopy Scores. A total of six studies measured the change in endoscopy scores from before and after sinus surgery. Using a weighted average of Lund–Kennedy endoscopy scores of different postoperative regimens, Rottenberg *et al.*²¹ showed that scores improved at 6 months postoperatively (from 9.9 [SD, 0.8] preoperatively to 1.4 [SD, 0.5]; $p < 0.167$). There was, however, interval worsening between 6 and 12 months postoperatively ($p < 0.167$) but was still significantly better than preoperative levels. Between-group testing failed to show any statistical or clinical differences among postoperative regimens ($p = 0.42$). McMains *et al.*²² also determined that revision ESS statistically lowered endoscopic scores at up to 24 months postoperatively (from 7.4 [SD, 0.0] at baseline to 2.0 [SD, 0.4]; $p = 0.0000$). In the context of extensive maxillary disease, canine fossa trephine (CFT) produced lower endoscopy grades than middle meatal antrostomy (MMA) at 6 months (CFT, 1.3 [SD, 0.1]; MMA, 1.3 [SD, 0.1]; $p = 0.0115$) and 12 months postoperatively (CFT, 1.26 [SD, 0.0]; MMA, 1.77 [SD, 0.12]; $p = 0.0042$), and subsequently, reduced the need for revision surgeries.³⁴

Studies comparing AERD with non-AERD subgroups have shown conflicting results. McMains *et al.*²² compared mean endoscopy grading between AERD and non-AERD and found no difference between groups at preoperative baseline (AERD, 7.6 [SE, 1.2]; non-AERD, 7.2 [SE, 0.5]; $p = 0.761$) and postoperative scores (AERD, 1.7 [SE, 0.4]; non-AERD, 2.2 [SE, 0.3]; $p = 0.558$). In contrast, Robinson *et al.*²³ reported that the AIA cohort had worse mean preoperative (AIA, 11.5 [SE, 1.2]; ATA, 7.4 [SE, 0.4]; $p < 0.0001$), intermediate (AIA, 6.9 [SE, 1.2]; ATA, 3.8 [SE, 0.4]; $p = 0.004$), and long-term postoperative Lund–Kennedy endoscopy scores (AIA, 7.3 [SE, 1.0]; ATA, 4.0 [SE, 0.4]; $p = 0.001$) than ATA patients. However, the proportion of patients that improved on endoscopy scores did not differ between groups at either intermediate (AIA, 74% of patients improved; ATA, 57%; $p = 0.17$) or long-term follow-up (AIA, 58% of patients improved; ATA, 56%; $p = 0.91$).

Three studies evaluated the additional impact of AD after surgery on endoscopy score. Using the Rasp polyp grading system, Havel *et al.*²⁵ reported that patients treated with AD had lower endoscopy scores at 12 months than the control group treated with ESS alone (AD, 1.00 [SD, 0.18]; control, 3.13 [SD, 0.15]; $p = 0.000$) and at a mean of 33.3 months follow-up (AD, 1.47 [SD, 0.186]; control, 3.06 [SD, 0.175]; $p = 0.000$). Fruth *et al.*²⁶ showed a trend toward lower nasal polyposis score in the therapy group than placebo; however, it did not reach significance (AD, median 0 [IQR 0.0–1.0]; control, median 2 [IQR, 0.0–4.0]; $p = 0.0702$). Similarly, McMains *et al.*²² found no statistical difference in postoperative endoscopy score at 24 months

between therapy and control groups (AD, 1.1 [SE, 0.4]; control, 2.0 [SE, 0.4]; $p > 0.05$), but failure to detect a change may be related to their small sample sizes ($n = 5$ and 10, respectively).

Revision Surgery Rates. The need for revision surgery in AERD was examined in six studies. With a mean follow-up duration of 46.5 months, Amar *et al.*²⁸ discovered a greater proportion of AERD patients required revision surgery compared with patients with CRS alone (38.9% versus 9.1%, respectively; no p value reported). Robinson *et al.*²³ reported that a greater proportion of ASA-intolerant patients required revision surgery compared with ASA-tolerant patients (84% versus 60%, respectively; $p = 0.04$) but no follow-up data were provided. Mendelsohn *et al.*³⁵ used a survival analysis technique with Kaplan–Meier analyses to assess disease-free and surgery-free survival of different subgroups of CRSwNP. They concluded that patients with AERD were most likely to have disease recurrence and did so earlier than CRSwNP alone (control group) and CRSwNP and asthma ($p < 0.001$). AERD patients also required a revision surgery more frequently and sooner than the other groups ($p < 0.001$). Overall actuarial surgery-free rates at 5 years were 90, 75, and 63% for control patients, patients with CRSwNP and asthma, and patients with AERD, respectively. By the 10-year mark, the rates were 83, 58, and 11%, respectively.

With respect to impact of surgical technique on revision rates, Seiberling *et al.*³⁴ found that fewer AERD patients treated with CFT for maxillary disease required additional surgery compared with MMA alone (16.7% versus 66.7%; no p value) but no comparative baseline statistics were provided.

Two studies contrasted surgical revision rates between those treated with and without AD. In the study by McMains *et al.*²² no patient in their therapy group required additional surgery at 24 months postoperatively compared with 80% in the control group, and this difference was statistically significant ($p = 0.003$). Havel *et al.*²⁵ similarly found that no patient with postoperative AD required further surgery at a follow-up of 35 months (SD, 20 months), in contrast to 16.7% of the control group (no p value reported).

Asthma Outcomes

Asthma Severity. The asthma severity score based on the NIH guidelines was longitudinally evaluated in the pre- and postoperative state in two studies.^{27,36} According to this scoring system, the severity is measured based on the frequency of daytime/nighttime symptoms, impact of asthma on physical activity, lung function, and the use of β_2 -agonists.³⁷ Nakamura *et al.*²⁷ showed a significant reduction in the degree of asthma severity in the postoperative state among 22 AERD patients with a mean follow-up of 49 months (no pre- or postoperative mean NIH score reported; $p = 0.0013$). On further examination of this study, 54.5% of patients improved on asthma severity, and among those who did not improve, 70% reported a reduction in emergency unit visits and/or admissions. Interestingly, there was no correlation found between preoperative sinus disease staging and severity of asthma ($p = 0.44$). Awad *et al.*³⁶ compared asthma severity between AIA and ATA patients. Preoperatively, the AIA group had significantly higher asthma severity scores (no average NIH asthma score reported; $p < 0.0001$). At 6 months postoperatively, NIH severity scores improved in 58.5% of AIA patients ($p < 0.001$) compared with 40.0% of ATA patients ($p < 0.001$), but this difference was not statistically significant ($p = 0.09$). Conversely, at 12 months postoperatively, improvement persisted in the same proportion of AIA patients but decreased to 30.0% in ATA group, and this represented a statistically significant difference ($p = 0.01$).

Postoperative Asthma-Related Emergency Room Visits, Physician Visits, and Hospitalizations. Loehrl *et al.*³⁸ showed that 62.1, 93.1, and 94.4% of patients had fewer asthma-related physician visits, emergency room visits, and hospitalizations, respectively, at 12 months after surgery. It was unknown, however, whether such reductions in health care usage were statistically significant. Nakamura *et al.*²⁷ showed a significant postoperative decline in the number of patients admitted to

the hospital for asthma attacks (from 45.5% of patients before surgery to 22.7% after surgery; $p = 0.007$), as well as those presenting to emergency units or physician's office for asthma-related reasons (from 3.1 visits per patient before surgery to 1.8 visits per person after surgery; no measures of variance; $p = 0.0004$). They, however, found no difference in outcomes between ESS and Caldwell-Luc operations (no p value reported). Comparing AIA and ATA patients, Awad *et al.*³⁶ detected a significant decrease in the number of asthma attacks requiring ER visits in the 12-month follow-up period in both groups ($p < 0.0001$ at 6 and 12 months postoperatively), but there was no statistical difference between groups at either time points ($p = 0.96$ and 0.28 , respectively).

DISCUSSION

Central to the evolution of sinus surgery in the context of CRS has been the core principle to restore sinus ventilation and mucociliary function. Despite its efficacy in achieving both subjective and objective outcomes, there are still upward of 26% of patients with persistent disease, thus highlighting the variable phenotypic expression of sinonasal inflammation and the spectrum of disease within CRS.³⁹ Prognostic studies have indicated that extensive sinonasal disease, high inflammatory load, and revision surgery to be factors predictive of recalcitrant disease.^{1,7} AERD represents the upper limits of the inflammatory spectrum of CRS, and, unfortunately, patients possess most of the aforementioned poor prognostic features.^{40–46} It is evident from the rhinologic literature that the surgical management of AERD continues to be a source of scientific inquiry, and interpreting the available literature has been complicated by small sample sizes, different surgical approaches, and varying outcome measures. Our study therefore attempted to systematically characterize the impact of surgery on AERD, to guide the practicing surgeon and underscore the deficiencies of our current knowledge.

From this study, the consensus appears to be that ESS leads to a significant improvement in QoL, symptom severity and frequency, radiographic grading, and endoscopic scores, as well as asthma severity. With prolonged follow-up, there was interval worsening of some measures, but they did not regress back to preoperative levels. What is interesting is that compared with ATA patients, AERD patients may have worse objective measures of disease severity (CT imaging and endoscopy) both preoperatively and after sinus surgery. However, patient-reported symptom improvement after ESS is similar in both groups.

This summary finding is significant when counseling patients regarding the potential impact of ESS and also for managing patient and surgeon expectations after surgery. Finally, this study has shown that patients with AERD required revision surgeries sooner and more frequently compared with other subtypes of CRS. Although this may not be surprising for clinicians, this may be an important consideration for patients as they contemplate surgical treatment.

A significant source of heterogeneity among all included studies in this systematic review can be attributed to the different surgical approaches used by each study. As shown in Table 1, the extent of surgery was highly inconsistent and its impact on postsurgical outcomes was ambiguous.^{27,34} In the case of Nakamura *et al.*,²⁷ applying their results comparing ESS and Caldwell-Luc is difficult because of the historic nature of the study and the uncertainty regarding extent of clearance. Some authors have advocated for the concept of “radical surgery” or “full-house ESS” in patients with high-grade eosinophilic inflammation, to widely open all sinus ostia and decrease the significant load of eosinophilia and inflammatory mediators both in the sinus mucosa and in the tenacious mucin.⁶ A more maximal approach can also address bony osteitis and biofilms, which have been shown to perpetuate mucosal inflammation and lead to recalcitrant disease.⁴⁶ Finally, such techniques facilitate adequate postoperative endoscopic visualization, in-office debridement, and improved delivery of topical medication.^{47,48} Ultimately, the goal of ESS in the context of AERD is

to provide the most complete surgery required for long-term disease control.

On the extreme end of the spectrum with regard to radical surgery for CRSwNP is the concept of nasalization, which was originally described by Jankowski and colleagues.⁴⁹ This procedure combines full-house ESS, wide opening of all sinus ostia, and stripping of the mucosa in the ethmoid roof and lamina papyracea, as well as middle turbinate resection. To date, the best evidence comes from a retrospective review comparing nasalization and standard ESS techniques for diffuse, severe nasal polyposis.⁴⁹ At 5 years postoperatively, the nasalization group had markedly lower recurrence rates (22.7% versus 58.3%), improved symptom scores, and endoscopic findings than their counterpart. Despite these results, this study was limited by its historical nature, lack of randomization, and a recall rate of <80%. Although stripping of mucosa is generally avoided to prevent reactive osteitis and ciliary dysfunction, there is some recent data that suggest that other concepts of the “nasalization” procedure can perhaps be applied in CRS patients with a high inflammatory burden. Wu *et al.*⁵⁰ examined the issue of middle turbinate resection in their retrospective review of CRSwNP patients. They were able to show that middle turbinate resection lengthened the duration of subsequent surgery compared with those whose turbinates were preserved (median, 4.56 versus 3.93 years, respectively; $p = 0.048$). Using Kaplan–Meier survival curves, the beneficial effect of middle turbinate resection in prolonging the time to revision surgery was observed for up to 8 years after surgery. Additionally, the concept of total ethmoidectomy was examined by Masterson *et al.*⁵¹ who found that a complete clean out of the ethmoid labyrinth in CRSwNP patients led to a significantly lower revision rate at 3 years postoperatively compared with a cohort who had anterior ethmoidectomy alone. Undoubtedly, all of these studies need to be viewed with caution given their retrospective nature. However, what remains clear is that AERD patients represent a spectrum of CRS patients where the extent of disease and local inflammatory load may not be fully addressed by traditional, transition-space conservative ESS techniques. Further prospective studies are required to better systematically characterize the impact of surgical extent on disease control in this challenging patient population.

Although the focus of our article was primarily on the impact of surgical treatment of AERD, it also highlighted the additional benefit of postoperative adjunctive therapies. AERD patients treated with AD were more likely to have greater symptom reduction, better olfactory function, lower endoscopic scores, and fewer revision surgeries than those who did not receive treatment. A recent systematic review supports our findings, because they reported an overall trend toward greater benefit with adjuvant AD.⁵² Further rigorous trials are needed to define an optimal maintenance regimen and to clarify its influence on long-term sinonasal outcomes.

Although the lack of supporting evidence precluded its inclusion in our review, the use of leukotriene modifiers offers another adjunctive therapy for AERD. Leukotrienes trigger proinflammatory pathways that increase tissue eosinophilia and have been targeted in the treatment of asthma by cysteinyl leukotriene 1 receptor antagonists (montelukast, pranlukast, and zafirlukast) and the 5-LO inhibitors (zileuton).⁵³ Pauli *et al.*⁵⁴ compared montelukast with placebo as a monotherapy for AERD and showed benefit in patient symptom scores but no statistical improvement in objective polyp grading or eosinophilic parameters. Similarly, Ulualp *et al.*⁵⁵ showed an overall improved symptoms score, but, again, lacked objective measurements of improvement in AERD patients who had previously underwent sinus surgery. Overall, there is a lack of studies on the effect of leukotriene modifiers as an adjunct to sinus surgery for AERD. However, available studies suggest a possible role for antileukotriene therapy in the treatment of specific subpopulations of AERD.

In the future, improving local delivery of anti-inflammatory medications such as through steroid-eluting stents may be an important adjunct in this patient population. Early trials have shown its useful-

ness in reducing the need for postoperative oral steroids, as well as improving inflammation of the sinus cavity.⁵⁶ What remains to be seen is whether these local therapies can minimize the need for revision surgery and provide long-term symptom relief.

CONCLUSION

AERD represents a subgroup of CRS characterized by a higher grade of mucosal eosinophilia as well as a higher burden of disease. It continues to be a challenging disease entity to manage; and surgery is aimed toward symptom control rather than cure. From this systematic review, it is evident that these patients do, in fact, benefit from ESS; specifically, they experience improved QoL, decreased symptom profiles, and better objective measures (radiographic and endoscopy severity scores), as well as improved asthma control. In the future, more rigorous studies evaluating the comprehensiveness of surgery are required to understand the impact of surgical technique on long-term patient outcomes. Furthermore, adjunctive treatment protocols including AD must be properly evaluated in conjunction with surgical therapy such that a standardized management paradigm can be established. For now, the state of the art in the management of AERD definitely suggests that surgery does play an important role in helping establish symptomatic control.

REFERENCES

- Kennedy DW. Prognostic factors, outcomes and staging in ethmoid sinus surgery. *Laryngoscope* 102(suppl 57):1-18, 1992.
- Levine HL. Functional endoscopic sinus surgery: Evaluation, surgery, and follow-up of 250 patients. *Laryngoscope* 100:79-84, 1990.
- Ramadan HH. Surgical causes of failure in endoscopic sinus surgery. *Laryngoscope* 109:27-29, 1999.
- Gliklich RE, and Metson R. Effect of sinus surgery on quality of life. *Otolaryngol Head Neck Surg* 117:12-17, 1997.
- Senior BA, Kennedy DW, Tanabodee J, et al. Long-term results of functional endoscopic sinus surgery. *Laryngoscope* 108:151-157, 1998.
- Bassiouni A, Naidoo Y, and Wormald PJ. When FESS fails: The inflammatory load hypothesis in refractory chronic rhinosinusitis. *Laryngoscope* 122:460-466, 2012.
- Sil A, Mackay I, and Rowe-Jones J. Assessment of predictive prognostic factors for functional endoscopic sinus surgery in a 5-year prospective outcome study. *Am J Rhinol* 21:289-296, 2007.
- Smith TL, Litvack JR, Hwang PH, Let al. Determinants of outcomes of sinus surgery: A multi-institutional prospective cohort study. *Otolaryngol Head Neck Surg* 142:55-63, 2010.
- Stevenson DD. Aspirin sensitivity and desensitization for asthma and sinusitis. *Curr Allergy Asthma Rep* 9:155-163, 2009.
- Szczeklik A, and Stevenson DD. Aspirin-induced asthma: Advances in pathogenesis, diagnosis, and management. *J Allergy Clin Immunol* 111:913-921, 2003.
- Robinson JL, Griest S, James KE, and Smith TL. Impact of aspirin intolerance on outcomes of sinus surgery. *Laryngoscope* 117:825-830, 2007.
- Szczeklik A, Sanak M, Nizankowska-Mogilnicka E, and Kielbasa B. Aspirin-intolerance and cyclooxygenase-leukotriene pathways. *Curr Opin Pulm Med* 10:51-56, 2004.
- 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* 160:291-296, 1999.
- 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* 161:391-398, 2000.
- Chaaban MR, Walsh EM, and Woodworth BA. Epidemiology and differential diagnosis of nasal polyps. *Am J Rhinol* 27:473-478, 2013.
- Lee JM, and Grewal A. Middle meatal spacers for the prevention of synechiae following endoscopic sinus surgery: A systematic review and meta-analysis of randomized controlled trials. *Int Forum Allergy Rhinol* 2:477-486, 2012.
- OCEBM Levels of Evidence Working Group (2011). The Oxford 2011 Levels of Evidence. Oxford Centre for Evidence-Based Medicine. Available online at www.cebm.net/index.aspx?o=5653; accessed March 30, 2014.
- Thomas L, Drinnan M, Natesh B, et al. Open conservation partial laryngectomy for laryngeal cancer: A systematic review of English literature. *Cancer Treat Rev* 38:203-211, 2012.
- Macdonald KI, Gipsman A, Magit A, et al. Endoscopic sinus surgery in patients with cystic fibrosis: A systematic review and meta-analysis of pulmonary function. *Rhinology* 50:360-369, 2012.
- Hopkins C, Gillett S, Slack R, et al. Psychometric validity of the 22-item Sinonasal Outcome Test. *Clin Otolaryngol* 34:447-454, 2009.
- Rotenberg BW, Zhang I, Arra J, and Payton KB. Postoperative care for Samter's triad patients undergoing endoscopic sinus surgery: A double-blinded, randomized controlled trial. *Laryngoscope* 121:2702-2705, 2011.
- McMains KC, and Kountakis SE. Medical and surgical considerations in patients with Samter's triad. *Am J Rhinol* 20:573-576, 2006.
- Robinson JL, Griest S, James KE, and Smith TL. Impact of aspirin intolerance on outcomes of sinus surgery. *Laryngoscope* 117:825-830, 2007.
- Gliklich RE, and Metson R. Techniques for outcomes research in chronic sinusitis. *Laryngoscope* 105:387-390, 1995.
- Havel M, Ertl L, Braunschweig F, et al. Sinonasal outcome under aspirin desensitization following functional endoscopic sinus surgery in patients with aspirin triad. *Eur Arch Otorhinolaryngol* 270:571-578, 2013.
- Fruth K, Pogorzelski B, Schmidtman I, et al. Low-dose aspirin desensitization in individuals with aspirin-exacerbated respiratory disease. *Allergy* 68:659-665, 2013.
- Nakamura H, Kawasaki M, Higuchi Y, and Takahashi S. Effects of sinus surgery on asthma in aspirin triad patients. *Acta Otolaryngol* 119:592-598, 1999.
- Amar YG, Frenkiel S, and Sobol SE. Outcome analysis of endoscopic sinus surgery for chronic sinusitis in patients having Samter's triad. *J Otolaryngol* 29:7-12, 2000.
- Young J, Frenkiel S, Tewfik MA, and Mouadeb DA. Long-term outcome analysis of endoscopic sinus surgery for chronic sinusitis. *Am J Rhinol* 21:743-747, 2007.
- Katotomichelakis M, Riga M, Davris S, et al. Allergic rhinitis and aspirin-exacerbated respiratory disease as predictors of the olfactory outcome after endoscopic sinus surgery. *Am J Rhinol Allergy* 23:348-353, 2009.
- Sobol SE, Wright ED, and Frenkiel S. One-year outcome analysis of functional endoscopic sinus surgery for chronic sinusitis. *J Otolaryngol* 27:252-257, 1998.
- Batra PS, Kern RC, Tripathi A, et al. Outcome analysis of endoscopic sinus surgery in patients with nasal polyps and asthma. *Laryngoscope* 113:1703-1706, 2003.
- Awad OG, Lee JH, Fasano MB, and Graham SM. Sinonasal outcomes after endoscopic sinus surgery in asthmatic patients with nasal polyps: A difference between aspirin-tolerant and aspirin-induced asthma? *Laryngoscope* 118:1282-1286, 2008.
- Seiberling KA, Church CA, Tewfik M, et al. Canine fossa trephine is a beneficial procedure in patients with Samter's triad. *Rhinology* 50:104-108, 2012.
- Mendelsohn D, Jeremic G, Wright ED, and Rotenberg BW. Revision rates after endoscopic sinus surgery: A recurrence analysis. *Ann Otol Rhinol Laryngol* 120:162-166, 2011.
- Awad OG, Fasano MB, Lee JH, and Graham SM. Asthma outcomes after endoscopic sinus surgery in aspirin-tolerant versus aspirin-induced asthmatic patients. *Am J Rhinol* 22:197-203, 2008.
- National Institutes of Health (NIH). Guidelines for the diagnosis and management of asthma. NIH Publication No. 97-4051, 1997.
- Loehrl TA, Ferre RM, Toohill RJ, and Smith TL. Long-term asthma outcomes after endoscopic sinus surgery in aspirin triad patients. *Am J Otolaryngol* 27:154-160, 2006.
- Bhattacharyya N. Clinical outcomes after revision endoscopic sinus surgery. *Arch Otolaryngol Head Neck Surg* 130:975-978, 2004.
- Staikuniene J, Vaitkus S, Japertiene LM, and Ryskiene S. Association of chronic rhinosinusitis with nasal polyps and asthma: Clinical and radiological features, allergy and inflammation markers. *Medicina (Kounas)* 44:257-265, 2008.
- Jankowski R, Bouchoua F, Coffinet L, and Vignaud JM. Clinical factors influencing the eosinophil infiltration of nasal polyps. *Rhinology* 40:173-178, 2002.

42. Bachert C, Gevaert P, Holtappels G, et al. Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. *J Allergy Clin Immunol* 107:607–614, 2001.
43. Dhong H-J, Kim HY, and Cho D-Y. Histopathologic characteristics of chronic sinusitis with bronchial asthma. *Acta Otolaryngol* 125:169–176, 2005.
44. Haruna S, Nakanishi M, Otori N, and Moriyama H. Histopathological features of nasal polyps with asthma association: An immunohistochemical study. *Am J Rhinol* 18:165–172, 2004.
45. Ardehali MM, Amali A, Bakhshae M, et al. The comparison of histopathological characteristics of polyps in asthmatic and nonasthmatic patients. *Otolaryngol Head Neck Surg* 140:748–751, 2009.
46. Smith TL, Mendolia-Loffredo S, Loehrl TA, et al. Predictive factors and outcomes in endoscopic sinus surgery for chronic rhinosinusitis. *Laryngoscope* 115:2199–2205, 2005.
47. Lee JM, and Chiu AG. Role of maximal endoscopic sinus surgery techniques in chronic rhinosinusitis. *Otolaryngol Clin North Am* 43:579–589, 2010.
48. Snidvongs K, Kalish L, Sacks R, et al. Sinus surgery and delivery method influence the effectiveness of topical corticosteroids for chronic rhinosinusitis: Systematic review and meta-analysis. *Am J Rhinol Allergy* 27:221–233, 2013.
49. Jankowski R, Pigret D, and Decroocq F. Comparison of functional results after ethmoidectomy and nasalization for diffuse and severe nasal polyposis. *Acta Otolaryngol* 117:601–608, 1997.
50. Wu AW, Ting JY, Platt MP, et al. Factors affecting time to revision sinus surgery for nasal polyps: A 25-year experience. *Laryngoscope* 124:29–33, 2014.
51. Masterson L, Tanweer F, Bueser T, and Leong P. Extensive endoscopic sinus surgery: Does this reduce the revision rate for nasal polyposis? *Eur Arch Otorhinolaryngol* 267:1557–1561, 2010.
52. Xu JJ, Sowerby L, and Rotenberg BW. Aspirin desensitization for aspirin-exacerbated respiratory disease (Samter's Triad): A systematic review of the literature. *Int Forum Allergy Rhinol* 3:915–920, 2013.
53. Dahlén B. Treatment of aspirin-intolerant asthma with antileukotrienes. *Am J Respir Crit Care Med* 161:S137–S141, 2000.
54. Pauli C, Fintelmann R, Klemens C, et al. Polyposis nasi—Improvement in quality of life by the influence of leukotriene receptor antagonists. *Laryngorhinootologie* 86:282–286, 2007.
55. Ulualp SO, Sterman BM, and Toohill RJ. Antileukotriene therapy for the relief of sinus symptoms in aspirin triad disease. *Ear Nose Throat J* 78:604–616, 1999.
56. Zhao X, Grewal A, Briel M, and Lee JM. A systematic review of nonabsorbable, absorbable, and steroid-impregnated spacers following endoscopic sinus surgery. *Int Forum Allergy Rhinol* 3:896–904, 2013. □

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.