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Rhinology and Allergic Disorders

Hsc
Home Study Course

Home Study Course

Section 5
September 2016

AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

THE
HOME STUDY COURSE
IN
OTOLARYNGOLOGY — HEAD AND NECK SURGERY

SECTION 5

Rhinology and Allergic Disorders

September 2016

SECTION FACULTY:

Christopher A. Church, MD*
David Poetker, MD*
Benjamin Saul Bleier, MD
Charles S. Ebert, Jr, MD, MPH
Adam J. Folbe, MD
Devyani Lal, MD
Abtin Tabaee, MD

American Academy of Otolaryngology - Head and Neck Surgery Foundation
1650 Diagonal Road, Alexandria, VA 22314

Section 5 suggested exam deadline: October 10, 2016
Expiration Date: August 4, 2017; CME credit not available after that date

Introduction
The Home Study Course is designed to provide relevant and timely clinical information for physicians in training and current practitioners in otolaryngology - head and neck surgery. The course, spanning four sections, allows participants the opportunity to explore current and cutting edge perspectives within each of the core specialty areas of otolaryngology.

The **Selected Recent Material** represents primary fundamentals, evidence-based research, and state of the art technologies in Rhinology and Allergic Disorders. The scientific literature included in this activity forms the basis of the assessment examination.

The number and length of articles selected are limited by editorial production schedules and copyright permission issues, and should not be considered an exhaustive compilation of knowledge rhinology and allergic disorders.

The **Additional Reference Material** is provided as an educational supplement to guide individual learning. This material is not included in the course examination and reprints are not provided.

Needs Assessment
AAO-HNSF's education activities are designed to improve healthcare provider competence through lifelong learning. The Foundation focuses its education activities on the needs of providers within the specialized scope of practice of otolaryngologists. Emphasis is placed on practice gaps and education needs identified within eight subspecialties. The *Home Study Course* selects content that addresses these gaps and needs within all subspecialties.

Target Audience
The primary audience for this activity is physicians and physicians-in-training who specialize in otolaryngology-head and neck surgery.

Outcomes Objectives

1. Discuss olfactory dysfunction and potential therapies to treat.
2. Consider treatment options for empty nose syndrome.
3. Articulate the role of computed tomography in disease staging and management of chronic rhinosinusitis.
4. Describe subtypes of chronic rhinosinusitis and new developments in the pathophysiology of the disease.
5. Discuss recent advancements in the understanding of the role of the innate immune system in chronic rhinosinusitis.
6. Implement most recent systemic, topical, and biologic therapies for chronic rhinosinusitis.
7. Review updates on advanced endoscopic surgical techniques including those involving the orbit and the skull base.
8. Explore concepts of the unified airway.

Medium Used
The Home Study Course is available as printed text. The activity includes a review of outcomes objectives, selected scientific literature, and a self-assessment examination.

Method of Physician Participation in the Learning Process
The physician learner will read the selected scientific literature, reflect on what they have read, and complete the self-assessment exam. After completing this section, participants should have a greater understanding of rhinology and allergic disorders as they affect the head and neck area, as well as useful information for clinical application.

Estimated time to complete this activity: 40.0 hours

Accreditation Statement
The American Academy of Otolaryngology—Head and Neck Surgery Foundation (AAO-HNSF) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Designation
The AAO-HNSF designates this enduring material for a maximum of 40.0 *AMA PRA Category 1 Credit(s)*™. Physicians should claim credit commensurate with the extent of their participation in the activity.

ALL PARTICIPANTS must achieve a post-test score of 70% or higher for a passing completions to be recorded and a transcript to be produced. Residents' results will be provided to the Training Program Director.

PHYSICIANS ONLY: In order to receive *Credit* for this activity **a post-test score of 70% or higher is required**. Two retest opportunities will automatically be available if a minimum of 70% is not achieved.

Disclosure
The American Academy of Otolaryngology Head and Neck Surgery/Foundation (AAO-HNS/F) supports fair and unbiased participation of our volunteers in Academy/Foundation activities. All individuals who may be in a position to control an activity's content must disclose all relevant financial relationships or disclose that no relevant financial relationships exist. All relevant financial relationships with commercial interests[1] that directly impact and/or might conflict with Academy/Foundation activities must be disclosed. Any real or potential conflicts of interest[2] must be identified, managed, and disclosed to the learners. In addition, disclosure must be made of presentations on drugs or devices, or uses of drugs or devices that have not been approved by the Food and Drug Administration. This policy is intended to openly identify any potential conflict so that participants in an activity are able to form their own judgments about the presentation.

[1] A "Commercial interest" is any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

[2] "Conflict of interest" is defined as any real or potential situation that has competing professional or personal interests that would make it difficult to be unbiased. Conflicts of interest occur when an individual has an opportunity to affect education content about products or services of a commercial interest with which they have a financial relationship. **A conflict of interest depends on the situation and not on the character of the individual.**

2016 SECTION 5 RHINOLOGY AND ALLERGIC DISORDERS FACULTY

***Co-Chairs:**

Christopher A. Church, MD, Professor, Department of Otolaryngology-Head and Neck Surgery, Loma Linda University, Loma Linda, California.
Disclosure: No relationships to disclose.

David Poetker, MD, Associate Professor, Division of Rhinology and Sinus Surgery; Residency Program Director, Department of Otolaryngology and Communication Sciences, Medical College of Wisconsin, Milwaukee, Wisconsin.
Disclosure: Consulting Fee: Medtronic.
Honoraria: Intersect ENT.
Research Funding: Intersect ENT.

Faculty:

Benjamin Saul Bleier, MD, Assistant Professor, Department of Otolaryngology-Head and Neck Surgery, Harvard Medical School, Boston, Massachusetts.
Disclosure: Stock/Stock Options: Interscope, INC.

Charles S. Ebert, Jr, MD, MPH, FACS, FARS, FAAOA, Associate Professor, Department of Otolaryngology-Head & Neck Surgery Division of Rhinology, Allergy, and Endoscopic Skull Base Surgery University of North Carolina- Chapel Hill, Chapel Hill, North Carolina.
Disclosure: Consultant: Acclarent.

Adam J. Folbe, MD, **MS,** Associate Professor, Director, Rhinology, Allergy and Endoscopic Skull Base Surgery, Department of Otolaryngology-Head and Neck surgery Department of Neurosurgery, Wayne State University School of Medicine, Detroit, Michigan.
Disclosure: Speaker, Intersect ENT.
Equity interest: Intrinsic medical imaging; Quintree Medical.

Devyani Lal, MD, Consultant, Department of Otolaryngology, Assistant Professor, Mayo Clinic College of Medicine, Mayo Clinic, Phoenix, Arizona.
Disclosure: No relationships to disclose.

Abtin Tabaee, MD, Associate Professor, Department of Otolaryngology
Weill Cornell Medical College- New York Presbyterian Hospital, New York, New York.
Disclosure: Consulting Fee: Spirox.

Planner(s):

Linda Lee, AAO─HNSF Education Program Manager	No relationships to disclose
Stephanie Wilson, Stephanie Wilson Consulting, LLC; Production Manager	No relationships to disclose
Richard V. Smith, MD, chair, AAO-HNSF Education Steering Committee	Expert Witness: various legal firms
Brent A. Senior, MD, chair, AAO-HNSF Rhinology and Allergy Education Committee	Disclosure: Consultant: Olympus Leadership Role: International Rhologic Society; International Forum Allergy and Rhinology; Resource Exchange International Royalty: Springer Stock/stock options: Mimosa; Spirox; Laurimed; ENTvantage

This 2016 Section 5 Home Study Course includes discussion of off-label uses of the following drugs and devices which has not been approved by the United States Food and Drug Administration:

Name of Drug(s) or Device(s)	**Nature of Off-label Discussion**
Theophylline methylpropyl paraben	Used to try to improve taste and smell
Oral corticosteroids	Use in chronic rhinosinusitis
Macrolide antibiotics	Use in chronic rhinosinusitis
Topical antibiotic washes	Use in acute bacterial rhinosinusitis
Topical budesonide washes	Use in chronic rhinosinusitis
Oral antibiotics	Use in acute bacterial rhinosinusitis

Disclaimer

The information contained in this activity represents the views of those who created it and does not necessarily represent the official view or recommendations of the American Academy of Otolaryngology – Head and Neck Surgery Foundation.

October 10, 2016: Suggested Section 5 Exam submission deadline; course closed August 4, 2017.

EVIDENCE BASED MEDICINE

The AAO-HNSF Education Advisory Committee approved the assignment of the appropriate level of evidence to support each clinical and/or scientific journal reference used to authenticate a continuing medical education activity. Noted at the end of each reference, the level of evidence is displayed in this format: **[EBM Level 3]**.

Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)	
Level 1	Randomized[1] controlled trials[2] or a systematic review[3] (meta-analysis[4]) of randomized controlled trials[5].
Level 2	Prospective (cohort[6] or outcomes) study[7] with an internal control group or a systematic review of prospective, controlled trials.
Level 3	Retrospective (case-control[8]) study[9] with an internal control group or a systematic review of retrospective, controlled trials.
Level 4	Case series[10] without an internal control group (retrospective reviews; uncontrolled cohort or outcome studies).
Level 5	Expert opinion without explicit critical appraisal, or recommendation based on physiology/bench research.

Two *additional ratings* to be used for articles that do not fall into the above scale. Articles that are informational only can be rated N/A , and articles that are a review of an article can be rated as Review. All definitions adapted from Glossary of Terms, Evidence Based Emergency Medicine at New York Academy of Medicine at www.ebem.org.

[1] A technique which gives every patient an equal chance of being assigned to any particular arm of a controlled clinical trial.
[2] Any study which compares two groups by virtue of different therapies or exposures fulfills this definition.
[3] A formal review of a focused clinical question based on a comprehensive search strategy and structure critical appraisal.
[4] A review of a focused clinical question following rigorous methodological criteria and employing statistical techniques to combine data from independently performed studies on that question.
[5] A controlled clinical trial in which the study groups are created through randomizations.
[6] This design follows a group of patients, called a "cohort", over time to determine general outcomes as well as outcomes of different subgroups.
[7] Any study done forward in time. This is particularly important in studies on therapy, prognosis or harm, where retrospective studies make hidden biases very likely.
[8] This might be considered a randomized controlled trial played backwards. People who get sick or have a bad outcome are identified and "matched" with people who did better. Then, the effects of the therapy or harmful exposure which might have been administered at the start of the trial are evaluated.
[9] Any study in which the outcomes have already occurred before the study has begun.
[10] This includes single case reports and published case series.

OUTLINE
2016 SECTION 5
RHINOLOGY AND ALLERGIC DISORDERS

I. Rhinology

A. Olfaction

B. Nasal Cavity
   1. Septum, turbinates, empty nose

C. Paranasal Sinuses
   1. Diagnosis
      a. Imaging
      b. Guidelines
      c. Subtypes of CRS
   2. Pathophysiology
      a. Pathophysiology of CRS
         i. Role of innate and adaptive immunity
         ii. Microbiome
      b. Pathophysiology of tumors
   3. Treatment of sinus disease
      a. Outcomes (medical vs. surgery)
      b. Surgery
         i. Perioperative management
         ii. Complications
      c. Medical
         i. Systemic (antibiotics, steroids, and biologics)
         ii. Topical (saline, steroids, and antibiotics)

D. Advanced Techniques
   1. Orbital applications
   2. Endoscopic skull base surgery

II. Allergic and Immunologic Disorders

A. Allergy
   1. Immunology
   2. New diagnostics
   3. Treatment of allergic rhinitis
      a. SLIT/SCIT
      b. Pharmaceuticals

B. Asthma
   1. Unified airway

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Selected Recent Materials - Reproduced in this Study Guide

2016 SECTION 5: RHINOLOGY AND ALLERGIC DISORDERS

3. Treatment of sinus disease
    a. Outcomes (medical vs. surgery)

Summary: The authors evaluated the course of progress in patients after maximal medical therapy for chronic rhinosinusitis. They found that 50% were symptomatic with persistent radiographic disease, 14% were asymptomatic with no radiographic disease, 24% were asymptomatic with persistent radiographic disease, and 12% were symptomatic but with no radiographic disease. Patients with objective evidence of persistent disease had a high rate of relapse of symptoms, despite initial improvement in symptoms following maximal medical therapy.

Summary: In this prospective cohort study, patients who met criteria for endoscopic sinus surgery were allowed to choose either surgery or continued medical management, and cardinal symptoms (nasal obstruction, thick nasal discharge, facial pain/pressure, and olfactory dysfunction) were followed for at least 6 months. Surgical management proved more effective in managing the cardinal symptoms in question, with the exception of olfactory dysfunction.

Summary: Hopkins et al evaluated the duration of sinus symptoms to determine the impact on outcomes following sinus surgery. They hypothesized that patients with longer histories of sinus symptoms would be less responsive to surgery than those undergoing surgery earlier in the disease process. Their data demonstrated greater durability of benefits in patients with symptoms for less than 12 months as compared to those with symptoms for 12 to 60 months and those with symptoms for longer than 60 months.

Summary: In this study, chronic rhinosinusitis patients were prospectively enrolled and followed for 12 months. After initial medical therapy, patients were allowed to choose either continued medical therapy or endoscopic sinus surgery followed by medical therapy. The Medical Outcomes Study Short Form-6D was used to generate health utility values at baseline, 6 months, and 12 months. Patients who elected continued medical management were found to have better baseline health utility as compared to patients who elected surgery. Patients electing surgery showed significant improvement in health utility, while those electing continue medical management did not.

b. Surgery
   i. Perioperative management

Summary: This article examines the changes in the microbial flora after medical and surgical therapies of chronic sinusitis. It demonstrates that surgery and postoperative antibiotic treatment did not reduce bacterial burden, but instead shifted the microbial consortia.

Summary: This article compares low-volume saline to high-volume, high-pressure saline irrigation after endoscopic sinus surgery. The authors demonstrate that both methods result in improvement of sinus symptomology, but the study is not powered enough to rule out a difference in the two modalities.

   ii. Complications

Summary: This article examines complication rates of endoscopic sinus surgery (ESS) in a very large cohort of patients. It demonstrates that in the modern era, complications after ESS are uncommon, but the risk of orbital injury may be higher after previous surgical intervention.

c. Medical
   i. Systemic (antibiotics, steroids, and biologics)

Summary: Oral corticosteroids are frequently used in the management of chronic rhinosinusitis. In this review, an overview of the existing data on the risks of oral corticosteroids is presented, along with associated medicolegal risks, and a discussion of the data supporting the use of these drugs in patients with chronic rhinosinusitis.

Summary: In this prospective study, patients with chronic rhinosinusitis with nasal polyps undergoing endoscopic sinus surgery were postoperatively randomized to receive clarithromycin 250 mg daily for 12 weeks, 24 weeks, or to not receive any clarithromycin. All patients were treated with mometasone nasal spray. At intervals for 24 weeks, patients were assessed with visual analog scale (VAS), SNOT-20, acoustic rhinometry, rhinomanometry, saccharin transit time, nasal endoscopy, Lund-Mackay CT score, and eosinophilic cationic protein in nasal secretions. All parameters except for VAS and acoustic rhinometry were significantly improved in the clarithromycin groups as compared to the control.

ii. Topical (saline, steroids, and antibiotics)

Smith KA, French G, Mechor B, Rudmik L. Safety of long-term high-volume sinonasal budesonide irrigations for chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2016; 6(3):228-232. EBM level 3.....152-156

Summary: Smith et al evaluated the impact of high-dose topical budesonide on the hypothalamic-pituitary-adrenal (HPA) axis in chronic rhinosinusitis patients. These patients used 2 mg of budesonide in saline irrigations daily for over 2 years. The authors evaluated serum AM cortisol levels. Over half of the patients had lower-than-normal serum cortisol levels prompting a cosyntropin stimulation test. None of the 19 patients tested were found to have abnormal cosyntropin tests. The authors concluded no HPA axis suppression occurs with the use of budesonide, even at high doses.

Soudry E, Wang J, Vaezeafshar R, et al. Safety analysis of long-term budesonide nasal irrigations in patients with chronic rhinosinusitis post endoscopic sinus surgery. *Int Forum Allergy Rhinol*. 2016; 6(6):568-572. EBM level 3.....157-161

Summary: Soudry et al evaluated budesonide irrigations in 48 patients with chronic rhinosinusitis. The mean duration of use was 22 months, using 0.5 mg of budesonide in 240 mL saline, once or twice daily. The authors used the cosyntropin stimulation test on all patients and found that 23% showed evidence of adrenal suppression. Interestingly, none of these patients exhibited any other signs or symptoms of adrenal suppression. Logistic regression suggested the highest risk for adrenal suppression occurs when the budesonide irrigations were used with other exogenous corticosteroids such as nasal steroid sprays or inhaled steroids.

D. Advanced Techniques

1. Orbital applications

Bleier BS, Castelnuovo P, Battaglia P, et al. Endoscopic endonasal orbital cavernous hemangioma resection: global experience in techniques and outcomes. *Int Forum Allergy Rhinol*. 2016; 6(2):156-161. EBM level 4.....162-167

Summary: The purpose of this study was to combine the experience of multiple international centers to create a composite of the global experience on the endoscopic management of a single type of tumor, the orbital cavernous hemangioma. Extraconal lesions were managed similarly; however, greater variability was evident for intraconal lesions. These included the laterality and number of hands in the approach, methods of medial rectus retraction, and the need for reconstruction.

2. Endoscopic skull base surgery

Dixon BJ, Daly MJ, Chan H, et al. Augmented real-time navigation with critical structure proximity alerts for endoscopic skull base surgery. *Laryngoscope*. 2014; 124(4):853-859. EBM level NA.....168-174

Summary: Dixon et al present a cadaver study of a novel image guidance technology with proximity alerts.

Harvey RJ, Parmar P, Sacks R, Zanation AM. Endoscopic skull base reconstruction of large dural defects: a systematic review of published evidence. *Laryngoscope*. 2012; 122(2):452-459. EBM level 3.....175-182

Summary: Harvey et al present a systematic review of retrospective studies supporting overall success of skull base repair and the role of vascularized tissue.

II. Allergic and Immunologic Disorders

A. Allergy

1. Immunology
2. New diagnostics
3. Treatment of allergic rhinitis

a. SLIT/SCIT

Lin SY, Erekosima N, Kim JM, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *JAMA*. 2013; 309(12):1278-1288. EBM level 1a.....183-193

Summary: Sublingual immunotherapy (SLIT) provides a moderate-grade level of evidence to support effectiveness for the treatment of allergic rhinitis and asthma when combined. In the asthma group, the evidence was high in support of SLIT for improving symptoms. In the rhinitis group, the evidence was rated moderate in support of SLIT for rhinitis symptoms.

b. Pharmaceuticals

Li JT, Bernstein DI, Calderon MA, et al. Sublingual grass and ragweed immunotherapy: clinical considerations-a PRACTALL consensus report. *J Allergy Clin Immunol*. 2016; 137(2):369-376. EBM level 1a.....194-201

Summary: Sublingual allergen immunotherapy has been widely used and studied throughout Europe. Sublingual grass and ragweed immunotherapy tablets, used for allergic rhinitis, have proven efficacy studied through large multi-institutional trials. Sublingual immunotherapy (SLIT) is indicated for IgE atopy confirmed by positive skin test or *in vitro* testing. Most SLIT-induced local reactions occur soon after the beginning of treatment and cease within 2 weeks without intervention. SLIT is extremely safe. Based on the European experience, no SLIT related fatalities have occurred.

B. Asthma

1. Unified airway

Mener DJ, Lin SY. Improvement and prevention of asthma with concomitant treatment of allergic rhinitis and allergen-specific therapy. *Int Forum Allergy Rhinol*. 2015; 5 Suppl 1:S45-S50. EBM level 4.....202-207

Summary: This article is an expert review on the impact of management of allergic rhinitis on asthma treatment and prevention.

Stachler RJ. Comorbidities of asthma and the unified airway. *Int Forum Allergy Rhinol*. 2015; 5 Suppl 1:S17-S22. EBM level 4.....208-213

Summary: This article is a review of the current literature, studying asthma as a comorbidity of respiratory diseases such as allergic rhinitis.

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ORIGINAL ARTICLE

Intranasal Theophylline Treatment of Hyposmia and Hypogeusia

A Pilot Study

Robert I. Henkin, MD, PhD; Michael Schultz, RPh; Laura Minnick-Poppe, PharmD

Objective: To determine whether intranasal theophylline methylpropyl paraben can correct hyposmia and hypogeusia.

Design: We performed an open-label pilot study in patients with hyposmia and hypogeusia under the following 3 conditions: (1) before treatment, (2) after oral theophylline anhydrous treatment, and (3) after intranasal theophylline treatment. Under each condition, we performed subjective evaluations of taste and smell functions, quantitative measurements of taste (gustometry) and smell (olfactometry), and measurements of serum theophylline level and body weight.

Setting: The Taste and Smell Clinic in Washington, DC.

Patients: Ten patients with hyposmia and hypogeusia clinically related to the effects of viral illness, allergic rhinitis, traumatic brain injury, congenital hyposmia, and other chronic disease processes were selected.

Interventions: Oral theophylline anhydrous, 200 to 800 mg/d for 2 to 12 months, was administered to each patient. This treatment was discontinued for 3 weeks to 4 months when intranasal theophylline methylpropyl paraben, 20 µg/d in each naris, was administered for 4 weeks.

Main Outcome Measures: At termination of each condition, taste and smell function was determined subjectively, by means of gustometry and olfactometry, with measurement of serum theophylline levels and body weight.

Results: Oral theophylline treatment improved taste and smell acuity in 6 patients after 2 to 12 months of treatment. Intranasal theophylline treatment improved taste and smell acuity in 8 patients after 4 weeks, with improvement greater than after oral administration. No adverse effects accompanied intranasal drug use. Body weight increased with each treatment but was greater after intranasal than after oral administration.

Conclusions: Intranasal theophylline treatment is safer and more effective in improving hyposmia and hypogeusia than oral theophylline anhydrous treatment.

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Loss of smell (hyposmia) and taste (hypogeusia) are common symptoms that affect many thousands of patients in the United States, as reported by several investigators.[1-4] Effective treatment for these symptoms has been demonstrated only recently and has not been formally established.

Before effective treatment to correct loss of smell and taste can be established, a biochemical basis for the cause of these symptoms is necessary. To accomplish this, we determined that these symptoms are commonly caused by decreased secretion of several growth factors in the saliva and nasal mucus. The growth factors act on stem cells in taste buds and olfactory epithelial cells to generate the elegant repertoire of cellular components in these sensory organs.[5-11] Growth factor stimulation of these sensory organs is thought to maintain normal taste and smell function.[5-11] If these growth factors were diminished by any of several diseases and pathological conditions, then hyposmia and hypogeusia occur.[5,12,13] These conditions and diseases include trace metal deficiencies[14]; vitamin deficiencies[15,16]; liver disease[17]; diabetes mellitus[18]; other metabolic,[12,13] otolaryngological,[19,20] and neurodegenerative disorders, including multiple sclerosis,[21-23] Parkinson disease,[24-28] and Alzheimer disease[29-32]; and other neurological disorders.[33] Effective treatment to increase secretion of these growth factors is therefore

Author Affiliations: The Taste and Smell Clinic, Center for Molecular Nutrition and Sensory Disorders, Washington, DC (Dr Henkin); Foundation Care, Earth City, Missouri (Mr Schultz); and St Louis College of Pharmacy, St Louis, Missouri (Dr Minnick-Poppe).

necessary to improve hypogeusia and hyposmia[5,12,13] and return taste and smell function to normal as demonstrated by several previous studies.[5,12,13]

To understand more about these processes, a comprehensive study of many patients with loss of smell and taste determined that levels of the salivary[34,35] and nasal mucus[36,37] growth factors cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) were lower than in healthy subjects and were responsible for the onset of hyposmia and hypogeusia in many of these patients.[38,39] Indeed, as hyposmia increased in severity, levels of these salivary[35] and nasal mucus[37] growth factors decreased in a consistent manner.

To increase salivary and nasal mucus cAMP and cGMP levels and thereby correct hypogeusia and hyposmia, we hypothesized that treatment with a phosphodiesterase inhibitor would be useful. To test this hypothesis, a previous study from our institution administered oral theophylline anhydrous to 312 patients with hyposmia and hypogeusia in an open-label controlled clinical trial.[40] Results of this study demonstrated that oral theophylline treatment successfully corrected hyposmia in more than 50% of these patients.[40] Subsequent investigators have used other oral phosphodiesterase inhibitors to correct hyposmia.[41] An open-label study also demonstrated that, as nasal mucus cAMP and cGMP levels increased, hyposmia was corrected,[42] whereas in patients in whom these moieties did not increase, hyposmia was not corrected. These results suggested that some patients may be resistant to treatment with oral theophylline.[42]

However, successful treatment with oral theophylline that increased nasal mucus levels of cAMP and cGMP required increased theophylline doses,[40] sometimes prolonged treatment duration,[40] and endurance of adverse effects, including restlessness, gastrointestinal tract discomfort, sleep difficulties, tachycardia, and other unwanted symptoms.[40,43,44] Theophylline treatment also required regular determinations of blood theophylline levels to ensure adequate drug absorption and lack of toxic effects.[40] These efforts limited use of this orally administered drug.

Because of these adverse effects, we wished to learn more about the pharmacology of theophylline administration. After treatment with oral theophylline, the drug was found in blood, nasal mucus, and saliva in a dose-dependent manner.[45] These results were consistent with improvement in smell function as demonstrated in patients with hyposmia in the prior clinical trial.[40] Results of these studies[40,42] and efforts to improve therapeutic efficacy and reduce adverse effects of oral theophylline administration made it logical to administer the drug intranasally. In this manner, the drug could affect olfactory receptors more directly without causing the systemic adverse effects associated with oral therapy.

To accomplish this, with assistance of an established medical device company, an intranasal delivery device was developed. With assistance of an established pharmaceutical company, the drug was packaged for sterile, intranasal delivery. Using this device, an open-label, single-source, controlled pilot study in 10 patients with hyposmia and hypogeusia and with levels of parotid saliva[35,36] and nasal mucus[37,38] cAMP and cGMP below the reference range was performed to determine safety and to compare smell and taste responses after intranasal theophylline treatment, with patient responses before any treatment and after oral theophylline treatment.

METHODS

PATIENTS

We selected 10 patients with hyposmia and hypogeusia from the 312 patients who participated in the prior open-label controlled clinical trial at The Taste and Smell Clinic[40] for this pilot study. Each patient had undergone previous evaluation before any drug treatment,[12,13] followed by treatment with oral theophylline. These patients had hyposmia and hypogeusia and exhibited levels of cAMP and cGMP lower than their respective reference ranges in the saliva[35,36] and nasal mucus[37,38] before theophylline treatment. These 10 patients were selected from the group undergoing previous evaluation and treatment for the intranasal trial because (1) their response to oral theophylline was subjectively submaximal; (2) they developed adverse effects after attempts to increase the drug dose to obtain a more maximal clinical response, thus limiting the administered drug dose; and (3) they resided in an area in close proximity to The Clinic, which made their frequent return visits to The Clinic more practical for any additional clinical trial.

These 10 patients included 7 men, aged 37 to 77 (mean [SEM] age, 64 [6]) years, and 3 women, aged 47 to 77 (62 [11]) years. Patients had 1 of the following 5 different clinical causes of sensory dysfunction: allergic rhinitis[46] (n=3), post–influenzalike hyposmia and hypogeusia[47] (n=3), head injury[48] (n=2), congenital hyposmia[49] (n=1), and other disorders[12,13] (n=1).

Patients served as their own control throughout each condition of this study. The conditions included no treatment (before entry into the oral theophylline study), oral theophylline treatment, and intranasal theophylline treatment.

PROCEDURES

Subjective changes in smell and taste function under each study condition were measured by questionnaire before measurements of smell or taste function.[40,50] Responses were graded on a scale from 0 to 100, with 0 reflecting no subjective response in overall sensory function; 100, return to normal sensory function; and values between 0 and 100 intermediate responses.[40,50] Overall sensory function was defined as the ability to smell all odors and identify all tastants, although response intensity varied.[40,50]

Smell and taste functions under each study condition were measured by standardized psychophysical sensory testing techniques.[40,50] Measurements included determination of detection thresholds (DTs), recognition thresholds (RTs), magnitude estimation (ME), and hedonic response (HR) for 4 odors (ie, pyridine [dead fish], nitrobenzene [bitter almond], thiophene [petroleum], and amyl acetate [banana oil]) (olfactometry) and for 4 tastants (ie, sodium chloride [salt], sucrose [sweet], hydrochloride [sour], and urea [bitter]) (gustometry). These techniques have been previously described[40] with olfactometry confirmed in a prior controlled double-blind clinical trial.[51] Each measurement was performed independent of any prior knowledge of response.

Serum theophylline levels were measured by fluorescence polarization[40] at each treatment condition. Body weight was measured with a calibrated clinical scale during each study condition and reported at the final measurement in each study condition.

STUDY PROTOCOL

The patients each underwent initial clinical evaluation at The Clinic to establish the cause, degree, and character of hyposmia and hypogeusia[40] exhibited. Measurements in blood, urine, erythrocytes, saliva, and nasal mucus determined before their entry into the open trial of oral theophylline established the biochemical cause of their hyposmia and hypogeusia to be related to their levels of saliva and nasal mucus cAMP and cGMP being lower than the reference range.[35-38] These 10 patients were then selected for this study on the basis of the laboratory and clinical criteria noted previously.

The 10 patients in this intranasal pilot study entered into the previous oral theophylline study according to a protocol approved by the institutional review board of the Georgetown University Medical Center. In this prior trial, oral theophylline methylpropyl paraben was administered daily in 2 divided doses (at breakfast and lunch) of 200, 400, 600, or 800 mg for 2 to 12 months of treatment.[40] Treatment was divided into 2- to 4-month periods, at which time patients returned to The Clinic for measurements of subjective sensory responses, olfactometry, gustometry, serum theophylline level, and body weight. If oral theophylline treatment failed to correct hyposmia at a given dose, the theophylline methylpropyl paraben dose was increased by 200 mg, and the patient underwent reevaluation at 2- to 4-month intervals to a dose of 800 mg.[40] As noted previously, study patients did not obtain a maximal clinical response to oral theophylline[40] or, while taking oral theophylline at a given dose, demonstrated some clinical improvement but experienced significant adverse effects that limited increasing the oral dose as necessary to achieve maximum clinical benefit. In the 10 patients selected for the intranasal pilot study, oral theophylline treatment was discontinued 3 weeks to 4 months before initiation of the intranasal drug trial. At that time, the mean (SEM) serum theophylline level was unmeasurable in any patient (0 [0] mg/L).

A pilot study of intranasal theophylline treatment was then initiated among these 10 patients. This trial was an investigator-initiated phase 1, open-label, single-source, controlled pilot study. Intranasal drug therapy reflected a compassionate trial of a potentially more useful therapeutic method to improve hyposmia (and hypogeusia) than oral theophylline. Before the intranasal trial, risks and benefits were explained and the patients signed an informed consent.

The intranasal administration device was a calibrated 1-mL syringe fitted with a nozzle that fit comfortably into the anterior naris (Wolfe Tory Medical, Inc) and loaded under sterile conditions with 20 µg of theophylline methylpropyl paraben in a 0.4-mL saline solution (Foundation Care). Patients were instructed to direct the spray superiorly into the nasal cavity but not posteriorly into the nasopharynx. This technique was practiced before study initiation with sterile saline. Each patient used the technique easily and as demonstrated before drug administration.

Each patient delivered the theophylline dose in each naris once daily throughout the study. Patients underwent evaluation 1, 2, and 4 weeks during drug use with the same measurements used for the oral study.[40]

Values for the oral trial were taken from the last measurements made before discontinuation of oral drug treatment and before initiation of the intranasal trial. This period varied from 2 to 12 months after oral treatment initiation and reflected the maximal improvement in sensory function each patient experienced. Values for the intranasal pilot study were taken from measurements obtained after completion of 4 weeks of intranasal treatment.

The mean and standard error of the mean for all values obtained at each study condition were compared. Differences were considered significant if $P < .05$ by the unpaired t test. Paired comparison tests were also used with differences considered significant if $P < .05$ by the t test.

RESULTS

With oral theophylline administration, hypogeusia improved after 2 to 12 months of treatment, but hypogeusia improved further within 1 to 4 weeks of intranasal treatment (**Table 1**). Results of gustometry after oral and intranasal theophylline are shown in Table 1. Before treatment, DTs for sucrose, hydrochloride, and urea (less sensitive) and RTs for all tastants were elevated (less sensitive) above the reference levels. Magnitude estimations for all tastants were lower (less sensitive) than the reference level. Hedonic responses for sodium chloride, hydrochloride, and urea were lower (less unpleasant) than the reference levels. After oral theophylline treatment, DTs for sucrose and hydrochloride and RTs for sodium chloride, hydrochloride, and urea decreased (more sensitive). Magnitude estimations for all tastants increased (more sensitive) and HR for hydrochloride and urea increased (more unpleasant) as previously reported.[40] After intranasal theophylline treatment, DTs and RTs for all tastants were lower (more sensitive) than before treatment or after oral theophylline treatment. Magnitude estimations for all tastants after intranasal theophylline treatment were higher (more intense) than before any treatment or after oral theophylline treatment. Hedonic responses for sodium chloride, hydrochloride, and urea were more negative (more unpleasant), whereas HRs for sucrose were more positive (more pleasant) than before any treatment or after oral theophylline treatment.

After oral theophylline treatment, hyposmia improved with 2 to 12 months of treatment but improved more with intranasal theophylline after 1 to 4 weeks of treatment (**Table 2**). Olfactometry comparisons of oral and intranasal theophylline treatment are shown in Table 2. Before treatment, compared with reference levels, DTs and RTs for all odorants were elevated (less sensitive); MEs for all odorants were decreased (less sensitive); HRs for pyridine and thiophene were decreased (less unpleasant); and HRs for nitrobenzene and amyl acetate were decreased (less pleasant). After oral theophylline treatment, DTs and RTs for all odorants were decreased (more sensitive), MEs for all odorants were increased (more sensitive), and HRs for all odorants increased (for pyridine and thiophene, more unpleasant; for nitrobenzene and amyl acetate, more pleasant) as previously reported.[40] After intranasal theophylline treatment, DTs and RTs for each odor were lower (more sensitive) than before treatment or after oral theophylline treatment. Magnitude estimations for each odor were higher (more intense) than before treatment or after oral theophylline treatment. Hedonic responses to thiophene were more negative (more unpleasant) and to nitrobenzene were more positive (more pleasant) than before treatment or after oral theophylline treatment.

Smell and taste acuity were reported to be subjectively improved with oral theophylline treatment, but greater improvement was reported after 4 weeks of in-

Table 1. Gustometry in Patients With Hyposmia and Hypogeusia Before and After Treatment With Oral and Intranasal Theophylline

	Gustometry, Mean (SEM)															
	Sodium Chloride				Sucrose				Hydrochloride				Urea			
	BU, mmol/L		%		BU, mmol/L		%		BU, mmol/L		%		BU, mmol/L		%	
Condition	DT	RT	ME	HR	DT	RT	ME	HR	DT	RT	ME	HR	DT	RT	ME	HR
Before treatment	3.3 (0.2)	3.6 (0.3)	46 (12)	–38 (10)	3.6 (0.3)	3.8 (0.3)	38 (10)	28 (10)	4.2 (0.4)	5.2 (0.7)	38 (9)[a]	–28 (7)	5.1 (0.3)[b]	5.4 (0.5)	32 (8)[c]	–27 (8)[c]
After oral theophylline andhydrous treatment[d]	3.3 (0.2)	3.3 (0.2)	48 (9)	–35 (10)	3.5 (0.2)	4.0 (1.0)	40 (10)	28 (9)	3.5 (0.2)	3.5 (0.2)[e]	44 (10)	–32 (9)	4.3 (0.2)[e]	4.6 (0.4)	34 (11)[c]	–33 (11)[a]
After intranasal theophylline methylpropyl paraben treatment[f]	2.6 (0.4)	3.2 (0.3)	57 (11)	–48 (11)	2.2 (0.3)[g,h]	2.4 (0.3)[g]	50 (12)	34 (12)	2.1 (0.4)[h,i,j]	2.6 (0.4)[g,h]	52 (10)	–37 (10)	3.2 (0.5)[i,k]	3.7 (0.6)[g]	42 (9)[j]	–37 (10)[a]
Reference level	3.3 (0.3)	3.4 (0.2)	68 (4)	–51 (4)	3.3 (0.2)	3.4 (0.2)	60 (4)	26 (3)	3.4 (0.4)	3.5 (0.4)	66 (4)	–59 (3)	3.6 (0.4)	3.7 (0.4)	68 (4)	–66 (3)

Abbreviations: BU, bottle units[13,40]; DT, detection threshold; HR, arithmetic mean hedonic response; ME, mean magnitude estimation response; RT, recognition threshold.

[a] $P < .01$ compared with reference levels.
[b] $P < .005$ compared with reference levels.
[c] $P < .001$ compared with reference levels.
[d] Indicates maximal improvement after oral theophylline treatment.
[e] $P < .05$ compared with pretreatment.
[f] Indicates improvement after 4 weeks of intranasal theophylline treatment.
[g] $P < .005$ compared with before treatment.
[h] $P < .01$ compared with oral theophylline treatment.
[i] $P < .001$ compared with before treatment.
[j] $P < .05$ compared with reference levels.
[k] $P < .05$ compared with oral theophylline treatment.

tranasal theophylline treatment. After oral theophylline treatment, 6 patients reported overall increased taste and smell function, whereas 4 reported no improvement. After intranasal theophylline treatment, 8 of the 10 patients reported overall improvement in taste and smell functions, whereas 2 reported no improvement. This response frequency is higher than that previously reported among patients with hyposmia and treated with oral theophylline, in which slightly more than 50% reported improvement.[40]

Taste and smell acuity were measured as subjectively improved after oral theophylline treatment, but this improvement was measured as increased after 4 weeks of intranasal theophylline treatment (**Table 3**). After intranasal theophylline treatment, a 2-fold improvement was measured for taste and smell functions compared with oral treatment. Paired *t* test results showed that responses after intranasal theophylline were significantly greater than after oral theophylline treatment (taste, $P < .05$; smell, $P < .025$).

Body weight increased from pretreatment levels after oral theophylline treatment, but weight increased more after intranasal theophylline treatment. After oral theophylline treatment, mean (SEM) weight increased by 1.5 (0.4) kg from pretreatment values, whereas after intranasal theophylline treatment, weight increased by 2.5 (0.5) kg from pretreatment values. Patients related this change to increased food flavor obtained by improved smell function after intranasal theophylline treatment, which increased appetite and food enjoyment, resulting in subsequent weight gain. These changes were measured in each patient group despite no sensory improvement in 4 patients after oral theophylline treatment and none in 2 after intranasal theophylline treatment.

During oral theophylline treatment, the mean (SEM) serum theophylline level at the time of maximum improvement for these 10 patients was 6.4 (2.0) mg/L (to convert to micromoles per liter, multiply by 5.55). During intranasal theophylline treatment, the mean serum theophylline level was 0.0 (0.0). Discontinuation of intranasal theophylline treatment resulted in loss of smell and taste function within 1 week in 2 patients and after 6 weeks in 2. Four patients reported some persistence of improvement after 10 weeks.

COMMENT

Results of this open-label, single-source, controlled pilot trial demonstrate that oral theophylline effectively improved hyposmia, as previously reported.[40,42] The earliest this improvement was measured was after 2 months of treatment, but maximal improvement varied from 4 to 12 months. These results also demonstrate that oral theophylline was effective in improving hypogeusia in the same time frame as improvement in smell acuity.

In addition, intranasal theophylline was shown to be safe and more effective than oral theophylline in correcting hyposmia and hypogeusia. This improvement was measured as early as 1 week after starting treatment, but maximal improvement varied from 1 to 4 weeks.

Table 2. Olfactometry in Patients With Hyposmia and Hypogeusia Before and After Treatment With Oral and Intranasal Theophylline

	Olfactometry, Mean (SEM)															
	Pyridine				Nitrobenzene				Thiophene				Amyl Acetate			
	BU, mmol/L		%		BU, mmol/L		%		BU, mmol/L		%		BU, mmol/L		%	
Condition	DT	RT	ME	HR	DT	RT	ME	HR	DT	RT	ME	HR	DT	RT	ME	HR
Before treatment	8.9 (0.7)[a]	9.3 (0.8)[b]	16 (6)[a]	−14 (5)	9.1 (0.7)[a]	10.1 (0.6)[c]	6 (2)[a]	3 (2)	9.4 (0.7)[a]	10.2 (0.4)[a]	10 (2)[a]	−3 (2)[b]	9.5 (0.7)[a]	11.0 (0.5)[a]	0.6 (0.3)[a]	0 (0)
After oral theophylline anhydrous treatment[d]	6.3 (0.6)[a,e]	6.3 (0.6)[f]	25 (8)[a]	−24 (9)	5.9 (1.0)[g]	6.5 (0.9)[e]	23 (9)[c]	20 (10)	6.0 (0.8)[c,f]	6.3 (1.1)[f,h]	20 (9)[a]	−17 (8)	5.4 (0.9)[i,j]	6.1 (0.9)[h,k]	21 (8)[b,g]	20 (9)[e]
After intranasal theophylline methylpropyl paraben treatment[l]	5.9 (0.8)[a,e]	6.2 (0.9)[g]	27 (7)[a]	−22 (7)	4.2 (1.0)[i]	5.1 (1.1)[k]	24 (7)[c,g]	21 (7)[g,j]	4.7 (1.2)[i]	5.8 (1.1)[i,j]	23 (7)[a]	−18 (9)	3.3 (0.9)[k]	3.3 (0.9)[k,m]	22 (7)[b,i]	12 (8)
Reference level	3.7 (0.3)	6.0 (0.7)	64 (3)	−20 (2)	3.6 (0.4)	6.0 (0.6)	51 (4)	4 (1)	3.2 (0.6)	3.3 (0.5)	66 (4)	−13 (2)	3.1 (0.5)	3.3 (0.6)	51 (4)	1 (1)

Abbreviations: See Table 1.
[a] $P < .001$ compared with reference level.
[b] $P < .005$ compared with reference level.
[c] $P < .01$ compared with reference level.
[d] Indicates maximal improvement after oral theophylline treatment.
[e] $P < .05$ compared with before treatment.
[f] $P < .01$ compared with before treatment.
[g] $P < .02$ compared with before treatment.
[h] $P < .02$ compared with reference level.
[i] $P < .005$ compared with before treatment.
[j] $P < .05$ compared with reference level.
[k] $P < .001$ compared with before treatment.
[l] Indicates improvement after 4 weeks of intranasal theophylline treatment.
[m] $P < .05$ compared with oral theophylline treatment.

Table 3. Comparison of Quantitative Subjective Changes After Oral and Intranasal Theophylline Treatment in 10 Patients With Hyposmia and Hypogeusia

	Change, %			
	Taste		Smell	
Condition	Mean (SEM)	Range	Mean (SEM)	Range
Oral theophylline anhydrous treatment[a]	+10.5 (5.6)	0-50	+14.0 (6.3)	0-60
Intranasal theophylline methylpropyl paraben treatment[b]	+22.0 (7.8)[c]	0-80	+28.0 (8.6)[d]	0-90

[a] Indicates maximal improvement after oral theophylline treatment.
[b] Indicates improvement after 4 weeks of intranasal theophylline treatment.
[c] $P < .05$ compared with oral theophylline response.
[d] $P < .025$ compared with oral theophylline response.

Mechanisms by which intranasal theophylline was more effective than oral theophylline are not clearly defined. Intranasal drug delivery avoids the first-pass hepatic effect of an oral drug, bypassing initial cytochrome P450 metabolism and decreasing metabolism of the orally administered drug, thereby allowing for lower intranasally administered drug doses to be clinically efficacious. This lowering of the drug dose from a range of 200 to 800 mg orally to 40 µg intranasally was sufficient and specific enough to also avoid production of systemic adverse effects.[52] This delivery mechanism may also avoid development of drug resistance that has occurred with oral theophylline.[42] In addition, because more drug presumably contacts the olfactory epithelium with intranasal than with oral theophylline, direct nasal instillation may activate more olfactory receptors than does oral administration.

However, additional actions of intranasal theophylline might enhance its therapeutic efficacy. Theophylline has been shown to inhibit symptoms of allergic rhinitis,[53,54] which affected 3 patients in the intranasal trial. Many of the diseases and conditions that caused hyposmia and hypogeusia have an associated inflammatory component that may be suppressed by the anti-inflammatory effects of a phosphodiesterase inhibitor.[54,55] In addition, drugs introduced intranasally can be delivered into the brain (1) directly by absorption through the cribriform plate along the olfactory bulb,[56-60] (2) indi rectly by absorption through blood-brain barrier receptors,[61-65] or (3) through combinations of both methods. Although stud-

ies of theophylline absorption from nasal mucus into the brain have not been performed, studies of insulin,[58,66] nerve growth factor,[58] several neurotransmitters,[67,68] and other moieties[57,60,69,70] indicate uptake of these intranasally introduced moieties into the brain.[71]

Whatever its mechanism of action, intranasal theophylline in this pilot study corrected hyposmia and hypogeusia relatively rapidly in 8 of 10 patients with several clinical diagnoses. The 2 patients who did not experience improvement were men, one with allergic rhinitis and the other with the effects of viral illness.

These results are consistent with prior studies in which several intranasal drugs were more effective than oral drugs. Inhaled adrenocorticosteroids were more effective with fewer adverse effects for asthma treatment than oral adrenocorticosteroids,[72] and inhaled adrenocorticosteroids were more efficacious in asthma treatment than oral prednisolone acetate.[73] Intranasal zolmitriptan achieved faster control of migraine headaches with fewer effects than the orally administered drug.[74] Nasal administration of chicken type II collagen suppressed adjuvant arthritis in rats more effectively than oral administration.[75]

However, intranasally administered drugs have also been reported to be only as effective as these same drugs given orally. Intranasal estradiol valerate was as effective as oral administration in alleviating postmenopausal symptoms but produced less frequent mastalgia and uterine bleeding.[76] Intranasal desmopressin acetate was as effective for nocturnal enuresis as the oral drug but at a dose one-tenth that of the oral drug.[77] Intranasal desmopressin is the preferred route for management of central diabetes insipidus.[78]

At present, no generally clinically accepted method of treatment for hyposmia and hypogeusia exists. This pilot study suggests a simple, direct, and safe method to improve hyposmia and hypogeusia in a varied group of patients with both dysfunctions. However, this study has limitations. It was designed primarily to determine the safety of intranasal theophylline administration. Although results of its use compared with no treatment and treatment with oral theophylline demonstrate significant sensory improvement, results have to be considered with this intent in mind. Despite these detailed subjective, gustometric, and olfactometric improvements, this study was performed in only 10 subjects without placebo controls. These results, although useful, require repeated performance in larger numbers of patients with placebo controls during a longer treatment period to confirm efficacy. However, we systematically studied this group of 10 patients who served as their own controls throughout each study condition, and hyposmia and hypogeusia improved and weight increased after each treatment condition. In conclusion, intranasal theophylline treatment was safe and effective in improving hyposmia and hypogeusia and was more efficacious than oral theophylline treatment.

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Correspondence: Robert I. Henkin, MD, PhD, The Taste and Smell Clinic, Center for Molecular Nutrition and Sensory Disorders, 5125 MacArthur Blvd NW, Ste 20, Washington, DC 20016 (doc@tasteandsmell.com).

Author Contributions: Drs Henkin, Schultz, and Minnick-Poppe had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Henkin. *Acquisition of data:* Henkin. *Analysis and interpretation of data:* Henkin, Schultz, and Minnick-Poppe. *Drafting of the manuscript:* Henkin. *Critical revision of the manuscript for important intellectual content:* Henkin, Schultz, and Minnick-Poppe. *Statistical analysis:* Henkin. *Obtained funding:* Henkin. *Administrative, technical, and material support:* Henkin. *Study supervision:* Henkin.
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Contemporary Review

The Clinical Efficacy of Surgical Interventions for Empty Nose Syndrome: A Systematic Review

Samuel C. Leong, MPhil, FRCSEd (ORL-HNS)

Objective: To evaluate the outcomes of surgical intervention for empty nose syndrome (ENS).

Data Source: Cochrane Collaboration database, U.S National Institutes of Health database (ClinicalTrials), U.S National Library of Medicine (PubMed).

Review Methods: Structured search using medical subject-heading terms: nose, turbinate, surgery, atrophic rhinitis, and empty nose syndrome.

Results: A total of 128 patients were collated from eight studies with an age range of 18 to 64 years. Most patients had been suffering with ENS for many years, up to 29.7 years. The most common surgical technique involved a transnasal approach with implant material secured within a submucosal pocket. Common implant material used in the studies included biosynthetic, and autologous cartilage. The weighted mean preoperative Sino-Nasal Outcome Test (SNOT)−20 and SNOT-25 scores were 48.3 and 65.9, respectively. At latest follow-up, these scores improved significantly to 24.4 and 33.3, respectively. Although all SNOT subdomains improved following surgery, the highest improvement was observed in ENS symptoms and psychological issues. SNOT scores improved by 3 months postsurgery and this trend continued over time, although available data was limited to only 12 months follow-up. Nevertheless, 10 patients had less than 10 points improvement, including three patients who had no change in SNOT scores. Extrusion of the implant occurred in six cases, and one developed chronic rhinosinusitis.

Conclusion: Surgical intervention for ENS appears to result in clinical improvement, although not all patients derived benefit. Long-term follow-up should be considered utilizing using both subjective (SNOT-25) and objective (rhinomanometry) measures of clinical outcome.

Key Words: Atrophic rhinitis, turbinate, paranasal sinus, surgery, empty nose syndrome.

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INTRODUCTION

Empty nose syndrome (ENS) is a poorly recognized but undoubtedly devastating clinical entity. In their 2001 article on atrophic rhinitis, Moore and Kern[1] stated in reference to those suffering from this affliction that, "the absence of normal nasal structures is universal in these patients, and the symptoms of atrophic rhinitis coupled with a cavernous nasal airway lacking identifiable turbinate tissue has been termed the empty nose syndrome." Both clinical cases presented Kern at the American Rhinologic Society meeting committed suicide as a result of their disabling sinonasal symptoms.[2] Similar sentiments against radical turbinate surgery were echoed by Huizing and De Groot, who stated that "a wide nasal cavity syndrome due to reduction of the inferior turbinate (and/or middle turbinate) is still frequently seen. In our opinion, it is a 'nasal crime'."[3]

For many years, ENS was thought to be a form of secondary atrophic rhinitis.[4] The existence of ENS has been hotly debated, and it remains to be answered why some patients develop ENS following turbinate surgery. The inability to diagnose ENS objectively has fuelled further speculation that it could be either a form of nasal neuropathy or rhinitis hystericus.[5] After years of careful assessment and follow-up of ENS patients, Houser proposed that ENS should be redefined as a symptom complex that includes a paradoxical sense of obstruction in spite of partial or complete turbinate resection.[6–8]

The management of ENS is challenging and the evidence base for most treatment modalities remains low.[9] Recommended conservative management does not differ significantly from atrophic rhinitis, which includes nasal lavage, lubricant drops, and topical corticosteroids.[10] Surgical intervention for ENS aims to increase nasal airway resistance by narrowing the nasal valve region or reconstructing a pseudoturbinate. The purpose of this review was to evaluate the efficacy of surgical treatments for ENS. It is envisaged that the results would provide

From the Division of Rhinology and Anterior Skull Base Surgery, Department of Otorhinolaryngology–Head and Neck Surgery, University Hospital Aintree, Liverpool, United Kingdom

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Send correspondence to Mr. Samuel C. Leong, MPhil FRCSEd (ORL-HNS), Department of Otorhinolaryngology–Head and Neck Surgery, University Hospital Aintree, Liverpool L9 7AL, United Kingdom. E-mail: lcheel@doctors.org.uk

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clinicians (and ultimately patients) with a realistic viewpoint on contemporary surgical outcomes and also recommend a minimum dataset for reporting of outcomes.

METHODS

A structured search of the Cochrane Collaboration database, U.S National Institutes of Health database (ClinicalTrials), and U.S National Library of Medicine (PubMed) was undertaken using a combination of medical subject-heading (MeSH) terms: nose, turbinate, surgery, atrophic rhinitis, and empty nose syndrome. The review period was restricted from January 1, 2000, to June 30, 2014, and limited to the English language. The abstracts were appraised for relevance, and full-text articles were obtained as appropriate. The bibliography of each article was reviewed to identify any other potentially relevant study. The full-text version was then reviewed for patient demographics, surgical intervention, complications, and outcome. If single units had reported on more than one case series with overlapping review periods, the earlier study was excluded unless it contained more comprehensive data for analysis than the latter report. Finally, the studies were assessed according to criteria defined by the Oxford Centre for Evidence-Based Medicine (Oxford, UK).

For studies that utilized similar clinical outcome tools such as the Sino-Nasal Outcome Test (SNOT), data were collated according to individual patients and domain scores. Browne et al.[11] described four distinct subdomains within the SNOT-20: 1) rhinologic symptoms, 2) ear and facial symptoms, 3) sleep function, and 4) psychological issues. Houser proposed an additional five ENS-specific questions to aid with the assessment of ENS patients[7] (Table I).

Statistical analysis was performed using SigmaPlot version 12 (Systat Software, Inc., CA). A normality test (Shapiro-Wilk) was undertaken; as appropriate, the Student t test or Mann–Whitney U test was used to assess the difference between pre- and postsurgery SNOT scores. A P value of ≤ 0.05 was deemed to be statistically significant.

TABLE I.
The Sino-Nasal Outcome Test-25 for the Assessment of Empty Nose Syndrome.[6,7]

1	Need to blow nose
2	Sneezing
3	Runny nose
4	Cough
5	Postnasal discharge
6	Thick nasal discharge
7	Ear fullness
8	Dizziness
9	Ear pain
10	Facial pain/pressure
11	Difficulty falling asleep
12	Waking up at night
13	Lack of good night's sleep
14	Waking up tired
15	Fatigue
16	Reduced productivity
17	Reduced concentration
18	Frustration/restlessness/irritability
19	Sadness
20	Embarrassment
ENS-specific symptoms	
21	Dryness
22	Difficulty with nasal breathing
23	Suffocation
24	Nose is too open
25	Nasal crusting

Each question is evaluated on a Likert scale of 0 to 5, with 5 being most severe.
ENS = empty nose syndrome.

RESULTS

Literature Search

Fourteen studies were identified from the PubMed literature search. Five were excluded due to insufficient outcome data, including one that was exclusively managed medically.[12–16] The remaining nine were potentially suitable for review.[17–25] One other clinical trial was identified from the U.S National Institutes of Health electronic database, but this trial was terminated when the lead investigator left the sponsoring institution. Of the nine potentially suitable studies, one was excluded because a more recent report from the same institution yielded more data.[21] The remaining eight studies were eligible for inclusion (Fig. 1). Seven studies were graded as level 4 evidence base, whereas one study randomized patients to either the Silastic (Dow Corning, Midland, MI) or AlloDerm (LifeCell Corporation, NJ) implant group (level 2b).[22] The overall grade of recommendation was C.

Patient Demographics

A total of 128 patients (84 males) were collated from the eight studies, with an age range of 18 to 64 years (Table II). A diagnosis of ENS in all cases was achieved from clinical history and examination. Two studies undertook preoperative rhinomanometry and/or acoustic rhinometry, although the measurements did not influence a diagnosis or indication for ENS surgery.[22,25] The use of the cotton wool test to select suitable surgical

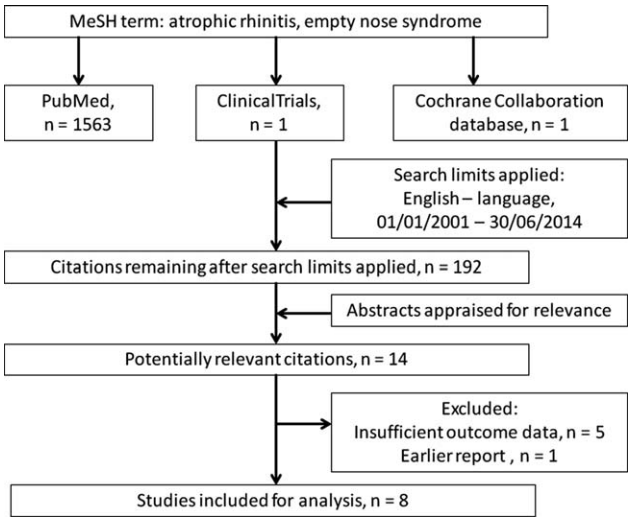

Fig. 1. Flow chart of literature search strategy.
MeSH = medical subject heading.

TABLE II.
Summary of Evaluated Studies Included in This Review in Chronological Order.

First Author (year of publication)	Number of Patients	Age (years)	Gender Distribution (male:female)	Implant Material	Surgical Approach	Outcome Measures	Follow-up (months)
Jiang (2014)	24	18–64	18:6	Medpor	Transnasal	SNOT-25	3,6,12
Tam (2014)	16	31–68	10:6	Medpor	Transnasal	SNOT-22	12
Jung (2013)	31	Mean 43.5	22:9	Conchal, costal cartilage	Transnasal	SNOT-25	6
Bastier (2013)	5	49.2–54.7	3:2	Nonporous β-tricalcium phosphate	Transoral	NOSE, RhinolQoL	Mean 13.5, Range 8.2–21
Saafan (2013)	24	Mean 27	11:13	12 × AlloDerm, 12 × Silastic	Transnasal	SNOT-25	Mean 18, Range 9–24
Modrzyński (2011)	3	48–64	2:1	Hyaluronic acid gel	Transnasal	Subjective, acoustic rhinometry	12
Jang (2011)	17	20–66	11:6	Cartilage (autologous, homologous)	Transnasal	10-point visual analogue scale	Mean 11.8, Range 6 - 27
Houser (2007)	8	18–45	7:1	AlloDerm	Transnasal	SNOT-20	Range 6–48

NOSE = Nasal Obstruction Symptom Evaluation; RhinolQOL = Rhinosinusitis Quality of Life; SNOT = Sino-Nasal Outcome Test.

candidates was undertaken in three studies.[18,21,23] Most patients had been suffering with ENS for many years (up to 29.7 years[12]), and there was general consensus that ENS surgery was deferred for at least 1 year after turbinectomy. Although all studies reported on patients who had inferior turbinectomy, the degree of turbinate resection (partial, total) was not consistently reported.

Surgical Technique

The most common surgical technique involved a transnasal approach, with implant material secured within a submucosal pocket. The amount and thickness of implant material was arbitrarily decided based on how much inferior turbinate reconstruction was necessary at the time of the operation. Multiple implant sites in the lateral nasal wall, remnant of the inferior turbinate or septal area adjacent to the resected turbinate, were normally performed to narrow the nasal valve region. Common implant material used in the studies included noncellular dermis (AlloDerm) and porous high-density polyethylene (Medpor, Porex Surgical, Inc., GA). These materials were used in 47% of cases, whereas autologous (septal, conchal) and homologous (Tutoplast-processed costal cartilage; Tutogen Medical GmbH, Neunkirchen am Brand, Germany) cartilage was utilized in 38% of cases. In three cases, small aliquots (0.3–0.4 mL) of hyaluronic acid gel (Juvéderm; Allergan, Inc., CA) was injected into the remnant of the head of inferior turbinate, and adjacent septum after the nasal mucosa was perforated with a CO2 laser.[25] One study involving five patients embedded nonporous β-tricalcium phosphate (SINUS UP; Kasios, Launaguet, France) via a gingival incision within a submucoperiosteal pocket in the lateral nasal wall.[12]

Clinical Outcomes

The follow-up period varied widely (range 6–48 months). Most studies reported postintervention data based on an aggregated follow-up period, although two presented results at 3-, 6-, and 12-month follow-up.[12,18] Of the eight studies, seven assessed clinical efficacy with a patient-reported outcome tool (Table II). Five studies utilized the SNOT, totaling 103 patients. The weighted mean preoperative SNOT-20 and SNOT-25 scores were 48.3 and 65.9 respectively. At the latest follow-up, these scores improved significantly ($P < 0.05$) to 24.4 and 33.3, respectively.

Averaged scores of individual SNOT questions were available from 64 patients, which enabled the analysis of SNOT subdomains.[12,18,22] High SNOT scores were attributed to issues of reduced productivity, poor concentration, and feeling frustrated. Although all SNOT subdomains improved subsequent to surgery, the largest improvement was observed in ENS symptoms and

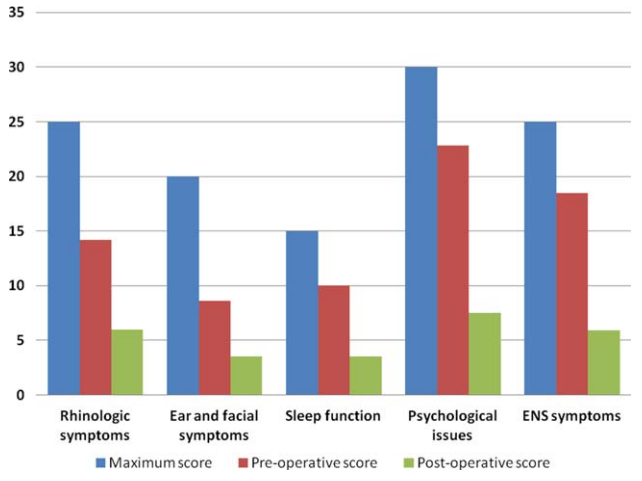

Fig. 2. Changes in average pre- and postoperative Sino-Nasal Outcome Test subdomain scores, based on data obtained from Jiang et al.,[17] Tam et al.,[18] Jung et al.,[19] and Saafan et al.[22] The maximum score column represents the maximum possible score for that particular subdomain. ENS = empty nose syndrome. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

psychological issues (Fig. 2). Total and subdomain scores improved by 3 months postsurgery, and this trend continued to improve over time, although available data was limited to only 12 months follow-up (Fig. 3).

Total pre- and postoperative SNOT scores were available from 48 patients derived from three studies.[18,22,23] The average total SNOT score improved significantly ($P < 0.001$) after surgery, with an average improvement of 29.0 (standard deviation, 15.9) points. At least 50% of patients reported an improvement of 30 SNOT points or more (Fig. 4). Nevertheless, 10 patients had less than 10 points improvement, including three patients who had no change in SNOT scores. Alloderm, Medpor, and Silastic were implanted in 20, 16, and 12 patients, respectively. ANOVA analysis of the pre- and postoperative scores was not possible due to the mix of SNOT-22 and −25 scores reported in these cohorts. Nevertheless, statistically significant improvements in mean postoperative SNOT scores were observed in all three implanted materials.

Instead of the SNOT, Bastier et al.[20] reported outcomes using the Nasal Obstruction Symptom Evaluation (NOSE) and Rhinosinusitis Quality of Life (RhinolQoL) questionnaires. All five patients in this study reported statistically significant improvement in NOSE and RhinolQoL scores. RhinoQOL symptom frequency, bothersomeness, and impact subscales improved after surgery.

The case series reported by Jang et al.[24] utilized a 10-point visual analogue scale for subjective symptoms such as excessive airflow, nasal obstruction, nasal/facial pain, rhinorrhoea/postnasal drip, and headache. Nine patients were satisfied with ENS surgery and reported significant improvement in excessive airflow, nasal obstruction, and nasal/facial pain.

Although two studies reported on nasal physiological parameters, only one had informative data. Modrzyński[25] merely reported that "acoustic rhinometry performed 7 days, and 3 and 6 months after surgery confirmed that the positive outcome of surgery was maintained"; however, follow-up examination performed after 12 months showed that the original effects of the surgery remained in only one of their patients."[25] In the earlier report by Jiang et al.,[21] Medpor implants resulted in a significant increase in the mean nasal resistance, nasal volume, and nasal minimum cross-sectional area at 12 months follow-up. There was an upward trend in the mean mucociliary clearance time, although the differences between pre- and postimplant did not achieve statistical significance.

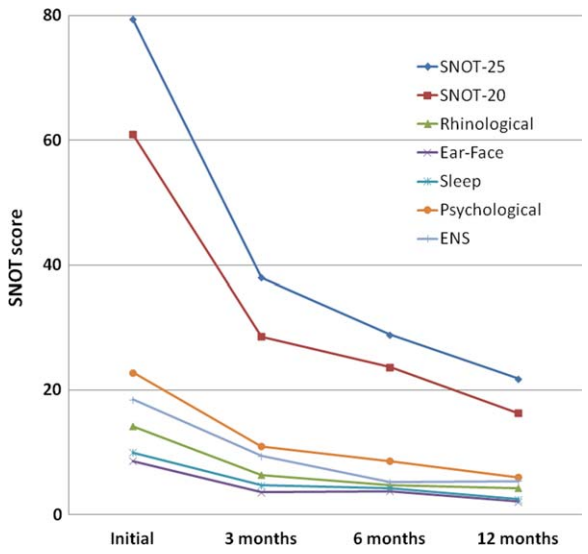

Fig. 3. Comparison of pre- and postoperative total and subdomain SNOT scores over time, based on data obtained from Jiang et al.[17] and Tam et al.[18]
ENS = empty nose syndrome; SNOT = Sino-Nasal Outcome Test. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

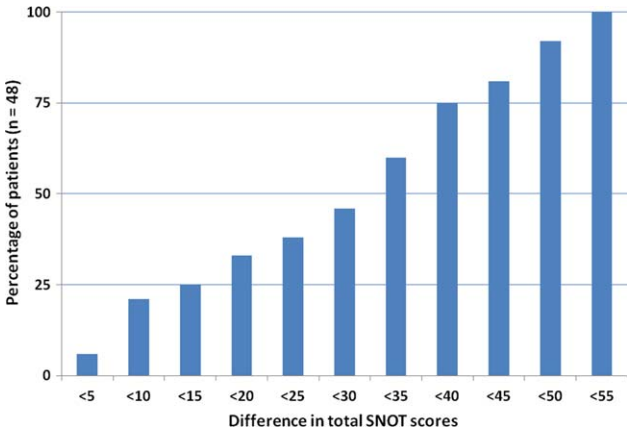

Fig. 4. Column bar graph demonstrating the percentage of patients based on the difference between pre- and postoperative total SNOT scores. SNOT = Sino-Nasal Outcome Test. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

Complications, Failure, and Extrusion of Implant

No intraoperative complications were reported in any of the studies. One patient was described to have developed postoperative chronic rhinosinusitis attributed to overcorrection of the nasal valve region.[18] In another study, two patients had under correction requiring further augmentation.[24] Of the three patients who had hyaluronic acid gel injections, the augmentation was found to be completely resorbed in two patients at the 12-month follow-up; one of who had further treatment.[25] Three patients reported no change in their SNOT score and another seven had < 10 SNOT points change after surgery, although it was unclear if these patients had revision surgery.[18,23] Extrusion of the implant occurred in six cases (1 β-tricalcium phosphate; 1 Medpor; 4 Silastic) however, because multiple layers of the implant were used, no adverse impact on final outcome was reported.[18,20,22]

DISCUSSION

The actual number of patients suffering with ENS is unknown. The relatively small cohort identified in this literature review undoubtedly belies the true figure, and it is unfortunate that many patients suffer without recourse to potentially effective surgical treatment.

Careful analysis of turbinectomy studies show that small numbers of patients continue to complain of nasal obstruction despite having turbinate resection, whereas others suffer with crusting and foul-smelling secretions. Whether these patients have ENS is unknown given that the existence of this condition has been contentious and will perhaps remain so. Because there is no empirical evidence to support the diagnosis of ENS at present, it is argued that many otolaryngologists remain skeptical about its existence and are not willing acknowledge the diagnosis and offer treatment. Nevertheless, Houser makes a compelling argument that ENS should be regarded as a condition that is distinct from atropic rhinitis, and that greater effort should be made to understand this clinical entity so that clinicians can be enabled to provide relief to those who have already been afflicted by it.[7,8,23]

Surgical implantation of biocompatible material to reconstruct a pseudoturbinate or to narrow the nasal valve region appears to result in improved patient-reported sinonasal symptoms, regardless of implant material used. There was insufficient evidence from this review to favor any particular implant material, although it was observed that Silastic had higher extrusion rate and that hyaluronic acid gel was resorbed within 12 months.

The magnitude of patient reported improvement varied widely and according to Houser[6] may be due to poor regeneration of sensory nerves to the resected area. Moore and Kern[1] postulated that the "wear and tear" on the mucosa under the circumstances of altered airflow leads to a disruption and degeneration of the mucosal nerve fibres, resulting in a decreased ability to sense airflow. This may explain why 21% (10 out of 48 patients) had less than 10 SNOT points improvement after surgery.[18,22,23] Furthermore, the bulk of nasal airflow streams predominate at the floor of the nasal cavity following radical turbinectomy.[26] In addition, it should be remembered that none of the patients in studies were blinded to surgical intervention; therefore, a degree of positive reporting bias may be expected.

The baseline total SNOT scores of ENS patients were higher than those suffering with nasal polyps or chronic rhinosinusitis.[27] This observation may represent greater functional and psychological burden, akin to patients suffering with nonsinogenic facial pain.[28] The modified SNOT questionnaire, which incorporates five additional questions specific to ENS, should form the baseline of future clinical reports. Psychometric validation of this modified questionnaire would be ideal, but challenging, given the relatively small number of ENS patients seen by individual otolaryngologists. Objective measures of nasal airflow such as rhinomanometry are an important adjunct to substantiate the results of ENS surgery. A total nasal airway resistance of 0.3 Pa/cm 3/s (3.0 cm H2O/l/s) is generally accepted as the upper limit of normal.[29] Jiang et al.[22] reported that the mean nasal airway resistance improved from 1.03 cm H2O/l/min to 1.9 cm H2O/l/min at 12 months follow-up. Computational fluid dynamic studies of nasal aerodynamics may have a role in ENS to plan placement and quantity of implants in order to predict neonasal airflow.[30]

The utility of the cotton test remains to be validated. This test is performed by placing cotton moistened with isotonic sodium chloride solution within the nonanaesthetized nasal cavity in a region where an implant would be feasible.[6] The patient is then asked to breathe comfortably with this in place for approximately 30 minutes and to gauge any change in sensation or symptoms. Patients who report a definite subjective improvement from the cotton test were, in some studies, offered implantation.[18,22,23] However, Bastier et al.[20] argued that it would stimulate trigeminal sensitivity and affect the patient's subjective assessment of their sinonasal symptoms.

CONCLUSION

Empty nose syndrome is a challenging condition to treat, compounded by the lack of objective tests to facilitate diagnosis. Nevertheless, a realistic but empathetic approach is required taking into account the current evidence (grade of recommendation C) for surgical intervention. Clinical response varies between patients; up to 21% may report only marginal improvement. Authors should be encouraged to consider long-term follow-up (> 12 months) of patients using both subjective (SNOT-25) and objective (rhinomanometry) measures of clinical outcome.

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ORIGINAL ARTICLE

Computer-assisted staging of chronic rhinosinusitis correlates with symptoms

Jonathan Garneau, MD[1], Michael Ramirez, BS[1], Samuel G. Armato III, PhD[2], William F. Sensakovic, PhD[3], Megan K. Ford, MD[2], Colin S. Poon, MD, PhD, FRCPC[2], Daniel T. Ginat, MD[2], Adam Starkey, BS[2], Fuad M. Baroody, MD[4] and Jayant M. Pinto, MD[4]

Background: **The Lund-Mackay (LM) staging system for chronic rhinosinusitis (CRS) does not correlate with clinical parameters, likely due to its coarse scale. We developed a "Modified Lund Mackay" (MLM) system, which uses a three-dimensional (3D), computerized method to quantify the volume of mucosal inflammation in the sinuses, and sought to determine whether the MLM would correlate with symptoms and disease-specific quality of life.**

Methods: **We obtained Total Nasal Symptom Score (TNSS) and 22-item Sino-Nasal Outcome Test (SNOT-22) data from 55 adult subjects immediately prior to sinus imaging. The volume of each sinus occupied by mucosal inflammation was measured using MATLAB algorithms created using customized, image analysis software after manual outlining of each sinus. Linear regression was used to model the relationship between the MLM and the SNOT-22 and TNSS. Correlation between the LM and MLM was tested using Spearman's rank correlation coefficient.**

Results: **Adjusting for age, gender, and smoking, a higher symptom burden was associated with increased sinonasal inflammation as captured by the MLM ($\beta = 0.453$, $p < 0.013$). As expected due to the differences in scales, the LM and MLM scores were significantly different ($p < 0.011$). No association between MLM and SNOT-22 scores was found.**

Conclusion: **The MLM is one of the first imaging-based scoring systems that correlates with sinonasal symptoms. Further development of this custom software, including full automation and validation in larger samples, may yield a biomarker with great utility for both treatment of patients and outcomes assessment in clinical trials.** © 2015 ARS-AAOA, LLC.

Key Words:
sinusitis; chronic sinusitis symptoms; computed tomography; computer-assisted image analysis; quality of life; Lund-Mackay; sinonasal

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Chronic rhinosinusitis (CRS) is a highly prevalent disease posing a substantial economic burden on the healthcare system.[1] Although significant effort has been devoted to investigating its pathophysiologic basis, efficacy of various therapies, and utility of diagnostic tools such as imaging and endoscopy, our understanding of these areas remains limited. A major barrier to progress in developing

[1]*Pritzker School of Medicine, The University of Chicago, Chicago, IL;* [2]*Department of Radiology, The University of Chicago, Chicago, IL;* [3]*Department of Radiology, Florida Hospital, Orlando, FL;* [4]*Section of Otolaryngology–Head and Neck Surgery, Department of Surgery, The University of Chicago, Chicago, IL*

Correspondence to: Jayant M. Pinto, MD, The University of Chicago, 5841 S. Maryland Ave., MC 1035, Chicago, IL 60637; e-mail: jpinto@surgery.bsd.uchicago.edu

Current affiliation of Jonathan Garneau: Department of Otolaryngology–Head and Neck Surgery, Icahn School of Medicine at Mount Sinai, New York, NY.
Current affiliation of Megan K. Ford: Department of Internal Medicine, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA.
Current affiliation of Colin S. Poon: Department of Radiology, Orillia Soldiers' Memorial Hospital, Orillia, ON, Canada.
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effective treatments is the lack of a biomarker for use in the evaluation of treatment efficacy. Thus, no therapies for CRS have been approved by the U.S. Food and Drug Administration (FDA) because there is no measure by which to validate them.

The most recent practice guidelines for CRS recommend radiologic evaluation with computed tomography (CT) imaging of the paranasal sinuses[2] for a variety of reasons, including assessment of disease extent and surgical planning.[3] Though clinically employed to localize and quantify chronic mucosal inflammation,[4] common CT-based staging systems[5] have failed to correlate with disease severity, so use of these systems remains controversial.[6] The most widely used scoring system is the Lund-Mackay (LM) system,[7] which assigns to each of 10 sinus cavities (left and right maxillary, anterior ethmoid, posterior ethmoid, sphenoid, and frontal) a score of 0 (no opacification), 1 (partial opacification), or 2 (total opacification) based on the extent of mucosal thickening within that sinus, plus a 0 to 2 score for the ostiomeatal complex (OMC). The total LM score for a CT scan ranges from 0 to 24. This system has been lauded for its low interobserver variability, objectivity, and ease of use,[8,9] but it does not correlate strongly with either patient symptoms or quality of life (QOL),[10] likely due to its inability to distinguish among varying degrees of "partial opacification." Zinreich[11] modified the LM system by creating subdivisions within "partial opacification" and increasing the range of scores to 0 to 5 based on percent opacification: 0 = 0%; 1 = 1% to 25%; 2 = 26% to 50%; 3 = 51% to 75%; 4 = 76% to 99%; and 5 = 100%. Such an expanded range of scores with finer resolution, however, leads to increased variability. Okushi et al.[12] attempted to modify the LM system by calculating percent opacification across CT sections. These authors did not assess the correlation between their LM scores and clinical symptoms, and their LM scoring system did not demonstrate clear superiority over the traditional LM staging system. The ideal scoring system for CRS imaging should combine elements of objectivity, simplicity, low interobserver variability, and fine resolution. Software automation might achieve these goals.

To meet this need, a novel software-based tool was developed to assess mucosal thickening using three-dimensional (3D), volumetric analysis. Image analysis has been used in various areas of otolaryngology, including sinus disease.[13] For example, Deeb et al.[14] used a computer program to investigate mucosal changes at the level of the maxillary sinuses based on manual outlines. Likness et al.[15] compared image-based CRS scoring systems by using volumetric calculations from CT scans as an objective measure of inflammation. Pallanch et al.[16] compared quantitative measurements of inflammation to symptoms and endoscopic examination findings.

In contrast to these previous studies, the software tool described in the present study uses a volumetric analysis technique to measure mucosal thickening of *each* paranasal sinus cavity and calculates a quantitative modification to the LM score, a "modified Lund-Mackay" (MLM) score, on a continuous scale. This study evolved from the hypothesis that the computerized, volume-based MLM score would correlate more strongly than the visual, subjective LM score with QOL and symptoms.

TABLE 1. Subject demographics, LM scores, quality of life scores, and symptom scores (n = 55)

Age (years), mean ± SD	50.5 ± 15.1
Male/female (n)	25/30
Tobacco use (n)	10
LM score (without OMC), median (range)	2 (0–18)
SNOT-22, median (range)	37 (0–80)
TNSS, median (range)	4.0 (0–12)

LM = Lund-Mackay; OMC = ostiomeatal complex; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test; TNSS = Total Nasal Symptom Score.

Patients and methods

Patients

Fifty-five adults undergoing routine sinus CT imaging at The University of Chicago were recruited to participate. Indications for imaging were unknown to the investigators and were based solely at the discretion of the ordering physicians who were not involved in the study; thus, the patients were not characterized for sinonasal disease and had a range of severity consistent with a sample of primary care patients. The study included adults (≥18 years of age) who were cognitively capable of providing written consent. The only exclusion criterion was refusal to provide written consent. Image data were collected, anonymized by the Human Imaging Research Office,[17] and processed as described below (3D Volumetric Analysis). Immediately prior to image acquisition, patients completed 2 validated surveys, the Sino-Nasal Outcome Test-22 (SNOT-22) and the Total Nasal Symptom Score (TNSS). The SNOT-22 is a quality of life-related measure of sinonasal function consisting of 22 questions rated from 0 (no problem) to 5 (problem as bad as it can be) with a theoretical range of 0 to 110 and higher scores indicative of poorer nasal function.[18] The TNSS is a 4-item questionnaire used to rate severity of sinonasal symptoms (sneezing, runny nose, stuffy nose, and other) on a scale of 0 (none) to 3 (severe) with a theoretical range of 0 to 12 and higher scores associated with increased symptom severity.[19] Demographic information including age, gender, and smoking status was also collected (Table 1). Written, informed consent was obtained for all subjects, and the Institutional Review Board approved the study.

3D volumetric analysis

Using an in-house software system (ABRAS), manual segmentations of the CT images were constructed for each patient. ABRAS is an image visualization and manipulation

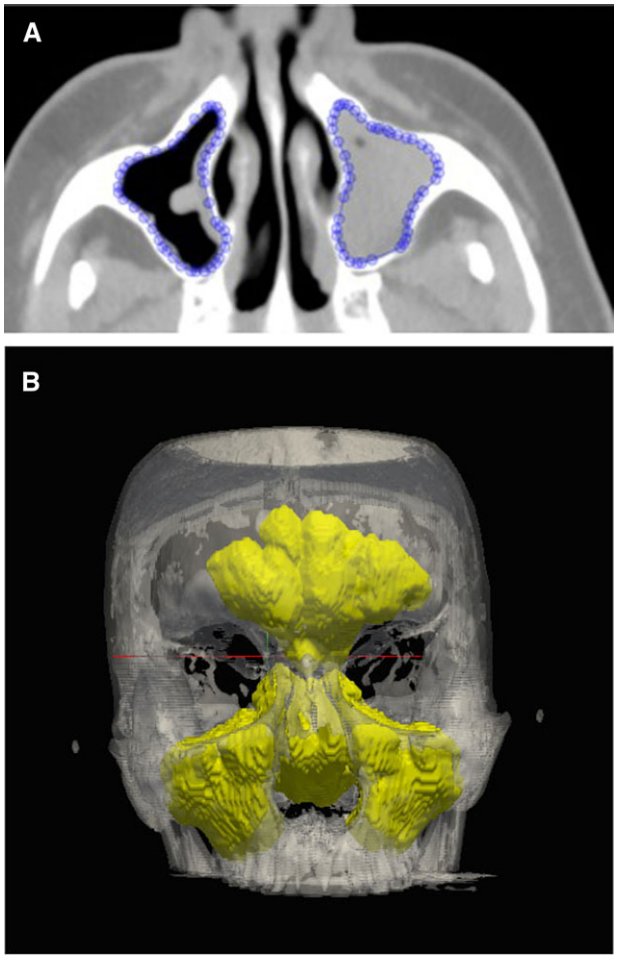

FIGURE 1. (A) Manually segmented outlines of the anatomic boundaries of the maxillary sinuses on a single CT section image using the ABRAS system (blue). (B) Volumetric analysis is performed by combining the sinus outlines from all CT sections in a scan to yield a 3D rendering (yellow). 3D = three-dimensional; CT = computed tomography.

tool that allows for window adjustment, magnification, and visualization for all sections of a CT scan.[20] All sinus cavities were outlined by trained observers (M.K.F., M.R.), who manually constructed outlines along the bony landmarks that define the sinuses (excluding the OMC) in each CT section image (Fig. 1). ABRAS allows the user to label the anatomic location (maxillary, anterior or posterior ethmoid, sphenoid, or frontal) of individual sinus outlines. All outlines were reviewed for accuracy by 1 of 3 experts in sinonasal imaging, 2 board-certified neuroradiologists (D.T.G., C.S.P.) and a board-certified rhinologist (J.P.). LM scores were assigned to each subject's scan separately in a similar fashion. Persons outlining, reviewing, and scoring these scans were blinded to all clinical characteristics and survey data for the subjects.

Modified Lund-Mackay score

The sinus outlines then were exported to the volumetric analysis software tool developed by our group.[21] This algorithm uses gray-level thresholding methods to subtract all airspace pixels contained within an outline from the total area encompassed by the outline to calculate the area occupied by inflammation within the outline in a single CT section image. Then, the algorithm sums these areas for individual sinuses across CT sections to yield (1) the total volume of inflammation, (2) the total sinus volume, and (3) the ratio of mucosal inflammation to sinus volume for each sinus. The MLM score then was calculated for each sinus cavity by multiplying the mucosa-to-sinus volume ratio (a continuous value between 0 and 1) by 2 to preserve the same range of values as the traditional LM system (which assigns a discrete value of 0, 1, or 2 to each sinus). The total MLM score was obtained by summing the MLM scores for all sinuses in a scan; the total LM score was obtained in an analogous manner. The OMC was excluded from both MLM and LM scores due to its nonstandard anatomic boundaries.

MLM scores were compared with LM scores, and the association of both scores with SNOT-22 and TNSS scores was evaluated. Multivariate regression models were constructed to investigate trends between scoring methods and the symptom severity measures. The impact of specific anatomic location on correlation also was evaluated.

Statistical analysis

Statistical analysis was performed using R-Console (www.r-project.org). Comparison of the LM and MLM scores was by the Mann-Whitney *U* test after both datasets were determined to have non-normal distributions by the Shapiro-Wilk test. Multivariate linear regression models were constructed with MLM as the dependent variable using TNSS and SNOT-22 scores as independent variables, with age, gender, and tobacco use as covariates. To investigate specific sinus MLM scores, stepwise regression was used to guide the selection of individual sinuses. The results of stepwise regression indicated that a combination of MLM scores from maxillary, ethmoid and frontal sinuses would achieve the best model fit (indicated by Akaike information criterion).[22] Multivariate regression models then were constructed to examine the effect of individual maxillary, ethmoid, and frontal sinus MLM scores on (1) patient symptom scores and (2) patient QOL scores.

Results

Total LM scores across all 55 patients ranged from 0 to 18, and total MLM scores ranged from 0.67 to 18.3 (Table 1). As expected due to differences in scale, the mean LM score was lower than the mean MLM score (3.9 ± 3.9, 4.9 ± 3.6, $p = 0.011$).

Multivariate regression models were constructed to analyze the relationship between imaging findings and clinical parameters. In bivariate analysis, increased symptom scores (ie, increased TNSS) were associated with greater mucosal inflammation as captured by the MLM score ($\beta = 0.437$, $p = 0.014$). Including age, gender,

TABLE 2. Multivariate linear regression models for MLM scores

Model MLM	A	B	C
TNSS	$\beta 1 = 0.437$	$\beta 1 = 0.435$	$\beta 1 = 0.453$
	$(p = 0.014)$	$(p = 0.018)$*	$(p = 0.013)$*
Age		$\beta 2 = 0.012$	$\beta 2 = 0.015$
		$(p = 0.702)$	$(p = 0.635)$
Gender		$\beta 3 = -0.259$	$\beta 3 = -0.187$
		$(p = 0.789)$	$(p = 0.845)$
Tobacco use			$\beta 4 = -1.85$
			$(p = 0.135)$

*Statistically significant β coefficient ($p < 0.05$).
MLM = Modified Lund-Mackay; TNSS = Total Nasal Symptom Score.

TABLE 3. Linear regression models for LM (without OMC) and MLM vs TNSS and SNOT-22

Model	LM (without OMC)	MLM
TNSS	$\beta = 0.314$	$\beta = 0.437$
	$(p = 0.108)$	$(p = 0.014)$*
SNOT-22	$\beta = 0.023$	$\beta = 0.042$
	$(p = 0.383)$	$(p = 0.082)$

*Statistically significant β coefficient ($p < 0.05$).
LM = Lund-Mackay; MLM = Modified Lund-Mackay; OMC = ostiomeatal complex; SNOT-22 = 22-item Sino-Nasal Outcome Test; TNSS = Total Nasal Symptom Score.

and smoking status strengthened this finding slightly ($\beta = 0.453$, $p < 0.013$) (Table 2). No significant association between the MLM and quality of life scores (ie, SNOT-22 score) was found. In contrast, the LM score demonstrated no association with either symptoms or quality of life in these models (Table 3)

Maxillary sinus MLM scores were found to have a significant effect on TNSS ($\beta = 2.38$, $p < 0.005$), as were posterior ethmoid MLM scores ($\beta = 2.75$, $p < 0.005$). A final model was developed based on maxillary, posterior ethmoid, and frontal sinus MLM scores that demonstrated a significant effect on TNSS ($\beta = 2.81$, $p = 0.040$; $\beta = 2.91$, $p = 0.056$; and $\beta = -2.95$, $p < 0.043$; $R^2 = 0.226$). None of the combined individual sinus MLM scores was found to correlate significantly with SNOT-22 scores. These results are summarized in Table 4.

TABLE 4. Multivariate regression models for TNSS based on specific sinus MLM scores

Model TNSS	A	B	C	D
Maxillary MLM score	$\beta 1 = 2.38$	–	–	$\beta 1 = 2.81$
	$(p = 0.005)$*			$(p = 0.040)$*
Posterior ethmoid MLM score	–	$\beta 2 = 2.75$	–	$\beta 2 = 2.91$
		$(p = 0.005)$*		$(p = 0.056)$
Frontal MLM score	–	–	$\beta 3 = 1.22$	$\beta 3 = -2.95$
			$(p = 0.168)$	$(p = 0.043)$*

*Statistically significant β coefficient ($p < 0.05$).
MLM = Modified Lund-Mackay; TNSS = Total Nasal Symptom Score.

Discussion

The results of this study are consistent with a growing trend in the literature that demonstrates the potential utility of volumetric assessment for staging sinus disease.[13,14,16] The goal of the present study was to develop a computerized approach to the CT-based volumetric quantification of sinonasal mucosal inflammation in order to enhance the utility of imaging for staging CRS. A modified scoring system was proposed and compared with symptom severity and QOL, both of which were captured immediately prior to clinically indicated CT scans by validated rhinology questionnaires. The MLM scoring system was significantly associated with patient symptoms, but neither the MLM nor the LM systems demonstrated significant association with patient quality of life. In addition to global scores, volumetric data was evaluated by individual sinus; the MLM scores for the maxillary, posterior ethmoid, and frontal sinuses were significantly associated with patient symptoms. To our knowledge, the dataset of 55 patients used in this study represents the largest cohort for a CRS study investigating volumetric image analysis.

Numerous studies have demonstrated the weak correlation between CT findings and symptoms.[6,9,23–26] The significant correlation between patient symptoms and the MLM score makes MLM 1 of only a few scoring systems that has demonstrated such a relationship.[15,16,27] The MLM system benefits from its objective nature and continuous scale. Rather than any intermediate degree of opacification receiving the same score of 1 in the standard LM scoring system, the MLM system allows for varying degrees of opacification to be distinctly quantified. These findings suggest a potential clinical use for the MLM scoring system and the software tool used to generate it.

Prior work has investigated the relationship among mucosal thickening on imaging, endoscopy findings on physical exam, and symptom severity in patients with severe CRS[15,16,27] and has focused on improving correlation between CT findings and symptom scores for patients with a narrow spectrum of severe disease defined by strict criteria. In contrast, the patients included in the present study were not confined to those with CRS and had relatively low burden of sinus inflammation (mean LM score of 3.9 relative to previous studies with an average LM score of 4.3 in patients without CRS and 9.8 in patients with CRS[28,29]). The present patient cohort included those receiving a sinus CT scan for any reason, not specifically

patients with diagnosed CRS or longstanding sinonasal pathology. Studying patients with low levels of disease may have made it difficult to find associations with quality of life. For example, it is well known that many asymptomatic patients have incidental CT findings such as mucosal thickening.[25,30,31] This heterogeneity and lack of focus on severe sinus disease may have contributed to the failure of this study to achieve statistical significance for quality of life, but the significant correlation between inflammation volume and symptom severity becomes even more notable. With entry criteria similar to those of previous studies, the MLM score could prove even more closely associated with symptoms. Repeating this study in patients with defined rhinologic conditions (eg, CRS with and without polyposis) across a range of clinically relevant and increased severities is the subject of planned future work.

Staging systems such as Lund-Mackay and Zinreich give equal weight to each sinus cavity in the total score. Holbrook et al.[32] attempted to identify potential surrogate markers of disease on imaging, other than diffuse mucosal thickening, such as segmental opacification, sinus cavity size, and hallmark anatomic variations associated with impeded sinus ostia drainage[33]; they failed, however, to show a meaningful association between opacification and various anatomic sites with patient symptoms. The results of the present study suggest that opacification in specific paranasal sinuses (namely, the maxillary and ethmoid sinuses) are most related to symptoms, a finding that matches clinical experience.[25,30] Therefore, weak correlation between CT-based staging systems and patient symptoms could be the result of less important sinuses being weighted the same as more influential sinuses; perhaps a weighted model based on anatomic location would improve imaging correlation with clinical symptoms. Indeed, Sedaghat and Bhattacharyya[27] described a weighted model for radiologic assessment of the paranasal sinuses and found (with a technique that did not involve volumetric analysis) that although Hounsfield unit (HU) values and LM scores alone were not correlated with symptoms, an HU-weighted LM-scoring system was correlated with symptoms. Software tools may make a volumetric weighted model feasible and strengthen correlation between MLM scores and symptom severity, but future studies with a more comprehensive assessment of all paranasal sinuses targeted at proposed weighted models are necessary to support this idea.

The software, although semiautomated, requires manual outlines of each CT image prior to the automated calculation of opacified volume. The potentially labor-intensive manual component limits the practicality of clinical deployment at this time. Moreover, the software currently is unable to assess inflammation within the OMC due to the inherent complexity of this clinically relevant anatomic location. The omission of the OMC limits the robustness of the volumetric analysis technique. Future work will refine the software to include the OMC and increase the level of automation.

Conclusion

This study demonstrated the potential utility of a modified scoring system that incorporates a CT-volume assessment of sinonasal inflammation as a potential biomarker for staging sinus disease. Significant correlation of this system with standardized subjective measures was found, which supports the role of mucosal inflammation in causing sinus symptoms. Further study is required to investigate the full potential and future applications of this system, especially in CRS patients, and the software tool used to capture the relevant quantitative information. Overall, these findings demonstrate promise for the use of CT-based volumetric analysis of sinus mucosal inflammation as an objective biomarker for clinical trials, pharmaceutical development, and objective monitoring of clinical improvement after medical or surgical intervention for CRS.

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Clinical Consensus Statement: Pediatric Chronic Rhinosinusitis

Scott E. Brietzke, MD, MPH[1], Jennifer J. Shin, MD[2], Sukgi Choi, MD[3], Jivianne T. Lee, MD[4], Sanjay R. Parikh, MD[5], Maria Pena, MD[6], Jeremy D. Prager, MD[7], Hassan Ramadan, MD[8], Maria Veling, MD[9], Maureen Corrigan[10], and Richard M. Rosenfeld, MD, MPH[11]

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract

Objective. To develop a clinical consensus statement on the optimal diagnosis and management of pediatric chronic rhinosinusitis (PCRS).

Methods. A representative 9-member panel of otolaryngologists with no relevant conflicts of interest was assembled to consider opportunities to optimize the diagnosis and management of PCRS. A working definition of PCRS and the scope of pertinent otolaryngologic practice were first established. Patients of ages 6 months to 18 years without craniofacial syndromes or immunodeficiency were defined as the targeted population of interest. A modified Delphi method was then used to distill expert opinion into clinical statements that met a standardized definition of consensus.

Results. After 2 iterative Delphi method surveys, 22 statements met the standardized definition of consensus while 12 statements did not. Four statements were omitted due to redundancy. The clinical statements were grouped into 4 categories for presentation and discussion: (1) definition and diagnosis of PCRS, (2) medical treatment of PCRS, (3) adenoiditis/adenoidectomy, and (4) endoscopic sinus surgery (ESS)/turbinoplasty.

Conclusion. Expert panel consensus may provide helpful information for the otolaryngologist in the diagnosis and management of PCRS in uncomplicated pediatric patients.

Keywords

pediatric otolaryngology, rhinosinusitis, chronic rhinosinusitis, evidence-based medicine, review, Delphi method

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Introduction

Pediatric chronic rhinosinusitis (PCRS) is a commonly encountered condition in otolaryngological practice. Five percent to 13% of childhood viral upper respiratory tract infections may progress to acute rhinosinusitis,[1-4] with a proportion of these progressing to a chronic condition. PCRS may also coexist and/or be exacerbated by other widespread conditions such as allergic rhinitis and adenoid disease,[5-9] and some suggest the incidence of PCRS may be rising.[10] In addition, PCRS has a meaningful impact on quality of life,[11] with its related adverse effects potentially exceeding that of chronic respiratory and arthritic disease.[12] PRCS also has the potential to exacerbate asthma,[13,14] a condition that negatively affects 2% to 20% of children.[15-17]

In spite of its prevalence and impact on affected families, many aspects of PCRS remain ill-defined. At the most basic level, even the diagnostic definition of PCRS has not been concretely elucidated among our specialty societies, creating challenges in discussing clinical presentations or establishing human study protocols. Similarly, while performing nasal endoscopy and obtaining site-specific cultures may be routine in the cooperative adult population, their role in the evaluation of children has not been clearly established. Likewise, the concept of maximal medical therapy has yet to be specifically delineated, although there is a broad spectrum

[1]Walter Reed National Military Medical Center, Bethesda, Maryland, USA
[2]Harvard Medical School, Boston, Massachusetts, USA
[3]University of Pittsburgh/Children's Hospital of Pittsburgh of UMPC, Pittsburgh, Pennsylvania, USA
[4]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, California, USA
[5]University of Washington/Seattle Children's Hospital, Seattle, Washington, USA
[6]Children's National Medical Center, Washington, DC, USA
[7]University of Colorado/Children's Hospital Colorado, Aurora, Colorado, USA
[8]West Virginia University, Morgantown, West Virginia, USA
[9]University of Texas–Southwestern Medical Center/Children's Medical Center-Dallas, Dallas, Texas, USA
[10]American Academy of Otolaryngology—Head and Neck Surgery Foundation, Alexandria, Virginia, USA
[11]SUNY Downstate Medical Center, Brooklyn, New York, USA

Corresponding Author:
Scott E. Brietzke, MD, MPH, Walter Reed Department of Otolaryngology, 8901 Wisconsin Ave., Bethesda, MD 20889.
Email: SEBrietzke@msn.com

of options, ranging from topical irrigations to longstanding intravenous antibiotic therapy. Both adenoidectomy and endoscopic sinus surgery (ESS) have been reported to produce associated improvements,[18,19] thus raising practical questions regarding whether these procedures are best done in tandem or concomitantly and whether that choice should depend on age, comorbidities, or additional patient factors. In addition, other related aspects of PCRS remain controversial, such as the potential impact of gastroesophageal reflux (GER), the effect of ESS on facial growth, the role of postoperative debridement, and emerging techniques such as balloon sinuplasty in children.

Nonetheless, PCRS occurs with sufficient frequency that otolaryngologists regularly encounter it in their practice, creating opportunities for optimizing practice patterns. While experience regarding the epidemiology, diagnosis, and management of PCRS is burgeoning, the associated evidence regarding optimal medical and surgical management has clear limits. Thus, the American Academy of Otolaryngology—Head and Neck Surgery Foundation (AAO-HNSF) Guidelines Task Force selected this topic for clinical consensus statement (CCS) development. The expert panel convened with the objectives of addressing opportunities to promote appropriate care, reduce inappropriate variations in care, and educate and empower clinicians and patients toward the optimal management of PCRS. This document describes the result of this process and focuses on diagnosis, medical therapy, and surgical interventions.

Methods

This clinical consensus statement was developed in discrete, predetermined steps: (1) evaluation of the suitability of PCRS as the subject of a clinical consensus statement; (2) panel recruitment; (3) vetting potential conflict of interests among proposed panel members; (4) systematic literature review; (5) determination of working definition of PCRS, intended scope of practice, and population of interest for the consensus statement; (6) modified Delphi survey development and completion; (7) iterative revision of clinical statements based on survey results; and (8) data aggregation, analysis, and presentation. The pertinent details of each of these steps will be briefly described.

Determination of PCRS as the Topic of a Consensus Statement, Panel Recruitment, and Vetting

PCRS was first considered as the subject of a clinical consensus statement based on suggestion from an American Academy of Otolaryngology—Head and Neck Surgery member. After deliberation, the Guidelines Task Force supported the suggestion, and consensus panel leadership was selected and administrative support allocated. Panel membership was strategically developed to ensure appropriate representation of all relevant subgroups within the specialty of otolaryngology. The various subgroups were contacted about the consensus statement project with the requirements and desired qualifications for panel membership,s and each subgroup then selected their own representative expert to participate. Participating subgroups include the American Society of Pediatric Otolaryngology (JJS), the American Academy of Otolaryngic Allergy (MV), the American Rhinologic Society (HHR), the Triologic Society (SC), and the appropriate committees within the American Academy of Otolaryngology—Head and Neck Surgery including the Board of Governors (SP), the Outcomes Research and Evidence Based Medicine Subcommittee (SEB), the Rhinology and Paranasal Sinus Committee (JL), the Pediatric Otolaryngology Committee (MP), and the Young Physicians Section (JP). Each member of the panel is either a fellowship-trained pediatric otolaryngologist or rhinologist in active clinical practice. Once the panel was assembled, complete disclosure of potential conflicts of interest were reported and vetted within the group. A panel vote was used to determine whether a disclosed conflict of interest necessitated disqualification from panel participation. The panel chair (SEB) and panel co-chair (JJS) led the development of the clinical statements and the Delphi process with input from a senior consultant/methodologist from the Academy leadership in the Guidelines Task Force (RMR) and administrative support from an Academy staff liaison (MC).

Literature Review and Determination of the Scope of the Consensus Statement

A systematic biomedical literature review was performed to identify current high-level evidence regarding the diagnosis and medical and surgical management of PCRS. The purpose of this literature search was to guide the CCS panel in developing clinical statements for standardized consensus evaluation that could help fill evidence gaps and assist otolaryngologists in the diagnosis and management of PCRS. The literature search was conducted in January 2014 with the assistance of a professional database search consultant. The systematic search included systematic reviews (including meta-analyses), clinical practice guidelines, and other relevant clinical consensus statements in English from Medline; National Guidelines Clearinghouse; CMA Infobase; National Library of Guidelines; National Institute for Health and Clinical Excellence (NICE); Scottish Intercollegiate Guidelines Network (SIGN); New Zealand Guidelines Group; Australian National Health and Medical Research Council; Trip Database; Guidelines International Network (G-I-N); Cochrane Database of Systematic Reviews; Excerpta Medica database (EMBASE); Cumulative Index to Nursing and Allied Health (CINAHL); Allied and Complementary Medicine Database (AMED); BIOSIS Citation Index; Web of Science; Agency for Healthcare Research and Quality (AHRQ) Research Summaries, Reviews, and Reports; and Health Services/Technology Assessment Texts (HSTAT) from 2003 using the search string: ''(chronic disease OR chronic) AND (sinusitis OR rhinosinusitis) AND (child OR adolescent OR teen).'' The gaps in literature were used as a framework for the qualitative survey.

The panel evaluated the recent AAO-HNSF CCS regarding the Appropriate Use of Computed Tomography for Paranasal Sinus Disease[20] and made an early decision to

accept the statements within this document regarding use of CT for the diagnosis of PCRS in children rather than readdress this topic within the current consensus statement.

The panel made several decisions regarding the scope of this clinical consensus statement before formally beginning the Delphi process. It was decided that the target audience of the statement would be specifically otolaryngologists. A working definition of PCRS was determined and consensus on this definition was confirmed using the Delphi process (see statement 1). The target population was defined as children ages 6 months to 18 years old with PCRS, although it was acknowledged that children of different ages have different factors in regards to the diagnosis and management of PCRS (statement 3). Children with craniofacial syndromes (eg, Trisomy 21) or relative immunodeficiency (eg, cystic fibrosis) were excluded as it was felt the treatment of this subgroup is very different from the typical PCRS patient. Once the target population and scope of practice were determined, the panel used the results of the literature review to prioritize the clinical areas that could most benefit from potential consensus from an expert panel. These areas were then used as the basis for the formulation of the initial statements that were then evaluated through the Delphi survey method.

Delphi Survey Method Process and Administration

A modified Delphi survey method was utilized to distill expert opinion into concise clinical consensus statements. The Delphi method involves using multiple anonymous surveys to assess for objective consensus within an expert panel.[21] This rigorous and standardized approach minimizes bias and facilitates expert consensus.

Web-based software (www.surveymonkey.com) was used to administer confidential surveys to panel members. The survey period was broken down into 3 iterations: 1 qualitative survey with free text boxes for responses and 2 subsequent Delphi rounds. All answers were de-identified and remained confidential; however, names were collected to ensure proper follow-up if needed. The qualitative survey included 54 questions on the definition and clinical areas of chronic pediatric sinusitis. The purpose of the qualitative survey was to narrow the scope and provide a framework for the subsequent Delphi rounds.

Based on the outcomes of the qualitative survey and resulting discussion, the panel chair developed the first Delphi survey, which consisted of 37 statements. Prior to dissemination to the panel, the Delphi surveys were reviewed by the consultant for content and clarity. Questions in the survey were answered using a 9-point Likert scale where 1 = strongly disagree, 3 = disagree, 5 = neutral, 7 = agree, and 9 = strongly agree. The surveys were distributed, and responses were aggregated, distributed back to the panel, discussed via teleconference, and revised if warranted. The purpose of the teleconference was to provide an opportunity to clarify any ambiguity, propose revisions, or drop any statements recommended by the panel.

The criterion for consensus was established a priori with reference to previous consensus statements[20,22] and followed the following criteria (outliers are defined as any rating at least 2 Likert points away from the mean):

- **consensus**: statements achieving a mean score of 7.00 or higher and have no more than 1 outlier,
- **near consensus**: statements achieving a mean score of 6.50 or higher and have no more than 2 outliers,
- **no consensus**: statements that did not meet the criteria of consensus or near consensus.

Additionally for the purposes of emphasis within the discussion, strong consensus was subsequently defined as a mean Likert score of 8.00 or higher with no outliers.

Two iterations of the Delphi survey were performed. The panel extensively discussed (via teleconference) the results of each item after the first Delphi survey. Items that reached consensus were accepted, and items that did not meet consensus were discussed to determine if wording or specific language was pivotal in the item not reaching consensus. Four items were found to be essentially redundant to other items and were omitted at this point. The second iteration of the survey was used to reassess items for which there was near consensus or for items for which there was suggestion of significant alterations in wording that could have affected survey results. The entire panel also extensively discussed the results of the second Delphi survey. All items reaching consensus were accepted. A third iteration of the Delphi process was considered but was not felt to be necessary. The factors leading to the remaining items not reaching consensus were not attributed to wording or other modifiable factors but rather a true lack of consensus.

The final version of the clinical consensus statements were grouped into 4 specific areas: (1) definition and diagnosis of PCRS, (2) medical treatment of PCRS, (3) adenoiditis/adenoidectomy, and (4) ESS/turbinoplasty. The final manuscript was drafted with participation and final review from each panel member.

Results

Thirty-eight clinical statements were developed for assessment with the Delphi survey method. All panelists completed all survey items. After 2 iterations of the Delphi survey, 22 statements (58%) met the standardized definition for consensus. Twelve clinical statements (31%) did not meet the criteria for consensus. Four clinical statements (11%) were omitted due to redundancy. The clinical statements were organized into 4 specific subject areas, and the results of each will be individually considered in the following.

Definition and Diagnosis of Pediatric Chronic Rhinosinusitis

In the area of definition and diagnosis of PCRS, 7 statements reached objective clinical consensus (see **Table 1**). The panel reached consensus on a working definition of PCRS that included both subjective symptoms and objective features. PCRS is defined as at least 90 continuous days of

Table 1. Definition and Diagnosis of Pediatric Chronic Rhinosinusitis Statements Reaching Consensus.

Number	Statement	Mean	Outliers	Quality Improvement Opportunity
1	Chronic rhinosinusitis (PCRS) is defined as at least 90 continuous days of 2 or more symptoms of purulent rhinorrhea, nasal obstruction, facial pressure/pain, or cough *and* either endoscopic signs of mucosal edema, purulent drainage, or nasal polyposis and/or CT scan changes showing mucosal changes within the ostiomeatal complex and/or sinuses in a pediatric patient aged 18 years or younger (Adapted from European Position Paper on Rhinosinusitis and Nasal Polyps 2012[23]).	7.56	0	Promoting appropriate care
2	Management of children aged 12 years and younger with CRS is distinctly different than management of children aged 13 to 18 years old with CRS.	7	0	Promoting appropriate care
3	Nasal endoscopy (flexible or rigid) is appropriate in evaluating a child with CRS to document purulent drainage, mucosal edema, nasal polyps, and/or adenoid pathology (hyperplasia, infection).	7.67	1	Promoting appropriate care
4	Management of the children with nasal polyps and CRS is distinctly different than management of children with CRS unaccompanied by nasal polyps.	8.22	0	Reducing inappropriate or harmful care
5	Allergic rhinitis is an important contributing factor to PCRS, especially in older children.	7.56	0	Promoting appropriate care
6	Adenoiditis is an important contributing factor to PCRS, especially in younger children.	7.67	1	Promoting appropriate care
7	The ability of adenoids to serve as a bacterial reservoir for PCRS is independent of adenoid size.	7.67	1	Reducing inappropriate or harmful care

symptoms of purulent rhinorrhea, nasal obstruction, facial pressure/pain, or cough with corresponding endoscopic and/or CT findings in a patient who is 18 years of age or younger (statement 1). Strong consensus (mean Likert score above 8.00) was achieved for the statement that pediatric patients with nasal polyps should be managed differently than those without polyps (statement 4). The panel reached consensus that age was an important distinguishing factor in the diagnosis of PCRS, with adenoid disease (independent of adenoid size) being a prominent factor in younger children and allergic rhinitis being a more important contributing factor in older children (statements 2, 5-7). Lastly, consensus was also reached that nasal endoscopic (flexible or rigid) is appropriate and useful in the diagnosis of PCRS (statement 3). There was no consensus regarding the contribution of gastroesophageal reflux disease (GERD) to PCRS (**Table 2**, statement 8).

Medical Treatment of PCRS

For medical management of PCRS, 5 statements reached consensus by the panel and 4 statements failed to reach consensus (see **Table 3**). Consensus was reached that daily, topical nasal steroid spray as well as daily, topical nasal irrigations are beneficial adjunctive medical therapies for PCRS (statements 11 and 12). Regarding antibiotic therapy, the panel failed to reach consensus on the statement that appropriate antibiotic therapy for PCRS includes a minimum of 10 consecutive days of an antimicrobial medication that is effective against typical rhinosinusitis pathogens (statement 14). However, the panel did reach consensus that 20 consecutive days of antibiotic therapy may produce a superior clinical response in PCRS patients compared to 10 days of antibiotic therapy (**Table 2**, statement 9). The panel also reached consensus that culture-directed antibiotic therapy may improve outcomes for PCRS patients who have not responded to empiric antibiotic therapy (statement 10).

The panel did not agree that medical therapy for PCRS should include treatment for GERD when signs or symptoms of GERD are present (**Table 2**, statement 15), instead agreeing that empiric treatment for GERD is not a beneficial adjunctive medical therapy for PCRS (statement 13). Additionally, the panel did not reach consensus that the current evidence supports a role for topical antibiotic therapy or antral irrigation in managing children with PCRS (**Table 2**, statements 16, 17).

Adenoiditis/Adenoidectomy

For adenoiditis/adenoidectomy, 4 statements reached consensus by the panel and 1 did not (see **Table 4**). Strong consensus was reached regarding the effectiveness of adenoidectomy as the initial surgical therapy for patients aged up to 6 years, and measurably less consensus was obtained for patients age 6 to 12 years (statements 18, 19). However, the panel could not reach consensus on whether adenoidectomy was an effective first-line procedure for patients aged 13 years and older with CRS (**Table 2**, statement 22). The panel agreed that adenoidectomy can have a beneficial effect in pediatric patients with PCRS that is independent of ESS (statement 20). There was strong consensus, in fact the highest Likert score of any statement in

Table 2. Clinical Statements that Did Not Meet the Criteria for Consensus.

Number	Statement	Subgroup	Status	Mean	Outliers
8	Gastroesophageal reflux disease (GERD) can contribute to pediatric chronic rhinosinusitis (PCRS).	Definition and Diagnosis of PCRS	No consensus	6.11	1
14	Appropriate antibiotic therapy for PCRS includes a minimum of 10 consecutive days of an antimicrobial medication that is effective against typical rhinosinusitis pathogens.	Medical Management of PCRS	No consensus	6.22	3
15	Medical therapy for PCRS should include treatment for GERD when signs or symptoms of GERD are present.	Medical Management of PCRS	No consensus	6.22	2
16	Current evidence supports a role for topical antibiotic therapy in managing selected children with CRS.	Medical Management of PCRS	No consensus	4.67	2
17	Current evidence supports a role for antral irrigation in managing selected children with CRS.	Medical Management of PCRS	No consensus	4.56	2
22	Adenoidectomy is an effective first-line surgical procedure for children aged 13 years and older with CRS.	Adenoidectomy/ Adenoiditis	No consensus	3.89	3
29	Balloon sinuplasty is safe for treating children with PCRS.	Endoscopic Sinus Surgery/ Turbinoplasty	Near consensus	6.56	2
30	Balloon sinuplasty is effective for treating patients with PCRS.	Endoscopic Sinus Surgery/ Turbinoplasty	No consensus	5.33	0
31	Inferior turbinate reduction can benefit children with CRS by reducing nasal congestion and improving penetration of topical medications.	Endoscopic Sinus Surgery/ Turbinoplasty	No consensus	6.22	1
32	Inferior turbinate reduction is a safe and minimally invasive adjunctive procedure for treating PCRS.	Endoscopic Sinus Surgery/ Turbinoplasty	No consensus	6.11	1
33	Children with swollen, enlarged inferior turbinates on preoperative assessment that have not responded to medical therapy are most likely to benefit from bilateral inferior turbinate reduction.	Endoscopic Sinus Surgery/ Turbinoplasty	No consensus	6.33	1
34	Reduction or removal of an obstructive middle turbinate concha bullosa when present is a valuable component of the surgical management of PCRS.	Endoscopic Sinus Surgery/ Turbinoplasty	Near consensus	6.78	0

Table 3. Medical Management of Pediatric Chronic Rhinosinusitis (PCRS) Statements Reaching Consensus.

Number	Statement	Mean	Outliers	Quality Improvement Opportunity
9	Twenty consecutive days of antibiotic therapy may produce a superior clinical response in PCRS patients compared to 10 days of antibiotic therapy.	7.44	0	Promoting appropriate care
10	Culture-directed antibiotic therapy may improve outcomes for PCRS patients who have not responded to empiric antibiotic therapy.	8	0	Promoting appropriate care
11	Daily, topical nasal steroids are a beneficial adjunctive medical therapy for PCRS.	7.44	0	Promoting appropriate care
12	Daily, topical nasal saline irrigations are a beneficial adjunctive medical therapy for PCRS.	7.78	0	Promoting appropriate care
13	Empiric treatment for gastroesophageal reflux disease (GERD) is not a beneficial adjunctive medical therapy for PCRS.	7	0	Reducing inappropriate or harmful care

Table 4. Adenoidectomy/Adenoiditis Statements Reaching Consensus.

Number	Statement	Mean	Outliers	Quality Improvement Opportunity
18	Adenoidectomy is an effective first line surgical procedure for children up to 6 years of age with chronic rhinosinusitis (CRS).	8.33	0	Promoting appropriate care
19	Adenoidectomy is an effective first-line surgical procedure for children aged 6 to 12 years with CRS.	7.11	1	Promoting appropriate care
20	Adenoidectomy can have a beneficial effect in patients with pediatric CRS that is independent of endoscopic sinus surgery (ESS).	7.33	1	Educating and empowering clinicians and patients
21	Tonsillectomy (without adenoidectomy) is ineffective treatment for PCRS.	8.56	0	Reducing inappropriate or harmful care

Table 5. Endoscopic Sinus Surgery/Turbinoplasty Statements Reaching Consensus.

	Statement	Mean	Outliers	Quality Improvement Opportunity
23	Endoscopic sinus surgery (ESS) is an effective procedure for treating pediatric chronic rhinosinusitis (PCRS) that is best performed after medical therapy, adenoidectomy, or both have failed.	7.89	0	Promoting appropriate care
24	A CT scan of the paranasal sinuses is indicated prior to ESS to assess structure, development, and extent of disease.	8.56	0	Promoting appropriate care
25	Image-guided ESS is useful for revision ESS cases and/or for patients with extensive nasal polyposis that can distort anatomical landmarks.	8.22	1	Promoting appropriate care
26	There is a lack of convincing evidence that ESS causes a clinically significant impairment of facial growth when performed in children with CRS.	7	0	Educating and empowering clinicians and patients
27	Postoperative debridement after ESS for PCRS is not essential for treatment success.	7	1	Reducing inappropriate or harmful care
28	The effectiveness of balloon sinuplasty compared to traditional ESS for PCRS cannot be determined based on current evidence	7.89	0	Reducing inappropriate or harmful care

the entire clinical consensus statement, that tonsillectomy (without adenoidectomy) is an ineffective treatment for PCRS (statement 21).

Endoscopic Sinus Surgery/Turbinoplasty

For the specific area of ESS/turbinoplasty, 6 statements reached consensus and 6 did not (see **Table 5**). Consensus was reached that ESS is an effective procedure for treating PCRS and that it is best performed when medical management, adenoidectomy, or both have failed to control the symptoms of PCRS (statement 23). Strong consensus was reached that a CT scan of the paranasal sinuses is indicated prior to ESS to assess the anatomy of the sinuses and development, extent, and severity of sinus disease and also that image-guided surgery is useful in revision cases and in patients with extensive nasal polyposis that can distort anatomical landmarks (statements 24, 25). There was consensus by the panel about the lack of convincing evidence that ESS causes a clinically significant impairment of facial growth when performed in children with CRS (statement 26). There was also consensus that postoperative debridement after ESS for PCRS is not an essential component for treatment success (statement 27).

The panel considered balloon sinuplasty for PCRS at length as it is a topic that receives a great deal of attention. The panel decided to assess an initial statement regarding the comparative effectiveness of balloon sinuplasty versus ESS in pediatric patients. Consensus was reached that there was insufficient current evidence to compare balloon sinuplasty to ESS for PCRS (statement 28). Not unexpectedly, the panel subsequently could not reach consensus regarding the effectiveness of balloon sinuplasty in treating PCRS although there was near consensus (mean Likert score = 6.56) regarding the safety of balloon sinuplasty (**Table 2**, statements 29, 30).

Turbinoplasty was extensively deliberated by the panel as consensus was actively sought for the appropriate role for this commonly performed, simple, noninvasive procedure. Unfortunately, the panel could not reach any consensus regarding the indications, potential benefits, or optimal candidates for inferior turbinoplasty (**Table 2**, statements 31-33). The primary reason noted in the panel discussion for this result was lack of pediatric-specific data. Near consensus (mean Likert score 6.78) was reached regarding the potential benefits of reducing an obstructive concha bullosa in PCRS patients (**Table 2**, statement 34).

Discussion

The purpose of this clinical consensus statement is to formulate evidence-enriched expert opinion into distinct clinical statements to promote high-quality care, reduce variations in care, and educate and empower clinicians and patients toward the goal of optimal management of PCRS. Specific discussion of the key elements in each of the 4 distinct clinical areas follows.

Definition and Diagnosis of PCRS

The definition of CRS that reached expert panel consensus for the pediatric population is similar to what has been accepted in adults.[23] Like the definition of CRS in adults, the panel agreed that an ideal definition of PCRS should include both subjective symptoms and objective signs. Specifically, the consensus definition specifies 2 or more symptoms of nasal congestion, nasal discharge, facial pressure/pain, or cough accompanied either by clinical signs on endoscopy such as nasal polyps, mucosal edema, or mucopurulent discharge or relevant findings on sinus CT scan over a 90-day continuous time span (statement 1). The chronicity requirement of 90 days is somewhat arbitrary but was felt to clearly represent a benchmark that distinguished PCRS from acute and subacute presentations of rhinosinusitis and is aligned with parallel adult definitions.[23-25]

The panel considered various pediatric age ranges to use as the target of this consensus statement. Clearly the typical medical-legal division between the pediatric and adult realms of 18 years old is not necessarily a physiologic threshold. Yet, since adult-based literature targets age 18 years and greater, the panel felt this was likely the appropriate limit to use for practical reasons. It is well known that sinus anatomic development continues throughout childhood and into adulthood.[26] Likewise, it would be expected that the pathophysiology of PCRS also evolves throughout childhood into adulthood. The age at which the frontal sinuses (the last to fully develop) reach an adult size is approximately age 19.[27] Similarly, the management CRS in children 13 to 18 may more closely approximate that of adults compared to children 12 years or younger, as the anatomic space and physiologic mechanisms incrementally approach that of adults. The panel's actions highlighted this concept of an age continuum by reaching consensus on a statement indicating patients 12 and under are typically managed differently than patients 13 to 18 years old (statement 2).

Although it may not always be feasible in the uncooperative pediatric patient, the use of nasal endoscopy to evaluate CRS is ideal and should be attempted. The panel reached consensus that either flexible or rigid nasal endoscopy is advantageous as it allows for direct assessment for the presence of purulence, mucosal edema, nasal polyps, and adenoid hypertrophy/adenoiditis (statement 3). Alternatively, lateral plain film x-ray or CT is less invasive but can only indirectly assess for some of these same vital factors, albeit with the requisite radiation exposure to the skull and brain, which carries a postulated risk of malignancy. Radiologic imaging studies (eg, lateral plain films) are not recommended to assess the adenoid in children with CRS because they provide limited information on adenoid size alone, which does not necessarily correlate with ability to serve as a bacterial reservoir for infection (statement 7). Moreover, imaging studies involve radiation of the skull and brain, which carries a postulated risk of malignancy. Although the relative risk ratios of cancer from childhood radiation exposure can be eye-catching, the absolute risk of malignancy from radiation exposure is extremely small. Specifically, the estimated absolute risk difference is approximately 1 resultant case of leukemia or brain tumor per 10,000 head CT scans obtained in childhood although this carries an imposing relative risk ratio of approximately 3.18 (95% CI, 1.46-6.94) for leukemia and 2.82 (95% CI, 1.33-6.03) for brain tumors.[28]

The panel reached strong consensus (mean Likert score = 8.22) that children who present with polyps as a component of PCRS represent a distinct patient subgroup (statement 4). Similar to adults, the presence of polyps in children constitutes a different subtype of CRS with differing pathophysiology and distinct optimal management.[23-25,29] Specifically, children presenting with nasal polyps carry a substantially increased risk of underlying cystic fibrosis and should be specifically assessed for this and other serious comorbid disorders such as allergic fungal sinusitis or antrochoanal polyps.[30]

Although some studies have shown possible association of allergic rhinitis (AR) to the development of PCRS, other studies suggest that allergy is not a significant factor in pediatric sinus disease. A study by Sedaghat et al[31] reported on a large series of 4044 pediatric patients with PCRS and found that AR was the most common comorbidity with 26.9% of patients carrying a diagnosis of AR. The authors concluded, ''formal allergy testing, guided by clinical history and regional allergen sensitivity prevalence, should be strongly considered in all children with CRS.''[31]

Interestingly, a later study from the same author group reported on a cohort of patients with allergic rhinitis with or without development of subsequent PCRS. They found that patients who developed subsequent PCRS did not have more severe subjective AR or more severe objective quantitative atopy measurements.[32] The only factor associated with development of PCRS was exposure to tobacco smoke (OR = 3.96, 95% CI, 1.50-10.48), and the authors concluded ''the degree of atopy, as reflected by the number of aeroallergen sensitivities or the presence of atopic comorbidities, is not associated with progression to CRS in the pediatric age group.''[32] Although this study does not directly contradict a possible causal relationship between AR and PCRS, it does suggest there is a not a measurable dose-dependent relationship between them. Clearly the association between AR and PCRS is complex and multifarious, and further study into this important question is required. The panel weighed this issue and the available evidence along with their own experience, and ultimately the majority felt that there was indeed a clinically relevant association between

AR and PCRS. This led to consensus being achieved for a statement supporting the association of AR as a contributing factor for PCRS, particularly in older children (statement 5).

Medical Treatment of PCRS

Published recommendations advocate the use of antibiotic therapy in PCRS as an essential element in the treatment of this disease.[23] Although no specific high-level evidence supports the effectiveness of broad-spectrum antibiotics in chronic rhinosinusitis in children, their use is understandably widespread. The optimal duration of antimicrobial therapy or duration that would constitute ''maximal medical therapy'' remains unclear. The panel struggled with the question of antibiotic duration in PCRS to be highly nuanced, as demonstrated by statement 9 achieving consensus while statement 14 did not (see **Table 3**). While guidelines from professional organizations have recommended 10 to 14 days of therapy for acute uncomplicated rhinosinusitis in children,[33,34] longer courses have generally been recommended for chronic rhinosinusitis with the inference that PCRS is a more advanced infection requiring more extended therapy.[23] As an extension of this concept, topical antibiotic therapy has been purported as a direct therapy that might be utilized over extended periods for the treatment of chronic rhinosinusitis.[35] However, based on the current limited body of related evidence, the panel did not reach consensus regarding a role for topical antimicrobials.

CRS is increasingly understood as a multifactorial process in which bacteria may play only 1 role of many.[36] Accordingly, therapies beyond antimicrobials have been utilized in PCRS, and there was more agreement among the panel regarding other topical adjuvant medical therapies. Intranasal topical corticosteroids suppress mucosal inflammation and have been widely prescribed. These anti-inflammatory agents have demonstrated efficacy in the adult population for chronic rhinosinusitis and are included in the consensus statement addressing adult sinusitis.[37] Evidence is more limited in the pediatric literature but supports topical steroid use in PCRS either alone or in combination with antibiotic therapy.[38] Nasal saline irrigations are thought to help primarily in the clearance of secretions, pathogens, and debris. Wei and colleagues demonstrated significant improvement in both quality of life and CT scan Lund-Mackay scores after 6 weeks of once-daily nasal saline irrigation[39] as well as long-term efficacy as a first-line treatment in PCRS and subsequent nasal symptoms.[40]

The panel directed special attention on the topic of gastroesophageal reflux disease and PCRS due to persistent controversy and uncertainty on this topic. An association between GERD and sinusitis has been repeatedly suggested in the pediatric population. However, no definitive causal relationship has been demonstrated in randomized, controlled studies in the PCRS patient.[41] The question has not been answered conclusively, but there is a lack of evidence to support a strong relationship between GERD and PCRS. This fact was reflected in the panel reaching consensus that empiric therapy for GERD in the context of PCRS is not indicated (statement 13). Similarly, consensus was not reached regarding a contribution of GERD in the pathogenesis of PCRS (**Table 2**, statement 8) and in the routine treatment of GERD as part of the comprehensive therapy of PCRS (**Table 2**, statement 15).

Adenoidectomy/Adenoiditis

Adenoidectomy is a simple, well-tolerated procedure that has always been an attractive surgical option to consider for the treatment of PCRS. Yet, the ideal role of adenoidectomy in the treatment of PCRS has been somewhat elusive. The panel desired to address this issue as part of the consensus statement. Although high-level, randomized sham surgery controlled studies are not available or even feasible, solid evidence supports the benefit of adenoidectomy in managing PCRS. From the microbiologic viewpoint, adenoidectomy (regardless of adenoid hypertrophy) has been shown to produce a dramatic decrease in nasopharyngeal pathogens that have been implicated in pediatric CRS.[8,42] From a clinical outcomes standpoint, a meta-analysis of 8 studies investigating the efficacy of adenoidectomy alone in pediatric CRS patients (mean age 5.8 years; range, 4.4-6.9 years) that failed medical management demonstrated that the majority of patients significantly improved sinusitis symptoms after adenoidectomy (subjective success rate = 69.3%, 95% CI, 56.8%-81.7%, $P < .001$).[43] The data from these studies helped the panel reach consensus that adenoidectomy is an effective first-line surgical procedure for younger children (statements 18, 19). The panel was unable to reach consensus on the utility of adenoidectomy in patients age 13 years and older due to the absence of supporting data for adolescent patients (**Table 2**, statement 23).

The panel reached agreement that adenoidectomy can have a beneficial effect on pediatric CRS independent of ESS (statement 24). This consensus was based in part on the highly published success rate of adenoidectomy in managing pediatric CRS[44] and the data from one prospective investigation that recommended adenoidectomy prior to ESS as part of a stepped treatment algorithm for the management of pediatric CRS.[45] It is recognized that adenoidectomy is frequently coupled with other minimally invasive procedures such as sinus irrigation. However, due to the practical limitations of the clinical consensus statement process, the panel chose to consider procedures on their own individual merit as opposed to in combination with other procedures. Panel consensus was achieved regarding the value of adenoidectomy by itself (statements 18, 19, 20) but not for antral irrigation by itself (statement 17).

Despite the general belief that infection in 1 part of the pharyngeal lymphoid tissue can spread to another part of Waldeyer's ring and that the bacteriology in the adenoid and palatine tonsils are similar,[46] the consensus panel strongly agreed that tonsillectomy is an ineffective treatment for pediatric CRS (statement 25). This was due to the lack

of any direct evidence supporting tonsillectomy for the management pediatric CRS.

Endoscopic Sinus Surgery and Turbinoplasty

ESS has been shown to be an effective mode of therapy in children with PCRS who have failed maximal medical management.[18,19] In a Cochrane/PubMed database review (1990-2012) conducted by Makary and Ramadan, success rates of 82% to 100% were reported for pediatric ESS with an overall complication rate of only 1.4%.[18] Similarly, in a meta-analysis of 15 interventional studies (levels II-IV, n = 1301), Vlastarakos et al[19] concluded that ESS improved sinus-related symptoms and quality of life in PCRS patients, giving the procedure a grade B strength of recommendation. PCRS patients undergoing ESS have also been found to harbor more severe disease than those treated with adenoidectomy or medical therapy.[18] Given such evidence, the panel reached consensus that ESS is an effective procedure for treating PCRS and is best performed when medical therapy, adenoidectomy, or both have proven unsuccessful (statement 23).

A comprehensive clinical consensus statement regarding the appropriate use of computed tomography in the context of PCRS has been published previously[20] and was not further addressed by the current panel. However, the panel did agree that CT scan of the paranasal sinuses is indicated prior to ESS to assess structure, development, and extent of disease (statement 24). Image guidance was also deemed particularly useful for revision ESS cases and in children with extensive nasal polyposis that could obscure typical anatomical landmarks (statement 25). Data regarding post-ESS debridement in pediatric patients differ from the related data in adults. Multiple level 1b studies have shown that sinus cavity debridement significantly improved symptoms and endoscopic outcomes in adult CRS patients following ESS.[47-50] Based on the available evidence, debridement has been recommended in the early postoperative care of adult ESS patients.[51] However, no corresponding studies have been published investigating the impact of postoperative debridement on PCRS patients. In fact, several studies have shown that postoperative debridement was not necessary in children.[52,53] Consequently, the panel agreed that debridement is not essential for the successful outcome of pediatric ESS (statement 27).

Based on findings primarily from animal studies, there has been concern that pediatric ESS may lead to adverse sequelae on pediatric facial skeletal development. Both Mair et al[54] and Carpenter et al[55] reported significant alterations in midface and sinus growth following ESS in a piglet model. In humans, Kosko et al[56] presented a series of 5 patients who developed maxillary sinus hypoplasia after ESS but no clinically apparent facial asymmetry or midface hypoplasia. Three longitudinal studies of human children with follow-up times ranging from 6.9 to 13.2 years reported no deleterious effects on facial growth after pediatric ESS using both volumetric and anthropomorphic measurements.[57-59] Therefore, after reviewing the evidence, the panel reached consensus that there is a lack of convincing evidence that ESS causes clinically significant impairment of facial growth when performed in children with CRS (statement 26).

Balloon catheter sinuplasty (BCS) has recently emerged as another therapeutic option in the surgical management of PCRS, having been more extensively studied in adult patients to this point. In a nonrandomized prospective review of 30 PCRS patients who failed medical therapy, 80% treated with BCS showed symptomatic improvement.[60] Likewise, in a follow-up study by the same author, a success rate of 81% was reported in children with CRS who underwent BCS after adenoidectomy failure.[61] However, no studies have directly compared the efficacy of BCS to ESS in the treatment of PCRS. Therefore, the panel reached consensus that the effectiveness of BCS versus traditional ESS for PCRS cannot be determined with the current evidence (statement 28). The further evaluation of BCS in children as a simple, potentially less traumatic procedure in the management of PCRS would be an appropriate research priority for the near future.

With respect to inferior turbinoplasty, no consensus could be reached regarding its role in the treatment of PCRS. The panel explored this issue extensively as turbinoplasty is a commonly performed procedure whose precise clinical role remains ill defined. Although some panelists agreed that inferior turbinate reduction is a safe, minimally invasive procedure that could potentially benefit children with PCRS, others disagreed due to the lack of supportive evidence in the literature. To date, no clinical studies specifically investigating the efficacy of inferior turbinoplasty in the context of PCRS have been reported. Moreover, there is also no data to determine that PCRS patients would derive the most benefit from inferior turbinate reduction or what the potential mechanisms of improvement might be. Thus, no consensus statements pertaining to inferior turbinoplasty in the management of PCRS could be made by the panel (**Table 2**, statements 31-33). Given the attractiveness of turbinoplasty as an adjunctive procedure to adenoidectomy and/or ESS, further investigation into potential role of inferior turbinoplasty in the management of PCRS should be a research priority.

Similar to inferior turbinoplasty, there were no studies found in children examining whether reduction of a concha bullosa has any positive impact on the treatment of PCRS. Again similar to inferior turbinoplasty, reduction of a concha bullosa is also an attractive, simple, minimally invasive procedure that could be plausibly expected to improve nasal airflow and mucociliary clearance and potentially increase the permeation of topical medications. However, there is a dearth of evidence on the topic, so the panel only reached a near consensus that reduction of concha bullosa, when present, is a valuable component of the surgical management of PCRS (**Table 2**, statement 34).

Conclusion

This clinical consensus statement was developed by and for otolaryngologists and is intended to promote appropriate, and when possible, evidence-based care for pediatric patients with chronic rhinosinusitis. A series of clinical statements were developed by an expert panel using an objective survey method. A complete definition of PCRS was first developed, and additional statements addressing the diagnosis of PCRS, the medical management of PCRS, the appropriate role of adenoidectomy in the management of PCRS, and the appropriate role of endoscopic sinus surgery in the management of PCRS were subsequently produced and evaluated. It is anticipated that the application of these principles will result in decreased variations in the care of PCRS patients and an increase in the quality of care.

Disclaimers

The views herein are the private views of the authors and do not reflect the official views of the Department of the Army or the Department of Defense.

Clinical consensus statements are based on the opinions of carefully chosen expert panels and provided for informational and educational purposes only. The purpose of the expert panel is to synthesize information, along with possible conflicting interpretations of the data, into clear and accurate answers to the question of interest. Clinical consensus statements may reflect uncertainties, gaps in knowledge, opinions, or minority view points, but through a consensus development process, many of the uncertainties are overcome, a consensual opinion is reached, and statements are formed. Clinical consensus statements are not clinical practice guidelines and do not follow the same procedures as clinical practice guidelines. Clinical consensus statements do not purport to be a legal standard of care. The responsible physician, in light of all the circumstances presented by the individual patient, must determine the appropriate treatment, diagnosis, and management. Consideration of clinical consensus statements will not ensure successful patient outcomes in every situation. The AAO-HNSF emphasizes that these clinical consensus statements should not be deemed to include all proper diagnosis/management/treatment decisions or methods of care or to exclude other treatment decisions or methods of care reasonably directed to obtaining the same results.

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Author Contributions

Scott E. Brietzke, writer, chair; **Jennifer J. Shin**, writer, assistant chair; **Sukgi Choi**, writer, panel member; **Jivianne T. Lee**, writer, panel member; **Sanjay R. Parikh**, writer, panel member; **Maria Pena**, writer, panel member; **Jeremy D. Prager**, writer, panel member; **Hassan Ramadan**, writer, panel member; **Maria Veling**, writer, panel member; **Maureen Corrigan**, writer, AAO-HNSF staff liasion; **Richard M. Rosenfeld**, writer, consultant.

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REVIEW ARTICLE

Update on evidence-based reviews with recommendations in adult chronic rhinosinusitis

Richard R. Orlandi, MD[1], Timothy L. Smith, MD, MPH[2], Bradley F. Marple, MD[3], Richard J. Harvey, MD[4], Peter H. Hwang, MD[5], Robert C. Kern, MD[6], Todd T. Kingdom, MD[7], Amber Luong, MD, PhD[8], Luke Rudmik, MD, MSc[9], Brent A. Senior, MD[10], Elina Toskala, MD, PhD[11,12] and David W. Kennedy, MD[13]

Chronic rhinosinusitis (CRS) has a significant impact not only on individuals who are afflicted but also on society as a whole. An increasing emphasis is being placed on incorporating the best available evidence into the care of patients, in association with an individual clinician's expertise and the patient's values. Recent evidence-based reviews with recommendations (EBRRs) have distilled our knowledge of CRS treatment options and have also pointed out continued gaps in this knowledge. This review synthesizes the findings of 8 EBRRs regarding CRS published in the *International Forum of Allergy and Rhinology* between 2011 and 2014. The recommendations in this review are based on the best available evidence and are meant to be incorporated into each patient's individual care, along with the practitioner's expertise and the individual patient's values and expectations. It is hoped that the EBRRs, and the process that spawned them, can provide the foundation for future guidelines in the diagnosis and management of CRS.

Key Words:
chronic rhinosinusitis; CRS; evidence-based review with recommendation; EBRR; evidence-based medicine; EBM

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Executive summary

Chronic rhinosinusitis (CRS) has a significant impact not only on individuals who are afflicted but also on society as a whole. An increasing emphasis is being placed on incorporating the best available evidence into the care of patients, in association with an individual clinician's expertise and the patient's values. Recent evidence-based reviews with recommendations (EBRRs) have distilled our knowledge of CRS treatment options and have also pointed out continued gaps in this knowledge.

This review synthesizes the findings of 8 EBRRs regarding CRS published in the *International Forum of Allergy and Rhinology* between 2011 and 2014. These synthesized recommendations are summarized in Table 1. The authors used an online iterative process in evaluating and synthesizing these reviews. The process started with the development of an initial EBRR manuscript, which was then sequentially reviewed by additional authors, with special attention to the validity of the recommendations and the areas of knowledge gaps in current EBRRs. With each proposed revision, consensus of the prior authors was achieved before the input of the next author was sought.

[1]*Division of Otolaryngology–Head and Neck Surgery, University of Utah School of Medicine, Salt Lake City, UT;* [2]*Division of Rhinology and Sinus/Skull Base Surgery, Oregon Health and Science University, Portland, OR;* [3]*Department of Otolaryngology–Head and Neck Surgery, University of Texas Southwestern Medical Center, Dallas, TX;* [4]*Division of Rhinology and Endoscopic Skull Base Surgery, University of New South Wales and St. Vincent's Hospital, Sydney, Australia;* [5]*Department of Otolaryngology–Head and Neck Surgery, Stanford University School of Medicine, Stanford, CA;* [6]*Department of Otolaryngology, Head and Neck Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL;* [7]*Department of Otolaryngology–Head and Neck Surgery, University of Colorado, Aurora, CO;* [8]*Department of Otorhinolaryngology–Head and Neck Surgery, University of Texas Medical Center at Houston, Houston, TX;* [9]*Division of Otolaryngology–Head and Neck Surgery, Department of Surgery, University of Calgary, Alberta, Canada;* [10]*Department of Otolaryngology/Head and Neck Surgery, University of North Carolina School of Medicine, Chapel Hill, NC;* [11]*Center for Applied Genomics, Children's Hospital of Philadelphia, Philadelphia, PA;* [12]*Department of Otolaryngology–Head and Neck Surgery, Temple University, Philadelphia, PA;* [13]*Department of Otorhinolaryngology–Head and Neck Surgery, University of Pennsylvania School of Medicine, Philadelphia, PA*

Correspondence to: Richard R. Orlandi, MD, Division of Otolaryngology–Head and Neck Surgery, University of Utah School of Medicine, 50 North Medical Drive, 3C120, Salt Lake City, UT 84132; e-mail: richard.orlandi@hsc.utah.edu

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TABLE 1. Summary of recommendations synthesized from published EBRRs

Topic	Recommendation
Medical therapy for CRS	
Allergy testing and treatment	**Option** in CRSwNP and CRSsNP. **Recommendation for** subcutaneous immunotherapy for patient with seasonal or perennial allergic rhinitis not responsive to conservative medical therapy and whose symptoms significantly affect quality of life.
Standard topical (spray) corticosteroids	**Strong recommendation for** routine cases of CRS.
Nonstandard topical (off-label) corticosteroids	**Option**.
Systemic corticosteroids—CRSwNP	**Strong recommendation for** the use of oral steroids in the short-term management of CRSwNP. **Recommendation for** use in the perioperative period for CRSwNP.
Systemic corticosteroids—CRSsNP	**Option** in cases of CRSsNP. **No recommendation** regarding use in the perioperative period for CRSsNP.
Systemic corticosteroids—AFRS	**Recommendation for** the use of oral steroids in the management of AFRS. **Recommendation for** use in the perioperative period for AFRS.
Oral antibacterial therapy lasting less than 3 weeks (nonmacrolide therapy)	**Option.**
Oral antibacterial therapy lasting longer than 3 weeks (nonmacrolide therapy)	**Recommendation against** (except for macrolide class) for routine CRS cases.
Macrolide antibiotics	**Option**.
Intravenous antibacterials	**Recommendation against** use for uncomplicated CRS cases.
Topical antibacterials	**Recommendation against** use for routine CRS cases.
Oral antifungals	**Recommendation against** use for routine CRS cases.
Topical antifungals	**Strong recommendation against** use for routine CRS patients.
Distribution of topical therapies—effect of sinus surgery	**Recommendation for** increased penetration of topical therapy. Surgery can be recommended on a case by case basis as the surgeon and patient deem necessary.
Distribution of topical therapies—effect of topical therapy delivery device	**Recommendation for** use of disposable large volume devices for sinus delivery. **Recommendation against** low volume devices, such as simple nebulizers, drops and spray, which have limited sinus delivery. **Option** for low volume devices, such as drops or sprays, if large volume devices are not tolerated, but low volume devices must be used in optimal head position and even then sinus distribution is limited (see Head position).
Distribution of topical therapies—effect of head position	**Recommendation for** HDF when using high-volume devices if patient will tolerate. HDF for low-volume device, but with limited sinus penetration. **Recommendation for** LHB or LHL position when using low-volume devices, which will only reliably distribute to the nasal cavity.
Distribution of topical therapies—	**Recommend for u**se of high-volume delivery devices to achieve sinus delivery in patients with unfavorable nasal anatomy. **Option** for short-term (3–4 days or less) use of topical vasoconstrictor to improve nasal cavity delivery in cases of turbinate hypertrophy. **Recommend against** long-term use of topical vasoconstrictor to improve nasal cavity delivery.
Surgical therapy for CRS	
Image-guided surgery	**Option.**
Early postoperative care—nasal saline irrigation	**Recommendation for** use.
Early postoperative care—debridement	**Recommendation for** postoperative debridement.
Early postoperative care—systemic steroids	**Option.**

(*Continued*)

TABLE 1. Continued

Topic	Recommendation
Early postoperative care—topical corticosteroids	**Recommendation for** standard nasal steroid spray. **Option** for use of nonstandard delivery mechanisms for patients with severe mucosal inflammatory disease.
Early postoperative care—antibiotics	**Option** for routine endoscopic sinus surgery.
Early postoperative care —topical decongestants	**Recommendation against** use.
Early postoperative care —drug eluting spacers/stents	**Option.**

AFRS = allergic fungal rhinosinusitis; CRS = chronic rhinosinusitis; CRSwNP = CRS with nasal polyps; CRSsNP = CRS without nasal polyps; EBRR = evidence-based reviews with recommendations; HDF = head down forward; LHB = laying head back; LHL = lateral head low.

Diagnosis of CRS

No EBRRs dealing with the efficient diagnosis of CRS have yet been published and this topic would benefit from an EBRR.

Medical therapy for CRS

Allergy evaluation and management in CRS patients were found to have equivocal support in the literature and recommended as an option in CRS patients, both with polyps (CRSwNP) and without polyps (CRSsNP). Topical nasal steroid sprays were strongly recommended based on their efficacy and relatively low risk of harm. Nonstandard topical delivery of corticosteroids (eg, as a medicated irrigation) was recommended as an option, due mainly to the low level of evidence and poorly defined risks. Oral corticosteroids were recommended for the short-term management (up to 8–12 weeks' duration) of CRSwNP and in the perioperative period, although risks were acknowledged. For CRSsNP, the risk-benefit ratio is less well known and oral corticosteroids were considered an option, with no evidence for or against their use in the perioperative period. For allergic fungal rhinosinusitis (AFRS), steroids were again found to be advantageous and were recommended overall and in the perioperative period.

Antimicrobials in CRS were extensively reviewed and found to have both advantages and disadvantages in CRS. Short-term oral antibiotic use (less than 3 weeks' duration) was considered an option, while the authors recommend against the use of long-term oral antibiotics (greater than 3 weeks' duration) in routine CRS cases. The exception to this recommendation was macrolide antibiotics, which have some evidence of efficacy with prolonged use. They were considered an option in the treatment of CRS. The evidence for efficacy of both intravenous and topical antibiotics was found to be lacking. With the significant risk of intravenous antibiotics and costs associated with both intravenous and topical antibiotics, the authors recommended against their use in routine CRS cases. Similarly, the weight of evidence was against the use of topical or oral antifungals for routine CRS cases and the authors recommended against their use as well.

Distribution of topical agents to the sinuses was found to be affected by a number of factors, including the type of device, head position, nasal anatomy, and sinus surgery. Based on the evidence in these areas, high-volume irrigations were recommended and were found to overcome variances in nasal anatomy, such as septal deviation, and the effect of different head positions. Surgery appears to enhance the penetration of topical therapies into the sinuses.

Surgical therapy for CRS

The timing of surgery relative to medical therapy and patient symptoms, the appropriate extent of surgery, and the comparative efficacy of various techniques and tools are all areas that require additional evidence. Image-guided surgery (IGS) in sinus surgery has been studied much since its incorporation into surgery for CRS. The evidence is relatively low level and, with costs high, IGS was recommended as an option in surgery for CRS.

Postoperative care following sinus surgery was assessed and the following interventions were recommended: nasal saline irrigations, postoperative debridement, and topical nasal steroid sprays. Oral corticosteroids were considered an option, as were nonstandard topical corticosteroid delivery, antibiotics, and drug-eluting stents. Newer drug-eluting implants were not discussed. Topical decongestants were recommended against.

Future directions

While the EBRRs published to this point have explored a large number of important topics in CRS management, this review has also shown gaps in our collective knowledge of other areas of management and of evaluation as well. Possible topics for future EBRRs in CRS are the following:

- Cost-effective diagnosis
- Cost-effective evaluation of underlying conditions
- Etiologic factors
- Value of histopathologic assessment of sinus tissue
- Pediatric chronic rhinosinusitis
- Antibiotics in the management of acute exacerbations of CRS
- Other medical treatments (eg, aspirin desensitization, leukotriene modifiers, etc.)

- Optimal medical therapy to be employed prior to considering surgery
- Comparative efficacy of surgical instrumentation and techniques (eg, balloon dilation)
- Comparative efficacy of the extent of surgery
- Appropriate long-term sinus care.

The recommendations in this review are based on the best available evidence and are meant to be incorporated into each patient's individual care, along with the practitioner's expertise and the individual patient's values and expectations. They are not a "cookbook," nor are they official guidelines sanctioned by any official bodies. Additionally, they are not static, but will always be subject to new evidence as it comes forward. It is hoped that the EBRRs, and the process that spawned them, can provide the foundation for future guidelines in the diagnosis and management of CRS.

Introduction

The societal and individual impact of CRS is significant and well documented. Decrements in quality of life (QOL) and work productivity are substantial and produce an extensive economic burden to society and the health systems required to alleviate the suffering associated with CRS.[1–3] Over the last few decades, the pace of investigation into CRS has quickened and has led to a better understanding of many facets of this condition. Notwithstanding these significant advances in our understanding of CRS, it remains a condition, or more likely a group of conditions, with multiple potential etiologies and with many possible treatments.

Prolonged inflammation of the nose and sinuses can manifest with different symptoms in different patients and may present differing physical manifestations as well (eg, the presence or absence of polyps). Despite a determined search, a single unifying pathophysiologic mechanism remains elusive. Without a clear cause (or at least a few clear causes), effective treatments that target specific underlying pathophysiologic mechanisms also remain unidentified. Physicians and others who treat CRS patients are thus left with a large number of treatment options that have arisen out of dogged efforts to alleviate the significant amount of suffering associated with this condition.

EBM has been defined as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research."[4] To be clear, EBM is not a cookbook approach to all patients by all practitioners. Instead, EBM is a triad that incorporates the best available evidence into an individual practitioner's clinical expertise combined with the individual patient's values and desires. It is a method that maximizes the *value* of the care delivered, with value loosely defined as the ratio of outcome to cost. Clearly, a thorough understanding of the best available evidence is a key component in delivering maximum value through EBM.

In an effort to enhance the application of EBM to the treatment of CRS, Rudmik and Smith[5] proposed a streamlined method for reviewing topics in CRS treatment and making recommendations based on the evidence. These EBRRs result from a less formal but sufficiently robust process of evaluating the current evidence on a particular topic. Following an initial review and development of recommendations, other experts in the topic sequentially review the EBRR until a broad consensus is reached. Since the development of this process in late 2011, 8 EBRRs have been published. The purpose of this article is to comprehensively review these documents, synthesize their recommendations, and point out additional areas that would benefit from additional EBRRs.

Methods

All published EBRRs regarding CRS were reviewed, following the method of Rudmik and Smith.[5] The clinical topic selected was the current state of EBM as assessed by EBRRs in CRS. Potential authors were selected from a group of recognized experts in the field of CRS who were familiar with guideline development. Many had previously participated in development of EBRRs. Using an online iterative process, the initial review was sequentially reviewed by additional authors, with special attention to the validity of the recommendations and the areas of knowledge gaps in current EBRRs. Updates to the review were routed through the first author and the consensus of the prior authors was achieved before the input of the next author was sought. The identity of earlier authors was not revealed in order to minimize potential bias.

Results

Diagnosis of CRS

No EBRRs dealing with the efficient diagnosis of CRS have yet been published. Timing of referral to a specialist, role of nasal endoscopy, and impact of imaging are areas that would benefit from an EBRR.

Medical therapy for CRS

Allergy evaluation

In an effort to shed some light on the pathophysiology of CRS and 1 potential avenue of treatment, Wilson et al.[6] examined the role of allergy in CRS with and without nasal polyps (CRSwNP, CRSsNP). They reviewed 18 articles that dealt with the relationship between CRSwNP and allergy and found 10 articles supporting an association, 7 articles showing no association, and 1 article showing a possible association. The evidence for an association between CRSsNP and allergy was similarly equivocal, with 4 articles demonstrating an association and 5 showing no association. The strength of the articles in these analyses did not vary significantly, leaving the authors to conclude that

evidence for a pathophysiologic association between allergy and CRS was mixed. No articles examined the role of allergy treatment in outcomes of CRSwNP or CRSsNP. The authors summarized their findings as follows:

- Aggregate quality of evidence: D (Expert opinion and reasoning from first principles and conflicting prevalence data).
- Benefit: Allergy evaluation and management are generally well tolerated. Management theoretically reduces triggers of CRS while modifying symptoms of allergic rhinitis, possibly impacting chronic rhinosinusitis.
- Harm: Mild local irritation associated with testing and immunotherapy, mild sedation seen with some antihistamine drugs; severe complications are rare.
- Cost: Moderate direct costs for testing and treatment; some therapies require significant patient time (eg, office-administered subcutaneous immunotherapy).
- Benefits-Harm assessment: Preponderance of benefit over harm.
- Value Judgments: None.
- Recommendation: Allergy testing and treatment are an option in CRSwNP and CRSsNP.
- Intervention: Allergy testing (skin or in vitro) and allergy management (avoidance, pharmacotherapy, and/or immunotherapy).

Treatment for allergic rhinitis

While the exact pathophysiologic role of allergy in CRS remains unclear, there is significant symptom overlap. Treatment of allergy when it coexists with CRS will likely enhance patient outcome by mitigating the allergic contribution to the symptoms that are common to both allergic rhinitis and CRS. To that end, Purkey et al.[7] exhaustively reviewed the evidence on subcutaneous immunotherapy (SCIT) for allergic rhinitis (AR). Building upon the Cochrane Review of Allergen Injection Immunotherapy for Seasonal Allergic Rhinitis published in 2007,[8] they examined the literature published between 2006 and 2011. The authors assessed the literature on both seasonal and perennial allergic rhinitis and included only those studies graded as Level 1 evidence, yielding 12 articles for consideration. Primary outcome measurements were mostly symptoms scores, medications scores, or a combination of symptom and medication scores. Additional endpoints included the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), immunoglobulin assays, challenge tests, and adverse events. This EBRR found the studies examined showed uniform efficacy of SCIT in reducing symptoms and/or medication use in patients being treated for seasonal or perennial AR. Moreover, they found SCIT to be safe, with only 0.13% to 0.2% of conventional dosing injections producing a systemic reaction. The authors summarized their findings as follows:

- Aggregate quality of evidence: A (Level 1b: 12 studies).
- Benefit: Improvement in symptom and/or medication scores and validated quality of life measures. Associated changes in surrogate markers of immunologic protection.
- Harm: Local and systemic reactions (rare but with significant morbidity/mortality if they occur).
- Cost: Moderate in both monetary cost and time commitment.
- Benefits-harm assessment: Preponderance of benefit over harm in appropriately selected patients.
- Value judgments: None.
- Recommendation level: Recommend subcutaneous immunotherapy for patient with seasonal or perennial allergic rhinitis not responsive to conservative medical therapy and whose symptoms significantly affect QOL.

Sublingual immunotherapy (SLIT) has emerged as a popular treatment and a number of publications have examined its efficacy and safety, including a number of systematic analyses.

Corticosteroids

While the exact etiology (or etiologies) of CRS remains unknown, it is well accepted to be an inflammatory condition of the nose and paranasal sinuses. To that end, corticosteroid therapy has been a mainstay of treatment for many years. Two EBRRs have examined the role of corticosteroids in the treatment of CRS, with Rudmik et al.[9] examining topical therapy and Poetker et al.[10] exploring systemic therapy.

Standard topical (spray) corticosteroids. Rudmik et al.[9] identified 5 meta-analyses that examined the efficacy and safety of standard topical nasal corticosteroid sprays in both CRSwNP and CRSsNP. All were graded as 1a in quality and 4 of the 5 demonstrated significant improvements in symptoms and endoscopic appearance. Overall, the authors concluded the following:

- Aggregate quality of evidence: A (Level 1a: 5 studies).
- Benefit: Improved symptoms and endoscopic appearance. Reduced polyp size.
- Harm: Headache. Epistaxis. Cough.
- Cost: Low to moderate (range, $0.61/day to $4.80/day); depends on preparation.
- Benefits-harm assessment: Preponderance of benefit over harm.
- Value judgments: The authors recognize that other topical therapy options may be required when an adequate trial of standard metered-dose topical nasal steroid spray has failed to improve clinical outcomes.
- Recommendation level: Strong recommendation for routine cases of CRS.

Nonstandard topical corticosteroids. Rudmik et al.[9] also reviewed evidence regarding nonstandard or "off-label" applications of topical corticosteroids, such as high-volume irrigations, nebulized preparations, and low-volume drops.

They found a much less robust body of evidence, with 6 studies examining these nonstandard therapies. Only 1 was a randomized control trial (Level 1b) while the other 5 were Level 4 studies. Safety related to the potential for unwanted systemic absorption was addressed in several studies, with no evidence to substantiate this concern. The authors acknowledged the potential advantages of these nonstandard delivery methods but at the same time called for more robust data to guide medical decision-making. They summarized their findings as follows:

- Aggregate quality of evidence: C (Level 1b: 1 study; Level 4: 5 studies).
- Benefit: Potentially reduce risk of ostial stenosis postoperatively. May reduce systemic steroid rescue episodes. Potential alternative to systemic steroids.
- Harm: Known risks of steroids; unknown absorption.
- Cost: Moderate to high (range, $4.19 to $10.51), depends on preparation and dosing schedule.
- Benefits-harm assessment: Equal balance of benefit to harm.
- Value judgments: Challenging to provide a recommendation for or against the use of nonstandard topical sinonasal steroid therapy based on one Level 1b study that demonstrated no benefit in a highly select CRS cohort (Samter's triad), whereas five Level 4 studies suggested there may be a clinical benefit. Great preference for topical sinonasal steroid therapy vs systemic steroid therapy.
- Recommendation level: Option in cases of CRS.

Systemic corticosteroids—CRSwNP. An EBRR by Poetker et al.[10] thoroughly explored the efficacy and safety of oral corticosteroid therapy for both CRSwNP and CRSsNP. Sixteen studies examined oral corticosteroids in the management of CRSwNP, ranging from Level 2 to Level 4 in quality. The studies employed varying dosages and durations of therapy and evaluated both subjective and objective outcomes. All of the studies showed improvements in the majority of measurements examined, at least in the short term (8–12 weeks). Longer-term efficacy was not thoroughly examined and, while no substantial adverse events were noted, most of the studies contained relatively small sample sizes and were limited in duration. Known but rare adverse events of oral corticosteroids would likely become evident with larger, longer-duration studies.

The authors also examined the use of oral corticosteroids in the perioperative management of CRSwNP. They found 3 studies that showed improvements in surgical field visualization but no effect on total blood loss. One study examined the postoperative use of oral corticosteroids and found improvement in subjective olfaction at 2 weeks postoperatively. Otherwise, there was no difference in symptoms compared to placebo. The EBRR summarized the use of oral corticosteroids in CRSwNP as follows:

Summary for oral steroid use in the medical management of CRSwNP

- Aggregate quality of evidence: A (Level 2: 5 studies; Level 3: 2 studies; Level 4: 11 studies).
- Benefit: Significant short-term improvements in subjective and objective measures in CRSwNP patients. Duration of improvement may last 8 to 12 weeks in conjunction with topical nasal steroid use.
- Harm: More gastrointestinal (GI) symptoms in steroid group, no severe reactions reported. Other known risks of steroids. Cost: Low.
- Benefits-harm assessment: Preponderance of benefit vs harm in small, short-term follow-up.
- Value judgments: Significant improvements in subjective and objective measures based on high quality data, low risk, and low cost.
- Recommendation level: Strong recommendation.
- Intervention: Strong recommendation for the use of oral steroids in the short-term management of CRSwNP.

Summary for oral steroid use in the perioperative period for CRSwNP

- Aggregate quality of evidence: B (Level 2: 2 studies; Level 3: 1 study).
- Benefit: Improves surgical visualization, may decrease operative time.
- Harm: Known risks of steroids.
- Cost: Low.
- Benefits-harm assessment: Benefit over harm.
- Value judgments: Improved visualization during surgery and improved postoperative course.
- Recommendation level: Recommend.
- Intervention: Consider use of oral steroids in the perioperative management of CRSwNP.

Systemic corticosteroids—CRSsNP. For patients with CRSsNP, the data were substantially less robust. Poetker et al.[10] examined 4 studies, all of which were Level 4 in quality. All 4 studies included corticosteroids with other treatments; there were no studies that examined oral corticosteroids as sole modalities of therapy. Moreover, there were variable dosing regimens and durations of therapy for the corticosteroid treatments. With the potential risk associated with systemic corticosteroid therapy, higher-quality evidence in CRSsNP is clearly needed. As with CRSwNP, studies were sought that evaluated the use of oral corticosteroids perioperatively. None were found, pointing out the need for study in this area. Overall, this EBRR summarized its findings as follows:

Summary for oral steroid use in CRSsNP

- Aggregate quality of evidence: C (Level 4: 4 studies).
- Benefit: Subjective improvement in patient symptoms associated with CRS, objective improvement in imaging. May avoid need for surgery in some.

- Harm: No specific reports, but potential risks of steroids are well known. Optimum duration and dosage are not known.
- Cost: Low.
- Benefits-harm assessment: Perceived balance of benefit to harm.
- Value judgments: Significant improvement in patient symptoms is important.
- Recommendation level: Optional.
- Intervention: The use of oral steroid in CRS without polyposis is optional. Patients with more severe disease may have a more favorable benefit-to-harm ratio than patients with mild disease.

Summary for oral steroid use in the perioperative period for CRSsNP

- Aggregate quality of evidence: N/A; there is a significant gap in evidence for this topic.
- Recommendation level: No recommendation.

Systemic corticosteroids—AFRS. Poetker et al.[10] also examined the role of oral corticosteroids in the treatment of AFRS. While a number of retrospective reports were found to address this issue, only 4 studies met strict criteria for diagnosis of AFRS and were thus included. Overall, the findings were similar to those of the CRSwNP analysis, with the data supporting the use of oral corticosteroids in AFRS. While the dosing in AFRS was similar to that used in CRSwNP, the duration was longer and the risks of such prolonged use become more of an issue in AFRS. Inasmuch as oral corticosteroids are frequently used as an adjunct in the perioperative period, this use was separately evaluated in this EBRR:

Summary for oral steroid use in AFRS

- Aggregate quality of evidence: B (Level 2: 1 study; Level 4: 3 studies).
- Benefit: Improvement in subjective and objective measures and decreased markers of inflammation.
- Harm: Known risks of steroids.
- Cost: Low.
- Benefits-harm assessment: Benefit over harm in short term.
- Value judgments: High-dose, long courses of steroids showed improvement in symptoms with relatively low adverse events; given the difficulty in treating AFRS, this course is very reasonable.
- Recommendation level: Recommend.
- Intervention: Consider the use of oral steroids in the management of AFRS.

Summary for oral steroid use in the perioperative period for AFRS

- Aggregate quality of evidence: B (Level 2: 1 study; Level 4: 1 studies).
- Benefit: Improvement in endoscopic findings intraoperatively, as well as delayed recurrence of disease following surgical treatment.
- Harm: Known risks of steroids.
- Cost: Low.
- Benefits-harm assessment: Benefit over harm, particularly after surgical debridement of fungal debris.
- Value judgments: Improvement in control of disease postoperatively with moderate adverse events.
- Recommendation level: Recommend.
- Intervention: Consider the use of oral steroids in the perioperative management of AFRS.

Antimicrobials

Persistent infection has been traditionally thought to be a source of inflammation in CRS. While this concept has more recently come under increasing scrutiny, antimicrobials continue to play a large role in the treatment of CRS.[11] Different from the use of antimicrobials for acute exacerbations of CRS, especially when culture-driven, many practitioners appear to use of antimicrobials to diminish longstanding inflammation in CRS, and especially as an essential component of medical therapy prior to considering surgery. Despite this widespread practice, Soler et al.[12] noted a paucity of evidence-based recommendations for the use of antimicrobials in CRS. Their EBRR resulted from examination of the use of systemic and topical antibacterials and antifungal medications in CRS by an American Rhinologic Society ad hoc committee. The EBRR investigated 8 different methods for using antimicrobials in CRS.

Oral antibacterial therapy lasting less than 3 weeks (nonmacrolide therapy). Six studies examined this issue and, despite some being randomized controlled trials (RCTs), most did not include a placebo arm, making the effect of therapy difficult to assess. Soler et al.[12] found the evidence supporting oral nonmacrolide antibacterial use surprisingly weak given how commonly they are used in the treatment of CRS. Given the potential side effects and costs associated with this therapy, their aggregate recommendation was to use antibacterials as an *option* in treating CRS:

- Aggregate quality of evidence: B (Level 1b: 4 studies; Level 4: 2 studies).
- Benefit: Reduction in visible polyp size and patient reported postnasal drainage. Potential for overall clinical improvement in uncontrolled studies.
- Harm: GI upset. Elevated liver function tests. *Clostridium difficile* colitis. Anaphylaxis. Bacterial resistance. Rash.
- Cost: Variable (low to high).
- Benefits-harm assessment: Balance of benefit vs harm.
- Value judgments: Modest reduction in some symptoms vs side effects and cost.
- Recommendation level: Option.

Oral antibacterial therapy lasting longer than 3 weeks (nonmacrolide therapy). Soler et al.[12] examined nonmacrolide antibacterial use lasting more than 3 weeks and found no clear benefit. Again, balancing the risks and costs of this approach with the limited evidence of benefit, the authors recommended against the use of antibacterials for more than 3 weeks for routine cases of CRS:

- Aggregate quality of evidence: N/A (single study).
- Benefit: No clear benefit demonstrated for prolonged course.
- Harm: GI upset. Potential for *Clostridium difficile* colitis. Anaphylaxis. Bacterial resistance. Rash.
- Cost: Variable (low to high).
- Benefits-harm assessment: Preponderance of harm over benefit: known risk of medication side effects, quantifiable costs, and potential for bacterial resistance vs unproven benefit of prolonged course.
- Value judgments: None.
- Recommendation level: Recommend against a prolonged (>3week) course of oral antibacterial antibiotics (except for macrolide class) for routine CRS cases.

Macrolide antibiotics. Because of their anti-inflammatory properties as well as other effects beyond bactericide, macrolides have been relatively well-studied in CRS. Soler et al.[12] found 17 studies evaluating them in CRS, with 2 randomized, placebo-controlled trials, 1 retrospective case-control study, and 14 prospective observational studies. Specific medications and dosages varied and duration of therapy ranged from 2 weeks to 12 months. Outcome measures included validated questionnaires, radiology, endoscopy, as well as other measures. The EBRR found abundant Level 4 evidence supporting the use of macrolide antibiotics in CRS, with 1 RCT also demonstrating modest improvements. In weighing the benefits and potential risks and costs, the EBRR summarized the evidence as follows:

- Aggregate quality of evidence: B (Level 1b: 2 studies; Level 3b: 1 study; Level 4: 14 studies).
- Benefit: Improved patient symptoms and endoscopy findings vs placebo in 1 controlled study. Uncontrolled studies showed additional improvements in imaging findings, characteristics of nasal mucous, and reduction of inflammatory mediators in mucous.
- Harm: GI upset. Rash. Taste disturbance. Hand numbness. All graded as mild to moderate and none required discontinuation of the medication. Potential liver function abnormalities. Theoretical risk of antibiotic resistance but none confirmed in the studies.
- Cost: Moderate to high. Treatment duration ranged from 2 weeks to 12 months. Most treated for at least 3 months.
- Benefits-harm assessment: Balance of benefit vs harm.
- Value judgments: Consistent benefit shown in multiple observational studies and 1 controlled study vs cost and minimal side effects. No evidence for superiority of any individual macrolides.
- Recommendation level: Option.

Intravenous antibacterials. Two relatively lower-quality (Level 4) studies examined this method of therapy for CRS and, while they showed some efficacy, they also demonstrated substantial adverse events. Overall, Soler et al.[12] recommended against this therapy for routine cases of CRS:

- Aggregate quality of evidence: C (Level 4: 2 studies).
- Benefit: Potential for improvement in patient-reported symptoms in uncontrolled studies.
- Harm: Thrombophlebitis. Deep venous thrombosis. Elevated liver function tests. Neutropenia/septicemia. Drug reaction. Rash. Bleeding.
- Cost: High.
- Benefits-harm assessment: Preponderance of harm over benefit.
- Value judgments: Clear risk of harmful side effects and high cost vs modest benefits reported in uncontrolled studies.
- Recommendation level: Recommend against use of intravenous antibiotics for uncomplicated CRS cases.

Topical antibacterials. In their EBRR of topical therapies for CRS, Rudmik et al.[9] examined 3 RCTs and a systematic review of topical antibacterials. Soler et al.[12] additionally included 5 studies ranging from observational cohorts to retrospective case series in their EBRR on antimicrobials. All 3 RCTs failed to show a significant clinical benefit, although all were small and none provided the intrinsic power of the study to show a clinically relevant difference between groups. The majority of published studies either showed no adverse events from treatment or failed to report these data. Rudmik et al.[9] separated their recommendations, based on the evidence, into those involving nebulizer and spray delivery and those involving other delivery methods, such as irrigations. They recommended against nebulizers and spray delivery as questionably effective but costly and with potential risk. No recommendation was made regarding other delivery methods. Soler et al.'s[12] findings involved all delivery methods and recommended against their use in routine cases of CRS. Their summaries are synthesized below:

- Aggregate quality of evidence: B (Level 1b: 2 studies; Level 2b: 1 study; Level 2c: 2 studies; Level 3a: 1 study; Level 4:4 studies).
- Benefit: Potential for improvement in patient-reported symptoms, endoscopic appearance, and QOL in uncontrolled studies. Controlled clinical trials failed to show a benefit; however, it is unclear whether studies were adequately powered.
- Harm: Increased congestion was seen with nebulized tobramycin. Nebulized forms of some antibiotics can cause bronchospasm. Topically applied antibiotics have been detected systemically in serum, and potential systemic adverse effects (ototoxicity or nephrotoxicity)with

topical aminoglycosides must be considered. Bioavailability of most antibiotics and ideal dosing regimens remain unknown. Topical regimens can be time consuming for patients, depending on frequency and route of administration. Risk of bacterial resistance must be considered.
- Cost: Moderate to high.
- Benefits-harm assessment: Potential for harm over benefit.
- Value judgments: Clinical benefit seen only in uncontrolled observational studies vs monetary expense, time commitment, and unknown safety profile.
- Recommendation level: Recommendation against use of topical antibiotics for routine CRS cases.

Oral antifungals. Soler et al.'s[12] EBRR examined 3 studies concerning the use of antifungal antibiotics in CRS. One double-blind RCT with placebo and 2 retrospective studies showed differing outcomes. The RCT showed no difference in computed tomography (CT) scores, QOL, and patient and physician evaluations. The 2 unblinded observational studies showed improvement in some patients. Adverse events, such as elevation in liver function studies, were seen in about one-quarter of patients. Due to the lack of clear benefit and the significant potential harm and cost of therapy, this EBRR recommended against oral antifungal therapy for routine CRS:

- Aggregate quality of evidence: B (Level 1b: 1 study; Level 4: 1 study).
- Benefit: Potential for overall clinical improvement in uncontrolled studies not seen in the single RCT.
- Harm: Elevated liver function studies.
- Cost: Moderate to high.
- Benefits-harm assessment: Preponderance of harm over benefit.
- Value judgments: Low-level evidence showing clinical improvement vs risk of liver dysfunction and considerable costs.
- Recommendation level: Recommendation against use of oral antifungal antibiotics for routine CRS cases.

Topical antifungals. As with topical antibacterials, topical antifungal therapy has been addressed by 2 EBRRs, with identical findings and recommendations.[9,12] Eight Level 1b RCTs involving placebos, 1 non–placebo-controlled RCT, and 4 observational studies have examined the use of topical antifungal therapy in CRS. Most of the studies examined topical amphotericin B, either as a spray or as an irrigation and with varying dosages. One study involved fluconazole nasal spray. Symptom, radiologic, and endoscopic improvement were assessed by the studies. Overall, both EBRRs found that the abundance of evidence failed to show a clinical benefit from any of the topical antifungal treatments.

- Aggregate quality of evidence: A (Level 1a, 1 study; Level 1b: 9 studies; Level 4: 4 studies).
- Benefit: No consistent benefit shown in clinical symptoms, endoscopy, or CT scans compared to placebo controls.
- Harm: Nasal burning. GI upset. Rash. Asthma attack. Acute exacerbation of CRS. Epistaxis.
- Cost: Moderate to high.
- Benefits-harm assessment: Preponderance of harm over benefit.
- Value judgments: No demonstrable benefit over placebo in multiple RCTs vs side effects and cost.
- Recommendation level: Strong recommendation against the use of topical antifungals for routine CRS patients.

Topical alternative therapies

Rudmik et al.'s[9] EBRR also examined nontraditional topical therapies that have been suggested for CRS, baby shampoo surfactant, manuka honey, and xylitol. Their report on these 3 promising therapies was unable to generate evidence tables or recommendations in light of the relative paucity of evidence for their efficacy.

Distribution of topical therapies

EBRRs performed by Rudmik et al.[9] and Soler et al.[12] demonstrated that some topical therapies may be beneficial in the treatment of CRS. An EBRR completed by Thomas et al.[13] examined how the distribution of these therapies are affected by nasal anatomy, device, head position, and previous surgery. Thirty-two studies published between 1987 and 2011 examining topical medication distribution in the nose and sinuses were included.

Effect of sinus surgery. Eight studies examined the effect of sinus surgery on the distribution of topical medications in the nose and sinuses. Much of the evidence was obtained through staged dissection of cadaver heads (Level 4) although 1 case-control study was also included (Level 3b). Surgical interventions ranged from sinus ostium dilation to modified Lothrop frontal sinus surgery and medial maxillectomy. Unoperated sinuses appeared to receive little topical therapy, with more extensive procedures resulting in increasing distribution in general. Exceptions to this finding were seen with maxillary sinus ostial dilation, perhaps due to uncinate process deflection, and in nebulization, where poor distribution was seen regardless of surgical state. Thomas et al.[13] recommended sinus surgery as an effective method to increase topical therapy distribution in appropriate patients:

- Aggregate quality of evidence. C (Level 3b: 1 study, Level 4: 7 studies).
- Benefit. Standard sinus surgery increases distribution of topical therapies to all sinuses, but has no impact upon nasal cavity delivery.
- Harm. Surgery is associated with potential complications and recovery.
- Cost. Significant, with direct costs of procedure, postoperative debridement, and medical costs in 2008 of

$7554 to $7898. In addition, there are significant indirect costs in the immediate perioperative period due to missed work and decreased productivity. In contrast, during the 2 years following endoscopic sinus surgery (ESS), direct medical costs are lowered by$446 to $885. Reductions in indirect costs with improved productivity and fewer missed work days are not known.
- Benefits-harm assessment. Preponderance of benefit over harm when more aggressive local topical therapies to the sinuses are needed and systemic therapy carries significant risk.
- Value judgments. Patients and surgeons must decide if topical sinus therapies are needed and balance the risks and costs of surgery with ongoing systemic therapies.
- Recommendation level. Recommendation for: penetration of topical therapy is better in post-ESS patients.
- Intervention. Penetration of topical therapy is better in post-ESS patients. This is best done with large volume devices. Surgery can be recommended on a case-by-case basis as the surgeon and patient deem necessary.

Effect of topical therapy delivery devices. This EBRR found that the devices play an important role in the differing distribution of topical medications within the sinuses. Delivery devices were divided into low-volume (eg, spray, drops, atomizers, nebulizers) and high-volume (eg, squeeze bottles, neti pots, bulb syringes). Twenty-one of the 34 studies contained information regarding delivery-device efficacy, although no single paper compared all possible devices. Low-volume devices did not appear to reliably penetrate the sinuses, although delivery into the nasal cavity was demonstrated. Overall, high-volume devices were found to maximize delivery into the sinuses:

- Aggregate quality of evidence. C (Level 3b: 2 studies; Level 4: 18 studies).
- Benefit. High-volume (>50 mL) irrigation improves both sinus and nasal cavity distribution, which may be important for mechanical cleaning/lavage and potential drug delivery.
- Harm. High-volume devices can result in Eustachian tube dysfunction and local irritation up to 23% of patients. However, these are often mild and compliance is high. Low-volume devices (drops, sprays, and simple nebulizers) are reasonable nasal cavity treatments, but do not reliably reach the sinuses and may result in unnecessary expense without demonstrable clinical benefit.
- Cost. Varies depending upon device (range, $9.97 to $149.00). Simple disposable devices, such as neti pots, squeeze bottles, and droppers have relatively low cost in comparison to powered devices such as nebulizers or pulsed irrigators.
- Benefits-harm assessment. Preponderance of benefit over harm of using low-cost, high-volume devices. There is potential harm in using low-volume devices that do not reliably reach the sinus cavities due to needless cost and lack of appropriately treating the patient.
- Value judgments. None.
- Recommendation level. Recommend for: use of disposable high-volume devices for sinus delivery. Recommend against: low-volume devices, such as simple nebulizers, drops, and spray, which have limited sinus delivery. Option for: low-volume devices, such as drops or sprays, if high-volume devices are not tolerated, but low-volume devices must be used in optimal head position and even then sinus distribution is limited (see Effect of head position).
- Intervention. If effective paranasal sinus distribution is desired, use high-volume devices.

Effect of head position. Thomas et al.[13] found 10 studies that evaluated the impact of head position on topical delivery and separated their analysis for delivery to the paranasal sinuses and delivery to the nasal cavity. The head down and forward (HDF) position appeared to be optimal regardless of delivery device for topical delivery into the sinuses. The HDF position was effective for sinus delivery in postoperative patients but was associated with more discomfort than other positions. Distribution of large volumes does not appear to be affected by head position, inasmuch as the volume is likely sufficiently large to fill the nasal cavity. In postoperative patients, filling the nasal cavity with high-volume delivery appears to deliver agents into the widely-open sinuses. For nasal cavity delivery with low-volume devices, the lying head back (LHB) and lateral head low (LHL) positions appeared most effective. Summarizing the data, the EBRR recommended the following:

- Aggregate quality of evidence. C (Level 3b: 1 study; Level 4: 9 studies).
- Benefit. Sinus delivery is not seen in the unoperated patient regardless of head position; however, in the postoperative cavity, sinus delivery is improved with HDF position regardless of device, although head position has less impact when high-volume devices are used. Head position has the greatest impact when using low-volume devices. Nasal cavity delivery of low-volume devices is optimal in LHL or LHB positions.
- Harm. The HDF position was found to be the most uncomfortable and may not be needed for effective sinus delivery if using high-volume devices. When using low-volume devices, use of ineffective head position will impair even the limited nasal cavity distribution.
- Cost. Minimal cost in choosing optimal head position for effective delivery.
- Benefits-harm assessment. Preponderance of benefit over harm.
- Value judgments. For effective nasal delivery with low-volume devices, proper head position is critical.
- Recommendation level. Recommendation for #1: HDF when using high-volume devices if patient will tolerate. HDF for low-volume device, but with limited sinus penetration.

- Recommendation for #2: LHB or LHL position when using low-volume devices, which will only reliably distribute to the nasal cavity.
- Intervention. Only prescribe low-volume devices with concurrent education on the proper position in which to administer them.

Effect of nasal anatomy. Nasal cavity anatomy and nasal congestion was seen to impact distribution of topical therapies. Five studies examined this effect, although only 1 addressed sinus delivery. In balancing the potential benefits and harms of altering nasal anatomy and/or using longstanding decongestants to improve topical medication delivery, the EBRR found data supporting this practice lacking. It therefore recommended high-volume delivery to overcome these effects:

- Aggregate quality of evidence. C (Level 3b: 1 study; Level 4: 4 studies).
- Benefit. High-volume irrigations are able to overcome anatomic variations in the nasal cavity and achieve sinus delivery. Nasal cavity delivery with low-volume devices can be overcome with pharmacologic decongestion or LHL position. The impact of surgical correction of unfavorable nasal cavity anatomy upon delivery to the paranasal sinuses has not been studied.
- Harm. Achieving better delivery by using high-volume devices to overcome unfavorable nasal anatomy may be associated with side effects. Use of the LHL position to improve nasal cavity delivery of low-volume devices carries little harm. The impact of chronic topical vasoconstrictors upon nasal cavity delivery to the middle turbinate/middle meatus is not proven and may result in rhinitis medicamentosa.
- Cost. Optimal head position with low-volume devices or high-volume delivery devices to overcome unfavorable nasal cavity anatomy are low. Nasal surgery cost.
- Benefits-harm assessment. Proven benefit in using high-volume devices; optimal head position with low-volume devices has little harm.
- Value judgments. Chronic topical vasoconstrictor use or nasal surgery, in the absence of airflow obstruction, is unproven and carries the risk for harm and cost.
- Recommendation level. Recommend for: Use of high-volume delivery devices to achieve sinus delivery in patients with unfavorable nasal anatomy. Option for: Short-term (3–4 days or less) use of topical vasoconstrictor to improve nasal cavity delivery in cases of turbinate hypertrophy. Recommend against: Long-term use of topical vasoconstrictor to improve nasal cavity delivery.
- Intervention. Educate patients with unfavorable nasal cavity anatomy regarding optimal delivery position/device depending upon the desired site of topical delivery.

Surgical therapy for CRS

Rhinologic literature over the last 30 years is rich with descriptions of surgical therapies, with some outcome data for individual methods. Current evidence indicates that standard ESS provides clinically significant QOL improvements for CRS patients that have failed medical therapy.[14,15] Different approaches, devices, and techniques have been described in an effort to reduce the significant morbidity associated with CRS. Comparative efficacy is largely lacking, however, with knowledge gaps in extent of surgery, optimal ostial size, resection vs dilation, hemostasis methods, and postoperative packing. These and other areas would be well served by additional evidence and, where appropriate, a review of the available evidence with recommendations.

Two recent EBRRs have examined surgically-related topics . Ramakrishnan et al.[16] examined the role of image guidance in ESS, specifically addressing the ability of this technology to prevent complications and to improve outcomes. Rudmik et al.[17] reviewed the evidence pertaining to a number of postoperative therapies following sinus surgery in order to provide recommendations for the most beneficial treatment strategy.

IGS in ESS

IGS has evolved to become a common adjunct to ESS but has been challenged as having little evidence to support it. Ramakrishnan et al.[16] addressed this topic in a recent EBRR, acknowledging the relative paucity of evidence and delineating the significant barriers to overcoming this gap. Six studies were included in their analysis of complications associated with ESS; 4 were retrospective and 2 were prospective nonrandomized studies. The available evidence mostly showed nonsignificant trends and also showed some conflicting results. Due to the low incidence of complications associated with ESS, most studies were significantly underpowered to show a clinical difference. With regard to complications, the EBRR found IGS to be a valuable option:

- Aggregate quality of evidence: C (Level 2b: 2 studies, Level 4: 4 studies).
- Benefit: Potential for fewer surgical complications, particularly severe complications; provides additional anatomic information, particularly for cases in which anatomy can be significantly obscured.
- Harm: Local skin irritation, potential for poor IGS registration/calibration/accuracy; potential for more extensive surgery than otherwise necessary.
- Cost: Disposable supplies, equipment costs, possible extra operating room (OR) time.
- Benefits-Harm assessment: Preponderance of benefit over harm.
- Value judgments: IGS can provide critical information, particularly in the setting of altered anatomy or severe disease; avoiding major complications is essential; ideal studies are neither practical nor feasible.
- Policy level: Option.

Of note, a more recent analysis of the same literature using a meta-analysis has concluded that IGS, within selected populations, is associated with a lower risk of major and total complication compared to non-IG sinus surgery.[18]

Ramakrishnan et al.[16] also looked at surgical outcome following ESS associated with IGS. Five studies were examined, with 2 again being prospective nonrandomized studies and 3 being retrospective reviews. One prospective study showed improved QOL in the IGS group while 1 showed no difference. The 3 retrospective studies also demonstrated conflicting results. The EBRR again found a preponderance of benefit over harm, seeing IGS as a valuable option in selected ESS cases:

- Aggregate quality of evidence: C (Level 2b: 2 studies, Level 4: 3 studies).
- Benefit: More complete surgery with IGS; potential for improved surgical outcomes, including less need for revision surgery.
- Harm: Local skin irritation, potential for poor IGS registration/calibration/accuracy; potential for more extensive surgery than otherwise necessary.
- Cost: Disposable supplies, equipment costs, possible extra OR time.
- Benefits-Harm assessment: Preponderance of benefit over harm.
- Value judgments: Improving outcomes and decreasing need for revision surgery is highly desired.
- Policy level: Option.

Early postoperative care following ESS

Rudmik et al.[17] assayed the data on 7 different treatments that may be used following ESS: saline irrigations, sinus cavity debridements, systemic steroids, topical steroids, oral antibiotics, topical decongestants, and drug-eluting spacers/stents. They reviewed the evidence and provided recommendations based on this evidence for each of the 7 postoperative treatment strategies.

Nasal saline irrigation. Six studies examined the efficacy of high-volume nasal saline irrigation in the early postoperative period. All were RCTs and at least single-blinded. Outcomes assessed by these studies included patient symptoms, amount of crusting, endoscopic appearance, histology, and mucociliary clearance. The EBRR recommended the routine use of saline irrigations postoperatively as follows:

- Aggregate quality of evidence: B (Level 1b: 2 studies; Level 2b: 4 studies).
- Benefit: Generally well tolerated. Improved early postoperative symptoms and endoscopic appearance.
- Harm: Local irritation, nasal burning, headaches, ear pain (predominantly with hypertonic solutions).
- Cost: Minimal; patient time for application.
- Benefits-Harm assessment: Preponderance of benefit over harm.
- Value Judgments: None.
- Policy level: Recommendation for use of nasal saline irrigations.
- Intervention: Begin daily normal saline irrigations between 24 and 48 hours after ESS.

Postoperative debridement. The EBRR found 4 RCTs evaluating postoperative debridements' effects on clinical outcomes. Three studies were Level 1b and demonstrated significant benefit on symptoms and endoscopic appearance. An unblinded Level 2b pilot study that was underpowered and did not use a standardized endoscopic grading system showed no difference. These studies demonstrated heterogeneity in the frequency and timing of debridements. Overall, debridement was found to be beneficial and was recommended by the EBRR. Future studies will be necessary to determine the optimal frequency, duration, extent, and timing of debridements.

- Aggregate quality evidence: B (Level 1b: 3 studies; Level 2b: 1 study).
- Benefit: Improved postoperative symptoms and endoscopic appearance. Minimizes risk of synechiae and middle turbinate lateralization.
- Harm: Inconvenience of office visit. Procedure-related epistaxis, pain, and syncope. Mucosal avulsion.
- Cost: It is a surgical procedure (in-office) and has associated costs.
- Benefits-Harm assessment: Preponderance of benefit over harm.
- Value Judgments: Relating the surgeon's assessment of healing into the clinical need for debridement.
- Policy level: Recommendation for postoperative debridement.
- Intervention: Perform sinus cavity debridement after ESS.

Postoperative systemic steroids. The EBRR identified 1 study addressing systemic steroids specifically in the immediate postoperative period. This Level 1b RCT with placebo found no difference in symptoms in the CRSwNP patients treated with perioperative steroids but did find an improved endoscopic appearance in this group, compared to patients treated with placebo. As addressed by Poetker et al.'s[10] EBRR on oral corticosteroid treatment overall, the potential benefit of this treatment must be assessed in light of the potential harms as well, making this therapy an option in appropriate patients:

- Aggregate quality of evidence: N/A (Level 1b: 1 study).
- Benefit: Improvement in endoscopic appearance compared to placebo.
- Harm: Side effects of systemic steroids including: Insomnia. Psychiatric/mood changes. Hyperglycemia. Gastritis. Increased intraocular pressure. Avascular necrosis of the hip.
- Cost: Minimal.

- Benefits-Harm assessment: Relative balance of benefit and harm.
- Value Judgments: Difficult to develop a postoperative recommendation based on 1 study where the clinical benefit was limited to endoscopic appearance.
- Recommendation level: Option.

Topical corticosteroids. Similar to the findings in topical therapies overall,[9] topical corticosteroids were found to be a helpful adjunct in the early postoperative period. The use of topical corticosteroid sprays immediately postoperatively was found to be supported by 4 Level 1b studies, although the optimal timing for starting this therapy postoperatively has not been well defined. This postoperative care EBRR recommended topical nasal steroid sprays be initiated following ESS:

- Aggregate quality of evidence: A (Level 1b: 4 studies).
- Benefit: Improved symptoms and endoscopic appearance. Lengthen time to polyp recurrence.
- Harm: Headache. Epistaxis. Cough.
- Cost: Moderate; depends on preparation.
- Benefits-Harm assessment: Preponderance of benefit over harm.
- Value Judgments: None.
- Recommendation level: Recommendation for standard nasal steroid spray.
- Intervention: Begin standard topical nasal steroid spray after ESS.

The use of nonstandard delivery mechanisms for corticosteroids postoperatively was also examined in this EBRR. Examples include steroid-containing irrigations, drops, or nebulizers. A single Level 3b study addressed this topic, although the subjects of the study were patients with severe inflammatory disease who were felt to be at risk for ostial stenosis and further surgery. Further, since no comparison group was used, the relative efficacy of nonstandard corticosteroid delivery in the immediate postoperative period is difficult to assess. This EBRR found this therapy to be an option in selected cases, the same conclusion as that of the EBRR examining nonstandard corticosteroid delivery in CRS overall:

- Aggregate quality of evidence: N/A (Level 3b: 1 study).
- Benefit: Potentially reduce risk of ostial stenosis. May reduce systemic steroid rescue episodes. Potential alternative to course of systemic steroids.
- Harm: Poorly defined risks. Potential adrenal suppression, ocular absorption, wound healing, and other systemic steroid effects.
- Cost: Minimal to moderate, depends on preparation.
- Benefits-Harm assessment: Equal balance of benefit to harm.
- Value Judgments: Lack of data regarding systemic absorption is concerning but the only other option in many cases is a systemic steroid.
- Recommendation level: Option in patients with severe mucosal inflammatory disease.

Postoperative antibiotics. Rudmik et al.[17] found 3 studies examining the use of antibacterial antibiotics in the immediate period following ESS. An RCT examining a 2-day course showed no effect. Another RCT examining a longer course (3 weeks) also showed no effect at 3 weeks, although another double-blind RCT with placebo demonstrated 2 weeks of antibiotics led to improved patient symptoms at 5 days and improved endoscopic appearance at 12 days. In light of the disparate evidence on this topic, this EBRR found antibiotics to be an option in the early postoperative period:

- Aggregate evidence: B (Level 1b: 2 studies; Level 2b: 1 study).
- Benefit: Improved early postoperative symptoms and endoscopic appearance. Reduced sinonasal crusting.
- Harm: GI upset. *Clostridium difficile* colitis. Anaphylaxis. Bacterial resistance.
- Cost: Generally Moderate to high.
- Benefits-Harm assessment: Relative balance of benefit and harm.
- Value Judgments: Reducing early postoperative symptoms is important; active bacterial infection may trigger inflammation postoperatively.
- Recommendation level: Option in routine endoscopic sinus surgery.

Topical decongestants. Only 1 study has examined the effect of topical decongestants. They were used 4 times a day routinely in the early postoperative period and were found to be harmful. This EBRR thus recommended against their routine use, with the caveat that this recommendation does not relate to the management of postoperative epistaxis, where their use may be potentially beneficial:

- Aggregate evidence: N/A (Level 2b: 1 study).
- Benefit: Potential for reduced mucosal swelling and reduced bleeding.
- Harm: Increased pain. Potential for rhinitis medicamentosa.
- Cost: Minimal; over the counter medication.
- Benefits-Harm assessment: Preponderance of harm over benefit.
- Value Judgments: Increased pain and risk of rhinitis medicamentosa is concerning despite only one study evaluating this intervention.
- Recommendation level: Recommendation against.

Drug eluting spacers/stents. This EBRR lastly examined the role of these newer technologies in the early period following ESS. Three studies involving non–U.S. Food and Drug Administration (FDA)-approved stents or steroid-soaked ethmoid cavity packing materials were examined, with 2 being RCTs. All 3 showed benefit in the form of better symptom scores, reduced nasal polyp rate, and improved

overall endoscopic scores, both early and up to 6 months postoperatively. These potential benefits are balanced by the potential for systemic and ocular absorption and the variable cost of these materials. Moreover, the studies reviewed in this EBRR had rather small sample sizes. This EBRR, therefore, recommended this treatment as an option in the early postoperative period.

- Aggregate evidence: B (Level 1b: 1 study; Level 2b: 1 study; Level 3b: 1 study).
- Benefit: Improved endoscopic appearance. Reduced polyp recurrence.
- Harm: Potential for systemic steroid absorption. Potential for ocular absorption.
- Cost: Variable depending on the stent/spacer selected and medication utilized.
- Benefits-Harm assessment: Relative balance of benefit and harm.
- Value Judgments: Standard topical steroids have a proven role in postoperative management but nonstandard topical steroids require further study. Although some trials have been conducted, sample sizes are small and data is considered insufficient to extrapolate to larger populations, particularly with respect to safety concerns.
- Recommendation level: Option.

Following the publication of this EBRR on drug eluting spacers and stents in 2011, additional RCTs have been published using FDA-approved corticosteroid-eluting implants. The results of these RCTs have been partially summarized in a recent meta-analysis,[19] yielding Level 1a evidence in support of their effectiveness. This technology offers the potential to create a local drug-delivery platform for an array of therapeutic agents in the future. It is anticipated that this topic will be the subject of an updated EBRR in the near future.

Discussion

Since their development by Rudmik and Smith,[5] EBRRs have proven to be an effective method for comprehensively yet rapidly evaluating published evidence on a particular topic. Furthermore, these reviews have allowed for generation of useful evidence-based recommendations while at the same time pointing out deficiencies in the available evidence. Such publications are a crucial part of the triad of EBM, combined with the individual practitioner's clinical expertise and the individual patient's values and desires.

The rapid online iterative process used in the EBRR development ensures timeliness of the review and also facilitates updating the EBRR as additional evidence becomes available. It is assumed that the senior authors responsible for the production of these EBRRs will ensure their timely updating as needed.

The EBRR process, though robust, does have some limitations. First, no EBRR is a substitute for the individual practitioner's clinical judgment and expertise, nor are they to be universally applied to all patients. CRS is a heterogeneous condition and has been best described as a syndrome rather than a single disease. Indeed, the classification of CRS into CRSwNP, CRSsNP, AFRS, and other entities such as aspirin-exacerbated respiratory disease (AERD) underscores the heterogeneity of this condition. While the EBRRs provide valuable guidance to the clinician practicing EBM, as noted, they are only 1 part of the application of EBM to an individual clinical situation.

Another limitation of the EBRRs is the evidence on which they are based. Evidence is constantly changing so EBRRs should not be interpreted as being "carved in stone," but are dynamic, because the process is also dynamic. In addition, many recommendations are limited to options not because extensive data shows equivocal efficacy or safety, but because the evidence itself is scarce. Lack of evidence for clinical efficacy should not be confused with evidence for lack of clinical efficacy. In those circumstances where a treatment is recommended as an option, it may be entirely viable and indicated for an individual clinical situation.

Last, the EBRRs are not clinical guidelines sanctioned by the societies for which the *International Forum of Allergy and Rhinology* is the official publication. These societies, the American Academy of Otolaryngic Allergy, the American Rhinologic Society, and the International Rhinologic Society, may in the future choose to sanction the EBRRs or use them as the basis for a clinical guideline on CRS. While the development of the EBRR is meant to ensure these authors are a diverse representation of experts on the EBRR subjects, without such sanctioning however, the EBRRs remain the findings and opinions of their authors alone.

While the EBRRs published to this point have explored a large number of important topics in CRS management, this review has also shown gaps in our collective knowledge of other areas of management and evaluation. Possible topics for future EBRRs in CRS are:

- Cost-effective diagnosis
- Cost-effective evaluation of underlying conditions
- Etiologic factors
- Value of histopathologic assessment of sinus tissue
- Pediatric chronic rhinosinusitis
- Antibiotics in the management of acute exacerbations of CRS
- Other medical treatments (eg, aspirin desensitization, leukotriene modifiers, etc.)
- Optimal medical therapy to be employed prior to considering surgery
- Comparative efficacy of surgical instrumentation and techniques (eg, balloon dilation)
- Comparative efficacy of the extent of surgery
- Appropriate long-term sinus care.

Conclusion

EBRRs have individually and, as can be seen from this review, collectively enhanced the knowledge base for the

treatment of CRS. They form an effective template for additional reviews that will further enhance the use of EBM in the treatment of CRS. They also provide direction for future research efforts. Additionally, they may form a useful foundation for the development of evidence-based guidelines for the management of CRS.

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TRIOLOGICAL SOCIETY CANDIDATE THESIS

Subclassification of Chronic Rhinosinusitis

Joseph K. Han, MD

Objectives/Hypothesis: There are variants of chronic rhinosinusitis (CRS). Therefore, the objectives of this study were to phenotype the subclasses of CRS as well as characterize their polyps with histology and cellular–intracellular biomarkers.

Study Design: Prospective case-control study.

Methods: Demographic data, quality-of-life (QoL) questionnaires, nasal endoscopy (NE), and computed tomography (CT) scores were obtained. CRS was divided into seven subclasses: aspirin-exacerbated respiratory disease (AERD), asthmatic sinusitis with and without allergy, nonasthmatic sinusitis with and without allergy, allergic fungal sinusitis (AFS), and cystic fibrosis (CF). Histopathologic and immunohistochemistry of nasal polyps were recorded. CD3, CD4, CD8, CD19, CD45, and CD56 data were collected. Interleukin (IL)4, IL5, IL13, IL17, and interferon (IFN)-γ were measured.

Results: Eight-four subjects were in this study. Two QoL questionnaires were inadequate at distinguishing the control group from CRS. NE and CT were able to differentiate between the control group and all CRS subclasses ($P<.01$). Asthmatic sinusitis, AERD, and AFS had high NE and CT scores, nasal polyps, eosinophils, mast cell, and hypercellularity. Asthmatic sinusitis, nonasthmatic sinusitis, and AERD had higher CD4 cells than control group ($P<.05$). Even though asthmatic sinusitis and AFS are mediated by Th2, AFS had differing levels of Th2 cytokines. Each nonasthmatic sinusitis had purulence and low CT score. Each nonasthmatic sinusitis had higher CD4 cells and IFN-γ than control ($P<.05$). CF is associated with purulence, high CT score, high polymorphonuclear leukocytes, high plasma cells, and high mast cells.

Conclusions: Well-characterized and distinct groups of CRS have been defined for targeted treatment and research studies.

Key Words: Sinusitis, phenotype, asthma, allergy, aspirin triad, nasal polyp, subclassification, interleukin, inflammation, and cystic fibrosis.

Level of Evidence: 2b

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INTRODUCTION

Developing a universal treatment for chronic rhinosinusitis (CRS) has been elusive for many decades. When endoscopic sinus surgery (ESS) became available as a treatment for CRS, there was hope that ESS would cure many patients of their chronic ailments. Despite removing structural obstruction or chronic infection associated with CRS with ESS, sinus symptoms still persisted.[1] Antifungal treatment was hoped by some to cure all CRS. However, a prospective, randomized, controlled study evaluating topical antifungal medication to nasal saline demonstrated that topical antifungal irrigation had similar results to the control group and did not provide a cure for all CRS.[2] The best explanation as to why there is no single treatment for CRS is because there is no common pathophysiology for CRS. The most effective treatment for the difficult CRS patients is ESS followed by individualized long-term medical management that should be dictated by the patients' disease process.

To determine the proper medical management for CRS patients, the inflammatory process of the sinuses should define the treatment plan. In other words, a specific kind of medication should be used for a specific kind of sinus inflammation. An example is the use of macrolides for the treatment for CRS. Macrolides gained some interest as a treatment for CRS because of their anti-inflammatory properties. However, the use of macrolides for CRS patients has not been universally beneficial. A prospective, randomized, controlled study evaluating the use of macrolides for CRS has demonstrated some statistical improvement between the study and control group.[3] However, when the CRS patients were divided into patients with low- and high-serum immunoglobulin E (IgE), the low-IgE patients had a better response to the macrolides than the high-IgE patients. This finding is consistent with another study evaluating macrolides for CRS. In this study, patients with nasal polyps, asthma, and allergy did not have a good response

From the Division of Rhinology and Endoscopic Sinus and Skull Base Surgery, Department of Otolaryngology–Head and Neck Surgery, Eastern Virginia Medical School, Norfolk, Virginia, U.S.A.

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Send correspondence to Joseph K. Han, MD, Division of Rhinology and Endoscopic Sinus and Skull Base Surgery, Department of Otolaryngology–Head and Neck Surgery, Eastern Virginia Medical School, River Pavilion Suite 1100, 600 Gresham Drive, Norfolk, VA 23507. E-mail: hanjk@evms.edu

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TABLE I.
Definition of the CRS Subclasses.

CRS Subclass	History	Atopy	Asthma
AERD	Positive aspirin sensitivity	±	+
AFS	Positive fungal stain in eosinophilic mucin	+	±
AScA	Positive pulmonary function test and allergy test (in vitro or in vivo)	+	+
ASsA	Positive pulmonary function test and negative history or allergy test	−	+
NAScA	No history of asthma and positive allergy (in vitro or in vivo)	−	+
NASsA	No history of asthma or allergy	−	−
CF	Positive sweat test or gene test	±	±

AERD=aspirin exacerbated respiratory disease also known as aspirin triad; AFS=allergic fungal sinusitis; AScA=asthmatic sinusitis with allergy; ASsA-asthmatic sinusitis without allergy; CF=cystic fibrosis; CRS=chronic rhinosinusitis; NAScA=nonasthmatic sinusitis with allergy; NASsA=nonasthmatic sinusitis without allergy.

to the macrolides.[4] These two research study findings are consistent. Macrolides do not affect T helper 2 (Th2)-mediated inflammation seen in patients with allergic asthma or high serum IgE. Rather, macrolides target Th1 inflammation by decreasing interleukin (IL)6 and IL8 production.[5] Therefore, patients with an infection-based inflammation are more likely to have a response to macrolides, because these patients are more likely to have a Th1-mediated inflammation.

By definition, all CRS cases have sinonasal inflammation. The question is what type of inflammation is it? Currently, CRS is divided into CRS with polyp and CRS without polyp. In general, CRS with polyp is thought to be a Th2-mediated process, whereas CRS without polyp is mediated by Th1 process. However, this division of CRS is too simplistic and does not account for any possible difference that may exist for CRS with polyp. Also, the definition of CRS with polyp is not clearly defined. What criteria determine the definition of a nasal polyp in CRS? In other words, when does nasal mucosal swelling become a polyp? There is no clearly delineated size of a nasal mucosal engorgement defining a nasal polyp.

Two factors that have enormous impact on the development of CRS, especially in CRS with polyp, are allergy and asthma.[6] Therefore, using asthma and allergy, CRS was divided into different categories. The objectives of this study were to characterize the phenotype and the nasal polyp and understand the inflammatory pathway for each CRS subclass that has been defined. By characterizing the phenotype and pathway of nasal polyps formation for the various types of CRS, well-characterized and distinct groups of CRS can be described. By dividing CRS into specific distinguished entities, targeted medical and surgical treatment can be developed for each CRS subclass to improve efficacy of treatment. Also by delineating specific CRS entities, bench and clinical research results and outcomes may become more coherent.

MATERIALS AND METHODS

Study Group

Institutional review board approval was obtained for this prospective case-control study evaluating CRS. A total of seven subclasses of CRS and a control group were used in the study. The study groups for CRS were aspirin triad or aspirin exacerbated respiratory disease (AERD), asthmatic sinusitis with allergy (AScA), asthmatic sinusitis without allergy (ASsA), nonasthmatic sinusitis with allergy (NAScA), nonasthmatic sinusitis without allergy (NASsA), allergic fungal sinusitis (AFS), and cystic fibrosis (CF). Both AScA and ASsA will be defined as asthmatic sinusitis. Both NAScA and NASsA will be defined as nonasthmatic sinusitis. The CRS study group definition is described in Table I. The control group did not have any clinical, endoscopic, or radiographic evidence of CRS and presented for cerebrospinal fluid (CSF) leakage.

Phenotype

During the initial office visit, CRS patients completed two quality-of-life (QoL) questionnaires: the Rhinosinusitis Disability Index (RSDI) and the Chronic Sinusitis Survey (CSS). Demographic data, nasal endoscopy (NE), and computed tomography (CT) findings during the initial visits were documented. NE findings were recorded and scored according to a nasal NE score sheet (Fig. 1). The CT scans during the initial visit were scored based on the Lund-Mackay scoring system.

Data were collected and organized into the database. Fisher exact probability test was used to evaluate gender differences between CRS subclasses. Using SAS Statistical Software

NASAL ENDOSCOPY FINDINGS

(If no findings present, circle= 0)
(If present, circle= 1)

1.	Crusting	0	1
2.	Erythema	0	1
3.	Swelling	0	1
4.	Scar Band	0	1
5.	Purulent Drainage	0	1
6.	Thick Mucus	0	1

(If no polyp present, circle= 0)
(If polyp present in the middle meatus, circle= 1)
(If polyp present outside the middle meatus, circle= 2)

7.	Polyps	0	1	2

Fig. 1. The Nasal Endoscopy Findings Scoring system rates positive findings on nasal endoscopy. A total score is calculated on a scale of 0 to 8 possible points.

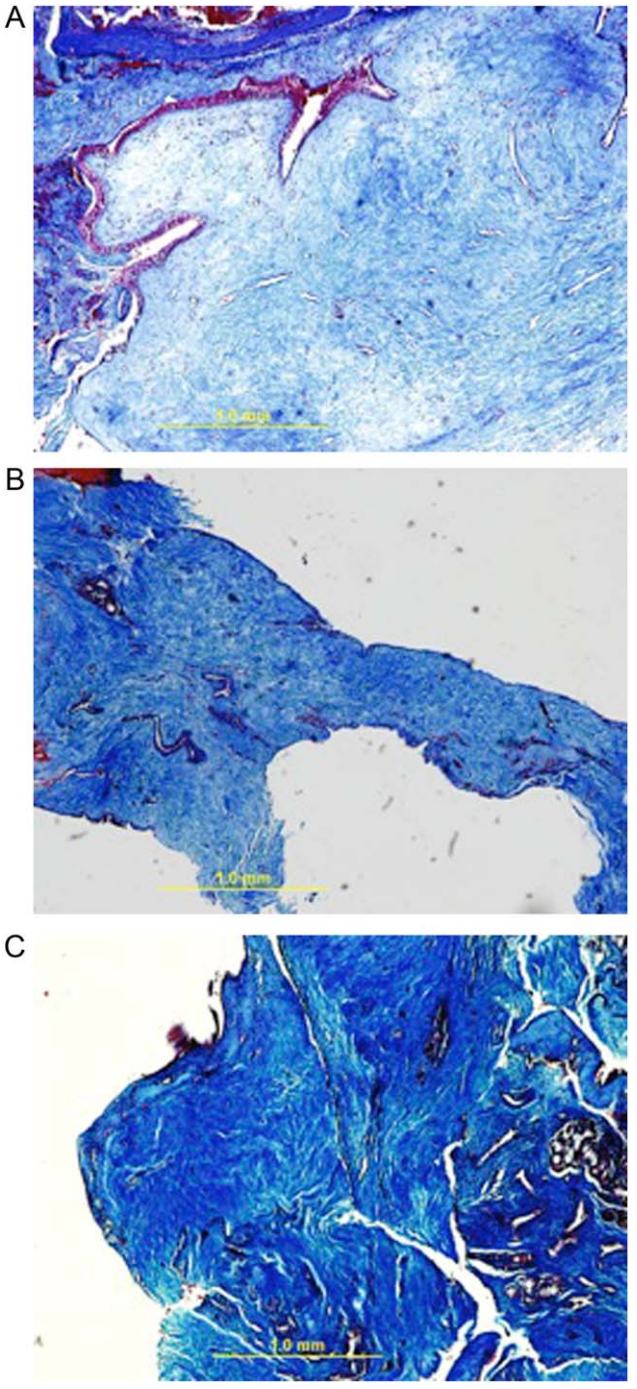

Fig. 2. Degree of fibrosis was graded on level of trichrome staining. (A, B, C) Representative scores 0, 1, and 2, respectively.

(SAS Institute Inc., Cary, NC), the nonparametric Wilcoxon ranked sum test was employed to assess significance of findings for all analyses between CRS subclasses. Spearman coefficient of rank correlation test was utilized to calculate correlations between the measurement tools for each subclass of CRS and control group.

Histopathology and Immunostaining

Informed consent was obtained prior to obtaining the nasal polyps in patients who failed medical treatment for CRS and were undergoing ESS. The nasal polyps specimens for the study groups were taken specifically from the ethmoid sinuses or polyps in the ostiomeatal complex. For the control group, ethmoid sinus mucosa was taken during the CSF leak repair. All of the patients did not receive oral steroid 4 weeks prior to the specimen collection. Tissue samples were then evaluated for eosinophils (EO), polymorphonuclear leukocytes (PMN), lymphocytes, and plasma cells with hematoxylin and eosin (H&E) staining. Degree of fibrosis was measured using Masson trichrome staining (Fig. 2). Mast cells were identified with CD117 immunostaining (Fig. 3).

For the H&E staining, nasal polyps were evaluated for the area with the most dense cell populations similar to standard clinical evaluation of any pathologic tissue. This location of the dense collection of inflammatory cells was determined as either

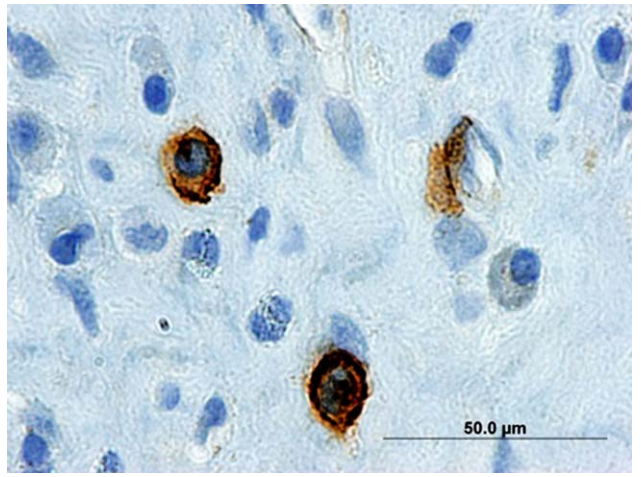

Fig. 3. Mast cells stained with CD117.

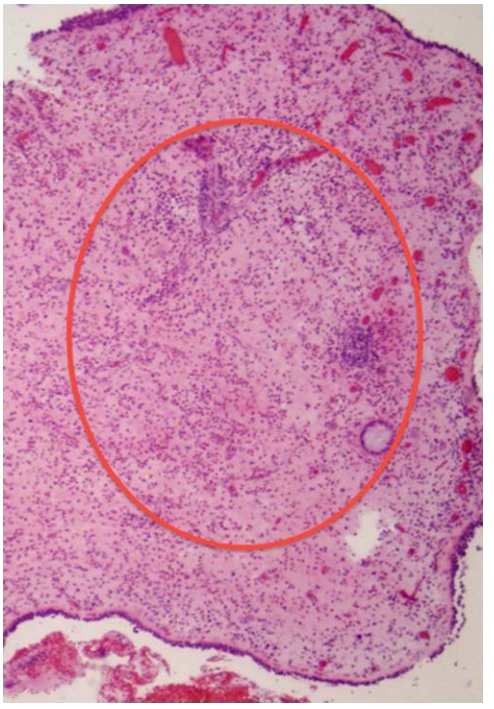

Fig. 4. Microscopic hematoxylin and eosin slide (2×) of a nasal polyp demonstrating stromal distribution of cells within the circle.

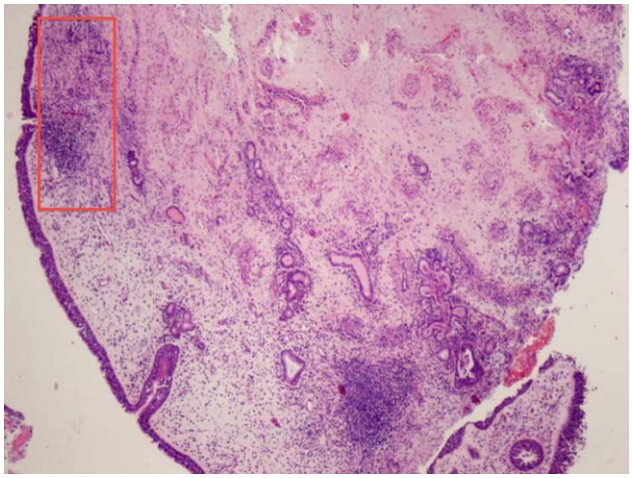

Fig. 5. Microscopic hematoxylin and eosin slide (2×) of a nasal polyp demonstrating superficial subepithelial distribution of cells within the rectangle.

stromal (Fig. 4) or subepithelial space distribution (Fig. 5). The inflammatory cells in this dense area were counted to a total of 500 cells or until all inflammatory cells (EO, PMN, lymphocyte, plasma cells) in the polyp sample were counted. Data were normalized as a ratio to the total cell count. To determine the cellularity of the polyp sample, five consecutive high power fields (HPFs) (1,000×) were used to count the total number of EO, PMN, lymphocyte, and plasma cells in one HPF. The average number of the total cell count from the five HPFs of each patient was defined as the cellularity of the nasal polyp.

Ten HPFs (1,000×) of the epithelium were analyzed to characterize and count the goblet cells present. The surface epithelial morphology was categorized as either pseudostratified ciliated columnar or transitional epithelium. The area of highest concentration of mast cells was identified. Ten consecutive HPFs (400×) were used to count for mast cells. The average number of mast cells for each patient was obtained.

Data analysis was performed using analysis of variance (ANOVA) on SPSS statistical software version 17.0 (IBM SPSS, Armonk, NY) with appropriate Tukey post hoc analyses. P values $<.05$ were considered to be statistically significant.

Flow Cytometry

The same polyp specimen used in the histologic examination was used for flow cytometry. Fresh tissue specimens were placed in Royal Park Memorial Institute (RPMI) 1640 1× medium (Cellgro, Manassas, VA) and processed within 1 hour of extraction. Under a category 2 sterile hood, tissue samples were disaggregated to allow separation of cells from the tissue. Cell suspensions were prepared from the resulting eluent, using a 70 μm BD Falcon cell strainer (BD Biosciences, Franklin Lakes, NJ).

Pelleted cells (400 × g, 4°C, 5 minutes) were stimulated in nonpolarizing stimulation media to facilitate production of intracellular cytokines. Results were achieved for leukocytes by reconstituting cells in 1 mL RPMI 1640 supplemented with 10% fetal bovine serum (Lonza Group, Ltd., Basle, Switzerland), 1% penicillin–streptomycin (Invitrogen, Carlsbad, CA), 1 ng/mL phorbol 12-myristate 13-acetate (PMA) (Sigma-Aldrich, St. Louis, MO), 0.6 μL BD Golgi stop protein transport inhibitor (BD Biosciences), and 500 ng/mL ionomycin (Sigma-Aldrich) and cultured for 5 hours at 37°C according to established BD Biosciences protocols.

A total of 100 μL aliquots of cells were distributed to polystyrene fluorescent activated cell sorter (FACS) tubes at room temperature, in the dark, for 30 minutes. Temperature single-cell suspensions were stained for CD3, CD4, CD8, CD19, CD45, and CD56 using antihuman fluorochrome conjugated antibodies and incubated at 4°C for 30 minutes according to established BD Biosciences protocols. Following the extracellular stain, 250 μL of BD Cytofix/Cytoperm fixation and permeabilization solution (BD Biosciences) was added to each sample for 20 minutes at 4°C in the dark.

Intracellular cytokines were stained for IL4, IL5, IL13, IL17, and interferon (IFN)-γ using specific antibodies or appropriate isotype controls for 30 minutes at 4°C in 1× BD perm/wash buffer (BD Biosciences). Cells were washed twice with perm/wash buffer according to the manufacturer's instructions (BD Biosciences). Cells were fixed with a preparation of 2% paraformaldehyde (PFA v/v in phosphate-buffered saline) and stored at 4°C covered in the dark.

Samples were run through a Cytek 8DXP upgraded (Cytek Development, Fremont, CA) FACSCalibur (BD Biosciences). Flow cytometer and fluorescence data were acquired using FlowJo software version 4.6 (TreeStar, Ashland, OR). Gates were created based on isotypes and fluorescence-minus-1 controls. For the intracellular cytokines, positive signal for CD45 was used to gate on polyp leukocytes. T helper cells were subgated from the leukocyte population using CD4 antibody. The resulting CD4+ leukocytes were then analyzed for IL4, IL5, IL13, IL17, and IFN-γ–producing cells. Intracellular cytokines were also analyzed for CD45+CD4−s cells.

Baseline significance for this study was set at α=.05. All groups were compared using ANOVA on SPSS statistical software (IBM SPSS) with appropriate Tukey post hoc analyses. In some analyses, Student t tests with Bonferroni-Holme corrections were conducted.

RESULTS

Phenotype

Eighty-four patients were included in the study, with ages ranging from 7 to 83 years of age (median age, 46 years) (Table II). CF was the youngest subclass and statistically lower than each asthmatic sinusitis group ($P<.01$). There were 48 females in the study, with significant higher females in the asthmatic sinusitis (AScA

TABLE II.
The Demographic Information for the CRS Subclasses.

CRS Subclass (n)	Mean Age (yr)	Female (n)
AERD (9)	46	5
AFS (11)	34	4
CF (7)	16	5
AScA (13)	48	11
ASsA (5)	35	4
NAScA (14)	54	7
NASsA (12)	59	3
Control (13)	50	9
Total (84)	46	48

AERD=aspirin exacerbated respiratory disease also known as aspirin triad; AFS=allergic fungal sinusitis; AScA=asthmatic sinusitis with allergy; ASsA=asthmatic sinusitis without allergy; CF=cystic fibrosis; CRS=chronic rhinosinusitis; NAScA=nonasthmatic sinusitis with allergy; NASsA=nonasthmatic sinusitis without allergy.

TABLE III.
The Average Objective and Subjective Measurement Tools for CRS.

CRS Subclass	NE	CT Score	CSS	RDSI
AERD	2.6	14.7	16.5	10.7
AFS	2.4	13.8	9.9	8.1
CF	2.1	14.3		
AScA	2.7	14	15.9	11.2
ASsA	2	12.5	13.3	18.3
NAScA	2.2	10.2	9.1	8.7
NASsA	1.4	9.3	7.4	8.3
Control	0.2	1.5	5.3	5.7
Total	1.9	10.5	10.7	9.2

AERD=aspirin exacerbated respiratory disease also known as aspirin triad; AFS=allergic fungal sinusitis; AScA=asthmatic sinusitis with allergy; ASsA=asthmatic sinusitis without allergy; CF=cystic fibrosis; CRS=chronic rhinosinusitis; CSS=chronic sinusitis survey; CT=computed tomography; NAScA=nonasthmatic sinusitis with allergy; NASsA=nonasthmatic sinusitis without allergy; NE=nasal endoscopy; RSDI=rhinosinusitis disability index.

and ASsA) compared to nonasthmatic sinusitis (NAScA and NASsA) ($P<.01$). Asthmatic sinusitis versus 50/50 gender split had a P value of .03 in favor of more females.

The results of the average nasal endoscopy, CT scores, CSS, and RSDI are listed in Table III. For the nasal endoscopy score, all of the CRS subclasses were significantly higher than the control group ($P<.01$). The nasal endoscopy score for AFS, AERD, and AScA was significantly higher than NASsA ($P<.01$). Aspirin triad, both AScA and ASsA, and NAScA ($P<.05$) had significantly more polyps on nasal endoscopy than the control group. Cystic fibrosis ($P=.08$) and NASsA ($P=.07$) was trending toward significance for the presence of purulence, but did not reach statistical significance when compared to control group.

For the CT scores, all of the CRS subclasses were significantly higher than the control group ($P<.01$). Aspirin triad, AFS, CF, and AScA had higher CT scores than NASsA ($P<.05$). When CT scores were evaluated for unilateral disease, allergic fungal sinusitis was significantly higher than the control group and all the other CRS subclasses ($P<.01$).

Because the two QoL questionnaires in the study were not validated in the pediatric population, and the majority of the CF patients were pediatric, CF was not included in the analysis for the QoL questionnaires. For the total CSS score, AERD was the only CRS subclass that was statistically different than the control group ($P<.05$). When CSS was broken into duration and symptom score, CSS symptom score was significantly higher in aspirin triad and AScA than the control group ($P<.01$).

For the RSDI score, there was no difference between the control group and any of the CRS subclasses. There was also no statistical difference between the control group and all of the CRS subclasses combined. Even when RSDI was divided into its different components, there was no statistical difference found between the control group and any of the CRS subclasses.

When evaluating all of the CRS patients, the correlation coefficient between RSDI to CSS was $r_s=0.52$ ($P<.01$). Correlation of CT to NE was $r_s=0.4$ ($P<.01$). Correlations of CSS to CT and NE were $r_s=0.28$ and $r_s=0.38$ ($P<.05$), respectively. Correlation of RSDI to CT and NE were $r_s=0.32$ and $r_s=0.34$ ($P<.05$), respectively.

Histopathology and Immunostaining

The eosinophil ratios were significantly higher for AFS, AERD, and AScA than both the control group and CF ($P<.05$) (Table IV). Aspirin triad and AScA had higher eosinophil ratios than each nonasthmatic sinusitis ($P<.05$) among the CRS subclasses.

For PMN analysis, CF had the highest ratio of PMN and was significantly higher than the control group, NASsA, and AScA ($P<.05$). There were no other significant differences.

For the plasma analysis, cystic fibrosis had the highest plasma cell count. Cystic fibrosis, AFS, ASsA,

TABLE IV.
The Average Ratio of Cells.

CRS Subclass	Eosinophil	PMN	Plasma	Lymphocyte	Mast	Cellularity	Goblet
AERD	0.44	0.03	0.14	0.39	92	150	45
AFS	0.35	0.03	0.3	0.31	101	141	19
CF	0.004	0.06	0.45	0.47	163	96	8
AScA	0.44	0.01	0.17	0.32	85	138	80
ASsA	0.17	0.04	0.35	0.44	63	130	43
NAScA	0.17	0.02	0.26	0.45	133	109	53
NASsA	0.08	0.01	0.32	0.49	64	39	89
Control	0.02	0.03	0.17	0.76	32	18	60
Total	0.23	0.02	0.25	0.44	92	104	55

AERD=aspirin exacerbated respiratory disease also known as aspirin triad; AFS=allergic fungal sinusitis; AScA=asthmatic sinusitis with allergy; ASsA-asthmatic sinusitis without allergy; CF=cystic fibrosis; CRS=chronic rhinosinusitis; NAScA=nonasthmatic sinusitis with allergy; NASsA=nonasthmatic sinusitis without allergy; PMN=polymorphonuclear leukocyte.

TABLE V.
The Average Percentage of Cells for CRS Subclasses.

CRS Subclass	% CD3	% CD4	% CD8	% CD19	% CD56
AERD	79	36	42	9	6
AFS	67	28	33	15	6
CF	71	26	38	21	5
AScA	76	36	37	9	6
ASsA	74	32	34	14	6
NAScA	68	37	33	18	7
NASsA	72	30	36	11	9
Control	76	21	53	3	12
Total	73	31	39	12	7

AERD=aspirin exacerbated respiratory disease also known as aspirin triad; AFS=allergic fungal sinusitis; AScA=asthmatic sinusitis with allergy; ASsA=asthmatic sinusitis without allergy; CF=cystic fibrosis; CRS=chronic rhinosinusitis; NAScA=nonasthmatic sinusitis with allergy; NASsA=nonasthmatic sinusitis without allergy.

and NAScA had statistically higher plasma cells than the control group ($P<.05$). Cystic fibrosis also had statistically higher plasma cells than AERD, AScA, and each nonasthmatic sinusitis ($P<.01$).

For the lymphocyte analysis, the control group had the highest ratios of lymphocytes, but no statistical difference was achieved between the control group and any of the CRS subclasses. In general, eosinophilic CRS subclasses (AFS, AERD, AScA, ASsA) had lower lymphocyte ratios.

For mast cell analysis, cystic fibrosis had the highest mast cell ratio, being statistically higher than the control group and all the CRS subtypes other than NAScA ($P<.01$). Both allergic-based CRS (AScA, NAScA), AERD, and AFS were higher than the control group ($P<.01$) for mast cells. NAScA had higher mast cells than each asthmatic sinusitis (AScA, ASsA) and NASsA ($P<.01$). Allergic fungal sinusitis was statistically higher than NASsA ($P<.05$) for mast cells.

Eosinophilic CRS subclasses (AScA, ASsA, AFS, AERD) had statistically higher cellularity than the control group ($P<.05$). Aspirin triad and AFS had higher cellularity than NASsA ($P<.05$). There was no statistical difference in the amount of fibrosis between the CRS and the control group.

Goblet cell counts ranged from an average eight/HPF in CF samples to 89/HPF in NASsA (Table IV). Cystic fibrosis had significantly lower number of goblet cells than AERD, AScA, NASsA, and the control group ($P<.05$). AFS also had lower goblet cells than AScA, NASsA, and the control group ($P<.05$). Eosinophilic CRS subclasses (AFS, AERD, AScA, ASsA) demonstrated the most metaplasia of the surface epithelium but did not reach statistical difference. Aspirin triad and each asthmatic sinusitis had significantly more transitional epithelium when compared to controls, nonasthmatic sinusitis, and CF ($P<.05$).

Cell distribution data showed that CF samples had a predominantly subepithelial cell distribution and was statistically higher than the control group ($P<.01$). Eosinophilic CRS subclasses (AScA, ASsA, AERD, AFS) were more likely to have a stromal cell distribution but did not reach statistical difference.

Flow Cytometry

Fresh mucosal and polyp samples were analyzed for CD3, CD4, CD8, CD19, and CD56 cells (Table V). In regard to the T cells, there was no difference seen for CD3 marker between the control group and CRS groups or among the CRS subclasses. There were higher CD4 cells in both AScA and ASsA, both NAScA and NASsA, and AERD than the control group ($P<.05$). The two allergy-based CRS subclasses (AScA, NAScA) had more CD4 cells than CF ($P<.05$). For the CD8 cells, the control group had a significantly higher amount of CD8 cells than each nonasthmatic group (NAScA, NASsA) ($P<.05$).

For the CD19 or B cells, both AFS ($P<.05$) and CF ($P<.01$) were significantly higher than the control group. Also, CF had significantly more CD19 cells than NASsA and AScA ($P<.05$). For the CD56 or natural killer cells, there was no statistical difference between the control group and CRS study groups. Also, there was no difference among the CRS subclasses.

We examined several intracellular cytokines: IFN-γ, IL4, IL5, IL13, and IL17 (Table VI) in CD45+, CD45+CD4+ and CD45+Cd4− cells. For IL5, IL13, and IL17, only five samples in each CRS subclass and control group were measured. When examining the CD45+ cells, there was statistical difference for IFN, IL4, and IL5. Nonasthmatic sinusitis without allergy had higher IFN than AFS ($P=.03$). For IL4, ASsA was statistically higher than the control group ($P=.03$) and all the CRS subclasses ($P<.05$) other than AERD. For IL5, AFS was statistically higher than AERD, both ASsA and AScA, and NASsA. Allergic fungal sinusitis was almost statistically higher for IL5 compared to the control group but did not reach significance ($P=.06$).

There was statistical difference among CD45+CD4+ cells for IFN-γ, IL4, IL5, and IL13. Both NAScA, NASsA had statistically elevated IFN-γ than the control group ($P<.01$) and eosinophilic CRS subclasses (AFS, AERD, AScA) ($P<.05$). For IL4 in CD45+CD4+, ASsA had elevated levels compared to CF ($P=.05$). For IL5, AFS was statistically higher than the control group ($P<.01$). Allergic fungal sinusitis also had higher IL5 than eosinophilic sinusitis (AERD, AScA, ASsA), NASsA, and CF ($P<.05$). Allergic fungal sinusitis also had elevated IL13 compared to CF ($P<.05$).

There was statistical difference among CD45+CD4− cells for IL4 and IL13. For IL4, ASsA had elevated levels of IL4 compared to CF and NAScA ($P<.05$). Aspirin-exacerbated respiratory disease was the second highest in the study, but did not reach statistical significance with any of the other groups. For IL13, CF did have higher IL13 than the control group ($P=.05$). Cystic fibrosis also had higher IL13 compared to both AScA and ASsA ($P<.03$) and was close to significance to AERD ($P=.06$). There were no statistical differences found for IL17 between CRS subclasses and control group or among the CRS subclasses.

TABLE VI.
Average Percentage of CD45+ Cells, CD45+CD4+ Cells, and CD45+CD4− Cells With Positive Intracellular Markers.

CRS Subclass	IFN	IL4	IL5	IL13	IL17
Average % of CD45+ cells with positive intracellular marker					
AERD	3.9	1.8	0.2	0.3	0.7
AFS	3.1	1	1.3	1.5	2.4
CF	14.6	0.2	0.8	2	2.7
AScA	12.1	1.3	0.04	0.1	1.3
ASsA	9	3.2	0.2	0.5	2.2
NAScA	14	1.2	0.4	0.3	0.7
NASsA	15.5	0.8	0.1	1.8	1.9
Control	4.4	1.2	0.3	0.4	1.8
Total	9.6	1.2	0.4	0.8	1.6
Average % of CD45+CD4+ cells with positive intracellular marker					
AERD	2.6	1.4	0.3	0.4	1.7
AFS	2.3	0.9	2.4	3.2	4
CF	8.6	0.4	0.5	0.3	3.9
AScA	9.7	1.8	0.04	0.2	3.4
ASsA	11.9	3.2	0.2	0.6	2.9
NAScA	22.1	1.3	0.6	0.4	1.9
NASsA	24.4	3	0.2	2.4	2.8
Control	4.1	1.2	0.2	0.6	3.1
Total	11.6	1.7	0.5	0.9	2.9
Average % of CD45+CD4− cells with positive intracellular marker					
AERD	6.5	1.9	0.4	0.6	0.4
AFS	3.6	1.2	0.7	0.6	1.7
CF	17.7	0.04	0.9	2.7	0.9
AScA	10.5	1	0.02	0.1	1.2
ASsA	10	2.5	0.02	0.2	0.6
NAScA	12.9	0.3	0.3	0.3	0.6
NASsA	14.7	0.7	0.07	0.3	1.2
Control	4.8	0.9	0.3	0.4	1.1
Total	9.7	1	0.4	0.6	0.9

AERD=aspirin exacerbated respiratory disease also known as aspirin triad; AFS=allergic fungal sinusitis; AScA=asthmatic sinusitis with allergy; ASsA=asthmatic sinusitis without allergy; CF=cystic fibrosis; CRS=chronic rhinosinusitis; IFN=interferon; IL=interleukin; NAScA=nonasthmatic sinusitis with allergy; NASsA=nonasthmatic sinusitis without allergy.

DISCUSSION

Physicians, from primary care physicians to otolaryngologists, can differentiate the proposed division of CRS. The subclasses of CRS can be easily determined from clinical history and readily accessible laboratory or office testing (Fig. 6). Diagnosis for CF, allergic fungal sinusitis, and aspirin triad are well described in the literature. Patients with allergy and asthma can be diagnosed with office or laboratory testing, and CRS can then be divided as described in Figure 6. The proposed subclassification of CRS does not require difficult and expensive laboratory testing such as proteomics or microarray. The general characteristics of the CRS subclasses are described in Figure 7**.** By dividing CRS into this subclassification, effective targeted management can be developed for each category of CRS. Also, by defining the type of CRS that is being evaluated in either bench or clinical research study, the research data will hopefully become coherent and produce better research outcomes.

Nonasthmatic Sinusitis Without Allergy

Typically, NASsA patients have purulence on their nasal endoscopy and do not have high CT scores (Fig. 8). The biopsy of the sinus mucosa is not hypercellular and does not have an abundant amount of eosinophils in the mucosa. Structural abnormality due to anatomic variants may be a factor in these patients, such as concha bullosa, infraorbital ethmoid air cell, and deviated septum, that predisposes them to persistent bacterial sinus infections.[7] These sinus infections can occur after a viral exacerbation that leads to persistent cyclical bacterial infections (Fig. 9).

NASsA is similar to noneosinophilic sinusitis, which has been previously described.[8] NASsA has an extrinsic mucosal inflammation that is steered through T helper cells, CD3+CD4+. The inflammation in NASsA is termed extrinsic, because the inflammation is not derived from the mucosa but rather from an external source such as an infection that has been distinguished with elevated levels of IFN-γ. IFN-γ is a Th1 cytokine commonly representing an infectious process. NASsA patients have elevated levels of IL6 or IL8, similar to noneosinophilic sinusitis and may benefit from long-term macrolide therapy.[8] It is possible that innate immunity may be involved in NASsA patients, but it was not evaluated in this study. Hypoxia is also likely to be a factor in these NASsA patients due to sinus ostium obstruction.[9]

NASsA patients can often improve with a combination of oral antibiotics and steroids. For those NASsA patients who do not improve with medical management, ESS is a good subsequent treatment. However, there are NASsA patients who have recalcitrant bacterial sinus infections that persist despite properly opening the sinuses and being treated with culture-directed antibiotics. The most likely explanation for the obstinate low-grade bacterial infection causing localized inflammation is bony bacterial infection or biofilm. Bacterial biofilm in CRS has been shown to be a Th1-mediated process.[10] Management of bacterial biofilm is difficult, and multimodality treatment may be necessary to improve these patients. Multimodality treatment will likely include high-dose topical antibiotics with or without topical surfactant after mechanical irritation such as ESS or high-pressure irrigation of the sinuses.

Nonasthmatic Sinusitis With Allergy

If an inflammatory pathway continuum existed with NASsA on one end and AScA on the other spectrum, then NAScA would be between them. NAScA inflammatory pathway is also likely to be directed by T helper cells, because CD3+CD4+ was higher in this group versus the control group. Even though NAScA had significantly higher levels of IFN-γ than the control group, NAScA is likely a combination of an infectious

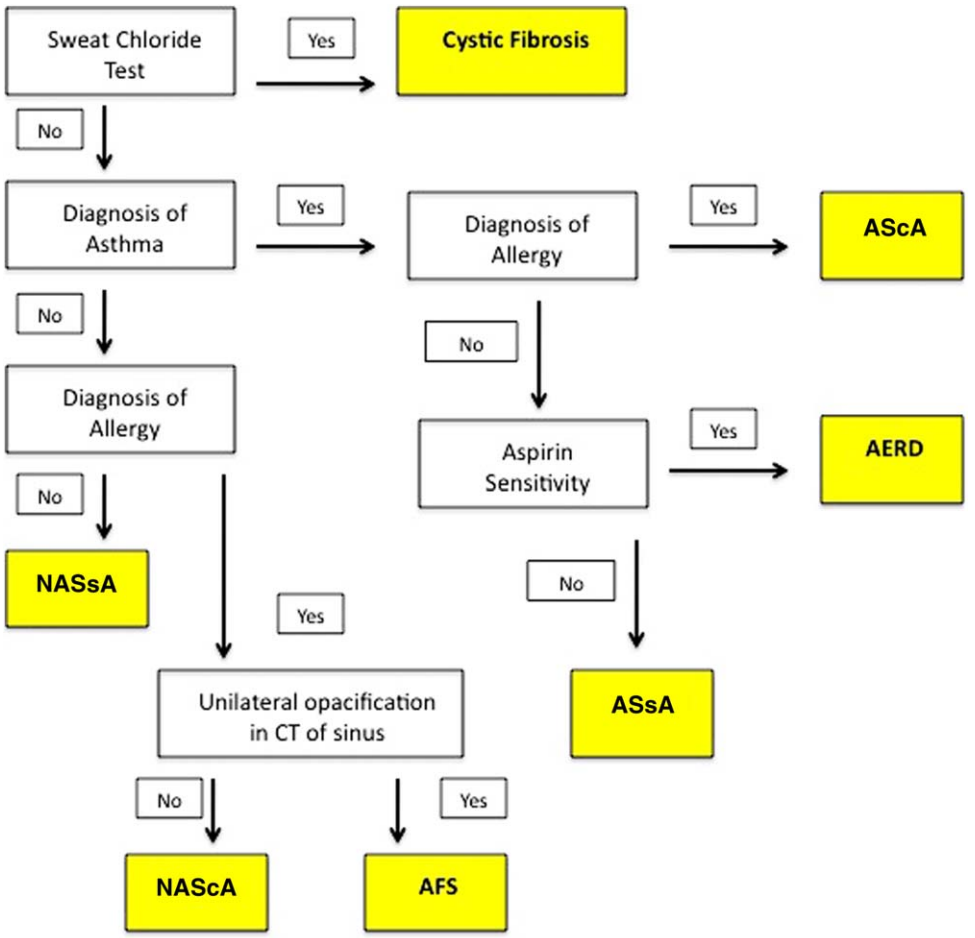

Fig. 6. Algorithm to diagnose the subclasses of chronic rhinosinusitis based on clinical history and testing. AERD=aspirin-exacerbated respiratory disease; AFS=allergic fungal sinusitis; AScA=asthmatic sinusitis with allergy; ASsA= asthmatic sinusitis without allergy; CT=computed tomography; NAScA=nonasthmatic sinusitis with allergy; NASsA=nonasthmatic sinusitis without allergy.

and inflammatory process. On nasal endoscopy, NAScA had significantly more polyps than the control group, whereas NASsA did not. On histologic examination, NAScA has higher amounts of eosinophils, mast cells, and cellularity than NASsA and control group. Mast cell, hypercellularity, and eosinophils are more consistent with a noninfectious inflammation that is similar to AScA. Therefore, for these NAScA patients, an acute

Type of Sinusitis	History	Nasal endoscopy findings	CT findings
NAS	No history of asthma or aspirin sensitivity	Mucosal swelling and purulence	Partial opacification of the sinuses
AS	History of asthma and no aspirin sensitivity	Abundant polyps with minimal purulence	Near total opacification of the sinuses
AFS	Usual unilateral symptom	Unilateral polyps with occasional purulence	Unilateral expansile heterogeneous mass
AERD	History of asthma and aspirin sensitivity	Abundant polyps with minimal purulence	Near total opacification for majority of the sinuses
CF	Positive sweat chloride test	Mucosal swelling with purulence	Near total opacification of hypoplastic sinuses

Fig. 7. Chart summarizing the phenotype for each subclass of CRS. AERD=aspirin-exacerbated respiratory disease; AFS=allergic fungal sinusitis; AS=aspirin sensitive; CF=cystic fibrosis; CT=computed tomography; NAS=nonasthmatic.

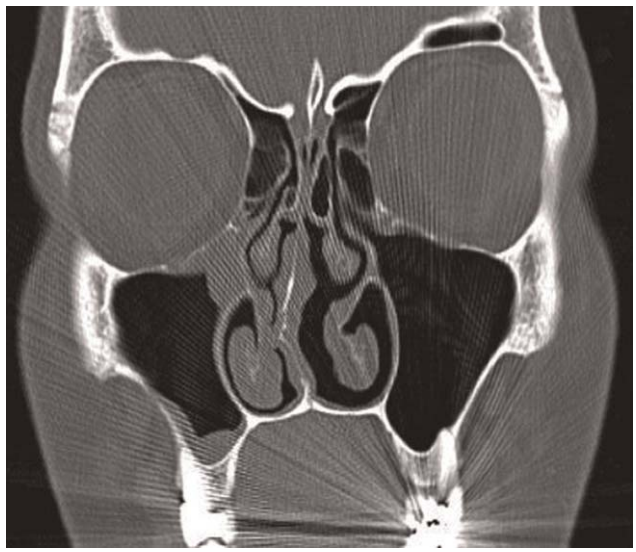

Fig. 8. Coronal computed tomography of the sinus demonstrating obstructive chronic sinusitis typical of nonasthmatic sinusitis without allergy.

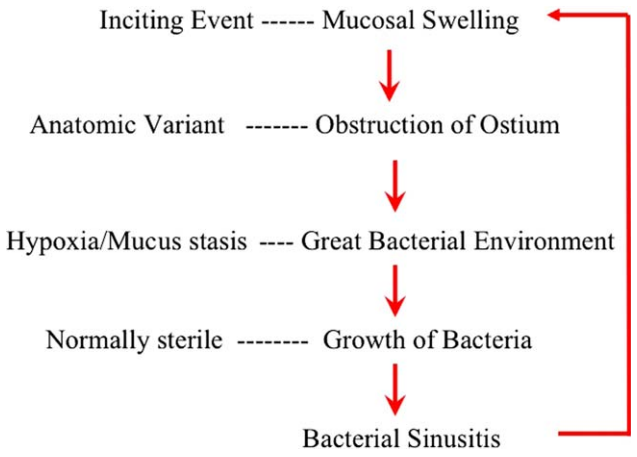

Fig. 9. Flow chart demonstrating the cyclical pattern of chronic sinusitis.

allergy exacerbation could lead to mucosal swelling and thus the cyclical sinusitis pattern (Fig. 9). In these patients, they may respond to pharmacotherapy for the allergy component of their CRS.

Asthmatic Sinusitis With Allergy

AScA represents the "unified airway" patients who have been described in the literature.[6] The unified airway patients have sinusitis, allergic rhinitis, and asthma but no aspirin sensitivity and is mediated via an IgE Th2 inflammatory process. Upper respiratory tract stimulation affects the lower respiratory tract and vice versa in these patients.[11] The most plausible explanation for the connection between the upper and lower airways is circulation of activated eosinophils that are very high in AScA CRS polyps. Eosinophils are activated in the sinus mucosa due to exposure of stimulants in the nose. The activated eosinophils are transported to the lung via the circulatory system. These circulating eosinophils can then bind to the adhesion molecules in the pulmonary epithelial tissue. The activated eosinophils in the lower respiratory tract can then create a local inflammatory response in the lung.

The amount of eosinophils in the nasal polyp appears to be a good histological marker or measure for intrinsic mucosal inflammation. This type of inflammation should be called intrinsic mucosal inflammation because the airway mucosa develops an abnormal response to an irritant within the mucosa due to a genetic predilection. Other intrinsic mucosal inflammatory CRS subclasses are AFS and AERD. Intrinsic inflammatory CRS has abundant eosinophils in tissue samples. Hypercellularity of nasal polyps is also high in intrinsic inflammatory CRS. However, hypercellularity, which is also represented in CF, may not always be representative of an intrinsic inflammation.

AScA patients commonly have a pediatric history of allergy or asthma. On nasal endoscopy, they have extensive nasal polyposis with little to no purulence. On CT findings, they have pansinusitis with complete or near complete opacification (Fig. 10). Because AScA had significantly higher levels of CD4+ cells than the control group, AScA mucosal inflammation is driven by T helper cells and most likely the Th2 process. Although Th2 mediated cytokines did not reach statistical difference in our study, IL4 and IL13 have been implicated in these IgE-associated atopic asthmatic patients.[12,13]

The inflammation in AScA is usually not driven by infection, and therefore AScA patients respond better to oral steroids rather than antibiotics. The mucosal inflammation in these patients is so severe that they are likely to fail medical treatment and often require ESS to debulk the nasal polyps. Removing the nasal polyps decreases the local inflammation by eliminating the eosinophils and associated inflammatory mediators to the level where the mucosal inflammation can be controlled with postoperative medications. Another reason for ESS is to debulk the obstructive nasal polyps and open the sinuses so that topical medications, such as topical budesonide, can be delivered into the sinuses. Topical budesonide has been shown to improve patient sinus score and hyposmia in chronic eosinophilic sinusitis.[14] Another method to control the inflammation is immunotherapy (sublingual and subcutaneous immunotherapy) that suppresses Th2-mediated response.[15] Immunomodulators using anti–IL4, anti-IL5, and anti-IL13 monoclonal antibodies are certainly options to be considered and have been evaluated in the past.[12,16]

Asthmatic Sinusitis Without Allergy

The phenotype and histology of ASsA is similar to AScA and AERD, but ASsA is more comparable to AERD than ASsA. An interesting thought is that ASsA could be a precursor to AERD. Unlike AScA, ASsA patients usually do not have a history of pediatric allergic rhinitis or asthma. As stated earlier, AScA or unified airway CRS commonly has a history of pediatric allergic

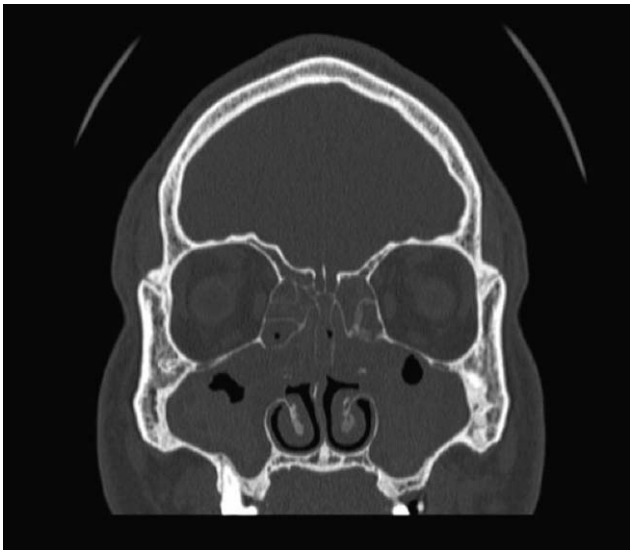

Fig. 10. Coronal computed tomography of the sinus demonstrating pansinusitis with near-complete opacification of all the sinuses.

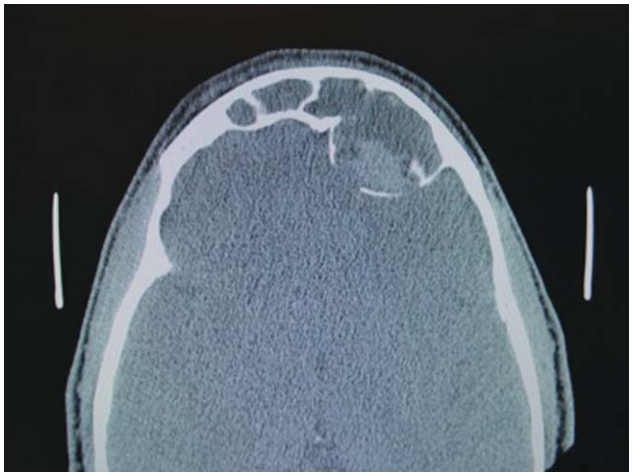

Fig. 11. Axial computed tomography of the frontal sinus demonstrating an expansile heterogenous mass in the right frontal sinus extending into the right frontal lobe. The inflammatory process has extended from the right frontal sinus to involve the left frontal sinus.

rhinitis and asthma. Interestingly AERD or aspirin triad patients commonly do not have a history of pediatric allergy or asthma. In fact, AERD patients have less atopy than aspirin-tolerant asthmatics or AScA (unified airway) patients.[17] Asthma in ASsA usually develops during the adult years. This is similar to AERD and unlike AScA. The natural progression of AERD patients demonstrates that rhinitis develops first. Asthma appears an average of 2 years after initial symptoms of rhinitis.[18] Nasal polyposis then ensues, followed finally by aspirin sensitivity. In other words, AERD patients can develop asthma and nasal polyposis while still being aspirin tolerant for a few years prior to eventually becoming aspirin intolerant. This is consistent with our study, because ASsA is younger than the AERD (Table II). The ASsA patient can represent a precursor of AERD prior to aspirin intolerance. In fact, a few patients under the author's care with adult onset asthma and severe nasal polyposis who were initially aspirin tolerant, eventually became aspirin intolerant during the course of their management. However, to confirm that ASsA might be a precursor to AERD, elevated levels of cysteinyl leukotrienes or urine LTE4 should be measured and confirmed. For now, these ASsA patients are counseled to avoid the use of NSAIDS.

It was interesting to note that CD4 cells were higher in ASsA than the control group. This finding implies that T helper cells may play a role for these patients. In fact, IL4 was higher in ASsA than CF. Another CRS subclass that had higher IL4 than CF but did not reach significance was AERD, which lends credence that ASsA may be a precursor to AERD.

Aspirin Triad or Aspirin Exacerbated Respiratory Disease

Aspirin triad or AERD patients have the worst sinus symptoms among CRS patients.[19] In our study they had the highest statistically significant CSS score. Aspirin triad patients have a history of adult onset asthma and usually do not have a history of pediatric asthma. Aspirin triad or AERD patients also have less atopy than aspirin-tolerant asthmatics.[17] Even when AERD patients do have a positive allergy test, the reaction to the allergy test is often mild and does not correlate to the severity of their nasal polyposis or asthma. In other words, the total serum IgE in AERD patients is lower than AScA (unified airway) CRS.[18]

On nasal endscopy, AERD patients had an abundant amount of polyps and the highest NE score (Table III). The nasal polyps biopsy demonstrates an extensive amount of eosinophils, mast cells, and hypercellularity. Even though AERD and AScA have similar phenotype, and both have intrinsic inflammation, they are different in terms of their immunologic inflammatory pathway.

Aspirin-exacerbated respiratory disease inflammation has been classically described by elevated levels of cysteinyl leukotrienes and not described as an adaptive immunity process.[19] However, in our study, the CD4 cells were elevated in AERD compared to the control group. If there is an adaptive immunity involved with AERD, it likely involves IL4, because IL4-producing cells were elevated in AERD. An interesting discovery was that the elevated IL4-producing cells in AERD were CD45+CD4− cells. That means that IL4 is not being produced by Th2 cells, but rather by another CD45+ cell. The most likely CD45+CD4− cell producing the IL4 is the mast cell, which was elevated in AERD and ASsA patients. The interplay between IL4 and cysteinyl leukotrienes is that IL4 stimulates expression of LTC_4 synthase and upregulates cysLT1 receptor expression. Also, IL4 can prolong eosinophil survival and is a cofactor for mast cell growth.

Similar to AScA, the amount of inflammation in AERD is so high that it is difficult to manage with medical treatment alone. In a study evaluating urine LTE4 in AERD patients, urine LTE4 was measured before and after ESS.[18] Urine LTE4 dropped from 227 pg/mg preoperatively to 72 pg/mg postoperatively ($P<.05$). Because urine LTE4 is a metabolite of cysteinyl leukotriene, this study demonstrated that debulking the nasal polyp during ESS decreases the primary inflammatory mediator in AERD patients.

Detailed management of aspirin triad has been described.[20] To summarize, initial medical management of oral steroid and oral zileuton should be considered. Zileuton is an inhibitor of 5-lipoxygenase and thus inhibits the production of cysteinyl leukotrienes. However, a baseline liver function test should be performed prior to the use of zileuton, because there is a 4% chance of liver toxicity. If the medical management does not control the patient's symptoms, ESS should be performed to debulk the inflammatory polyp to decrease the inflammatory load in the nasal polyps and to allow for topical medications into the sinuses. Postoperatively, zileuton should be continued with careful monitoring of the liver enzymes, specifically alanine aminotransferase. Topical steroid spray, irrigation, or drops should be considered in conjunction with the zileuton. Aspirin desensitization is another possibility, especially if pharmacotherapy is not effective. The exact mechanism for aspirin

desensitization has not been clearly defined, but one possible explanation is that aspirin inhibits IL4 transcription in peripheral T cells.[21] In a study examining IL4 after aspirin desensitization in AERD patients, IL4 levels were significantly decreased after 6 months of daily aspirin maintenance.[22]

Allergic Fungal Sinusitis

AFS is well defined in the literature.[23] It has been described as a IgE-mediated Th2 process, much like AScA or unified airway CRS. Even though AFS has an intrinsic inflammatory process like AScA, AFS does not share the same attributes as AScA. In a broad sense, the difference between AFS and AScA is that the AFS is a localized disease process, whereas AScA is more of a systemic issue. Allergic fungal sinusitis patients rarely have asthma as a confounding variable, but for AScA, asthma is part of it identity. Also, AFS has a specific allergic reaction to a fungus, whereas in AScA it has a more undifferentiated response to any sensitized inhalant allergens. Allergic fungal sinusitis is mostly a unilateral disease, whereas AScA commonly involves bilateral sinuses. In severe cases, allergic fungal sinusitis can have bilateral involvement (Fig. 11). Both AFS and AScA can have eosinophilic mucin deposited in the sinuses. However, AFS has fungus within the mucin detected with Grocott's silver stain, and AScA does not stain for fungus. Although the presence of purulence between AFS and AScA was not statistically different in our study, purulence is commonly seen in AFS and less so in AScA.

Interestingly, CD4 was not elevated in AFS as it was demonstrated in AScA. Even though CD4 was not higher than the control group for AFS, AFS is likely a Th2-mediated inflammatory process, because AFS had a significantly higher amount of Th2 cytokines expression such as IL5. Even though AScA and AFS are both mediated by an IgE inflammatory pathway, AScA and AFS do not have the same immunologic pathway. Interleukin 4 and IL13 are more likely to play a role in AScA, whereas AFS likely has IL4, IL5, and IL13 involved. In a study by Upadhyaya et al., Th2 cells were divided into two subpopulations.[24] One group of Th2 cells expressed IL4 and IL13 but not IL5, whereas another group of Th2 cells expressed IL4, IL5, and IL13. IL4 and IL13 can be coexpressed without IL5, because their genes are adjacent, and the IL5 gene is in the opposite orientation. Also, the expression of IL5 demonstrates a more differentiated Th2 inflammatory pathway.[25] The fact that IL5 is strongly expressed in AFS and not in AScA appears to be consistent, that AFS may be a more differentiated eosinophilic disease than AScA.

Another interesting finding for AFS was that AFS had elevated CD19 and plasma cells in comparison to the control group. Having elevated CD19 and plasma cells in AFS is coherent, because B cells (CD19) develop into plasma cells. A possible explanation that both CD19 and plasma cells were high for AFS is that immunoglobulin may play a large role in this disease process.

Fortunately, the inflammatory drive in AFS is not as severe as AERD or AScA, so complete evacuation of the eosinophilic fungal mucin with post-operative topical steroid irrigation reduces the recurrence rate of AFS to a minimum. One factor to consider in AFS is the coexistence of fungal and bacterial biofilms that can persist after the inflammatory process to fungus in AFS is removed.[26]

Cystic Fibrosis

CF patients are probably the most difficult CRS patients to manage. On nasal endoscopy, thick tenacious mucus and purulence is characteristic of the CF sinus-nasal cavities. CT scores are high and often demonstrate underdeveloped sinuses. On histopathology, CF tissue samples demonstrate subepithelial cell distribution that is consistent with an infectious pattern. Cystic fibrosis had the highest ratio of PMN, which also points to an infectious process. Even though CF is most likely an infectious process like NASsA, CF tissue samples were different than NASsA. Cystic fibrosis tissues were hypercellular with a high number of mast cells, which was also seen among eosinophilic-based CRS such as AERD, AFS, AScA, and ASsA.

Cystic fibrosis CRS had the highest quantity of mast cells, and it was statistically higher than all of the other CRS subclasses. Mast cells were higher in CRS subclasses with intrinsic mucosal inflammatory CRS subclasses such as asthmatic sinusitis and aspirin triad. This is an expected result, because the mast cell is second only to eosinophil as a potent inflammatory cell. CF tissue was expected to have low mast cells and low cellularity, because it was thought to be predominantly an infectious sinusitis. Cystic fibrosis did have low eosinophil counts as expected but then had the highest mast cell count.

Even though CF has traits that are consistent with an infectious process, CF CRS is not mediated by Th1 cells like NASsA. CF did not have statistical difference in CD4 cells or IFN-γ to control like NASsA. The most likely explanation to solidify the data for CF is that CF has an infectious inflammatory process that is associated with mast cells.

Cystic fibrosis involves an infectious or external inflammation that is associated with mast cell, LTB4, and IL6. In a study examining LTB4 and IL6 in breath condensate, LTB4 and IL6 were measured between CF and a control group.[27] Cystic fibrosis had elevated LTB4 and IL6 compared to the control group ($P<.01$). Also, when the CF patients were given antibiotics for their infections, there was a significant drop in the LTB4 and IL6 ($P<.01$). Another interesting finding in the study was that an active *Pseudomonas aeruginosa* infection increased LTB4 and IL6 production in comparison to other bacterial infections in CF patients.

The most likely source for the LTB4 in CF patients is the mast cells that were very high in CF. Leukotriene B4 is a strong PMN chemoattractant and therefore accounts for the high PMN count in CF patients.[28] The high PMN count in CF sinus tissue is also likely responsible for the destruction of the epithelium and goblet cells as seen in our study. Another interesting finding

from our study was that CF had high CD19 and plasma cells. This is consistent with the literature, which states that CF patients have elevated levels of IgG, IgM, and IgA, especially during an infection.[29] So it is very likely that immunoglobulin also contributes to combating the bacterial sinus infection commonly encountered in CF patients.

The treatment for CRS in CF patients will likely involve multimodal treatments. One treatment would be to loosen the tenacious mucus with inhaled dornase alfa[30] or hypertonic sinus irrigation. Topical nasal steroid spray can be used to decrease the local inflammation of the sinuses. Also, because LTB4 is increased in CF patients, especially with an active pseudomonas infection, zileuton could be used to block the production of LTB4 and minimize PMN recruitment that causes local epithelial destruction. By minimizing PMN recruitment and release of elastase, immunoglobulin can be spared to prevent bacterial infection along mucosal surfaces.[31] It is theoretical that zileuton has the possibility of improving the upper respiratory tract as well as the lower respiratory tract. However, the liver needs to be carefully monitored for liver toxicity when using of zileuton. As a last resort and after medical treatment has failed, if sinus surgery is needed, making large antrostomies and opening up all the sinuses should be considered. By creating large opening into the sinuses, this will allow for topical medication to get into the sinuses and to prevent future sinus surgery.[32]

Limitations

There are some limitations of the proposed subclassification of CRS. First, this classification of CRS may not address all the different forms of CRS, such as CRS due to vasculitis or sarcoidosis. Another limitation is that although the presence or absence of allergy and asthma was documented, the severity was not. For allergy, total serum IgE could be used as a measure to determine the severity of the allergy. However, this was difficult to do in this study because some of the patients received a radioallergosorbent test, whereas others received skin prick testing. One other limitation is that the innate immunity was not investigated in the CRS study group. It is likely that innate immunity may play a role for some of the CRS subclasses, especially for nonasthmatic sinusitis. Finally, the number of patients in each CRS subclasses was not large. With a higher number of specimens in each CRS subclass, statistical significance may be found that was not demonstrated in this study. However, this study nonetheless is an impressive undertaking. This is the first study to comprehensively compile the phenotype characteristics among CRS patients and also include the difference of biomarker with intracellular staining of cytokines among CRS patients.

CONCLUSION

Nasal mucosal swelling and polyps are the end product of sinus inflammation. By characterizing the phenotype and pathway of nasal polyp inflammation for various types of CRS, well-characterized and distinct groups of CRS have been defined. By defining the different discrete category for CRS, a targeted treatment plan for each CRS subclass has been discussed in the article. Also, by defining specific CRS entities, hopefully these CRS subclassifications can be use in future bench and clinical research studies.

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ORIGINAL ARTICLE

The bitter taste receptor T2R38 is an independent risk factor for chronic rhinosinusitis requiring sinus surgery

Nithin D. Adappa, MD[1], Zi Zhang, MD[1], James N. Palmer, MD[1], David W. Kennedy, MD[1], Laurel Doghramji, RN[1], Anna Lysenko, MS[2], Danielle R. Reed, PhD[2], Thomas Scott, BS[1], Nina W. Zhao, BS[1], David Owens, BS[1], Robert J. Lee, PhD[1] and Noam A. Cohen, MD, PhD[1,3]

Background: **The bitter taste receptor T2R38 was recently described to play a role in upper airway innate mucosal defense. When activated by bacterial quorum-sensing molecules, T2R38 stimulates the ciliated epithelial cells to produce nitric oxide (NO), resulting in bactericidal activity and an increase in mucociliary clearance (MCC). Polymorphisms within the T2R38 gene (*TAS2R38*) confer variability in activation of the receptor yielding dramatic differences in upper airway defensive responses (NO production and accelerated MCC) to microbial stimulation based on genotype. Our objective was to determine whether the nonprotective *TAS2R38* polymorphisms, which render the receptor inactive, correlate with medically recalcitrant chronic rhinosinusitis (CRS) necessitating surgical intervention in the context of known risk factors, and thus identify whether the *TAS2R38* genotype is an independent risk factor for patients undergoing functional endoscopic sinus surgery (FESS).**

Methods: **CRS patients undergoing primary FESS were prospectively genotyped for *TAS2R38*. Chi-square analysis was performed on the genotype distribution with respect to other risk factors, including allergies, asthma, nasal polyposis, aspirin sensitivity, diabetes, and smoking exposure.**

Results: **Seventy primary FESS patients were genotyped demonstrating a statistically significant skewing from the expected distribution of the general population ($p < 0.0383$). CRS patients with a particular polymorphism seemed less likely to have allergies, asthma, nasal polyposis, aspirin sensitivity, and diabetes, but this did not demonstrate statistical significance.**

Conclusion: **Our investigation suggests that *TAS2R38* genotype is an independent risk factor for patients failing medical therapy, necessitating surgical intervention.** © 2013 ARS-AAOA, LLC.

Key Words:
innate immunity; antimicrobial; nitric oxide; mucociliary clearance; endoscopic sinus surgery; genetics

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Chronic rhinosinusitis (CRS) affects 14% to 16% of the population.[1] This results in both a burden on patient quality of life (QoL) as well as a tremendous socioeconomic impact, with annual direct costs of the disease in excess of $8 billion in the United States alone.[2] Over the past 3 decades substantial effort has been invested in better understanding the disease process, with significant progress made in our understanding of mucosal immunology and microbiology.[3] Many contributing factors have been implicated in the development of CRS, including allergic responses, impaired mucociliary clearance, immune dysfunction, impaired epithelial defense, microbial colonization/infection, and exposure to environmental pollutants.[4,5] It has been conjectured that a genetic component may, in certain environmental situations, lead to the development of CRS. This is based on a number of factors. Individuals with CRS are more likely to report a positive family history than those without CRS.[6–8] Additionally, reports of families with unusually high prevalence of both CRS with and without nasal polyps have been published.[7–10] Two well-known genetic causes for

[1]*Department of Otorhinolaryngology–Head and Neck Surgery, University of Pennsylvania, Philadelphia, PA;* [2]*, Monell Chemical Senses Center, Philadelphia, PA;* [3]*Surgical Services, Philadelphia Veterans Affairs Medical Center, Philadelphia, PA*

Correspondence to: Nithin D. Adappa MD, Department of Otorhinolaryngology–Head and Neck Surgery, Ravdin Building 5th Floor, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia PA 19104; e-mail: Nithin.Adappa@uphs.upenn.edu

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CRS, cystic fibrosis (CF) and primary ciliary dyskinesia (PCD), have been well characterized (although they account for a small subset of CRS patients). Finally, the inflammatory changes associated with CRS have similarities to those seen in patients with allergic rhinitis and asthma, which are disease processes with well-established genetic components.[11,12] Although Hsu et al.[13] recently published a comprehensive review of the available literature on genetic studies in CRS, none have been definitively proven to contribute to the disease process.

An emerging gene family that may have a genetic contribution to CRS is the bitter taste receptor. Several recent reports have demonstrated the expression of bitter taste receptors in airway epithelium.[14–16] We have recently demonstrated that 1 particular bitter taste receptor expressed in the sinonasal ciliated cell, T2R38, is activated by acyl-homoserine lactones (AHLs). AHLs are Gram-negative quorum-sensing molecules used to regulate the expression of genes involved in biofilm formation, persistence, virulence, and other life cycle processes.[17–19] When activated by AHLs, in vitro, T2R38 generates a calcium-dependent increase in nitric oxide (NO) production, which subsequently increases mucociliary clearance (MCC) and diffuses into the overlying mucus layer where it also has bactericidal effects.[18] Thus, T2R38 contributes to sinonasal mucosal innate immunity by acting as a sentinel for detection of a subset of microbial quorum-sensing molecules and rapidly activating potent local defenses in response to imminent microbial attack.

The activity of this sinonasal innate defense response varies depending on 3 common polymorphisms within the *TAS2R38* gene. The differences lie in the amino acid residues at positions 49, 262, and 296; these 3 polymorphisms tend to segregate together, yielding 2 common haplotypes. The functional (protective) allele of the receptor encodes a proline, alanine, and valine (PAV) at the respective positions, and a nonfunctional (nonprotective) allele of the receptor encodes an alanine, valine, and isoleucine (AVI) at these positions.[20] The 2 common haplotypes generate 3 common genotypes: PAV/PAV, PAV/AVI, and AVI/AVI, which follow classic Mendelian genetics with a 25%, 50%, 25% population distribution, respectively.[20] This distribution varies by both geographic region as well as race and ethnicity. Our prior work demonstrated that primary human sinonasal epithelial cultures derived from patients that were PAV/PAV yielded a significant increase in NO production and MCC in response to low levels of AHLs, compared to the cultures derived from PAV/AVI or AVI/AVI patients. We previously reported on a pilot investigation of 28 medically recalcitrant CRS patients who progressed to require functional endoscopic sinus surgery (FESS), which demonstrated a statistically significant skewing from the expected population distribution, with higher than expected nonfunctional genotype (AVI/AVI) individuals and a lower than expected functional (protective) genotype (PAV/PAV) individuals.[21]

This is a follow-up investigation with a larger series, including those previously reported patients. Our goal was to further confirm the findings of our pilot study and thereby corroborate the relationship between increased risk of failing medical therapy and the AVI/AVI genotype as compared to the protective PAV/PAV genotype. To improve our methodology we also compared our patient population to a regional control population. We also explored whether other known risk factors for CRS, including asthma, allergies, smoking status, polyps, and aspirin sensitivity, segregated with the different *TAS2R38* genotypes.

Patients and methods

This was an institutional review board (IRB)-approved study of prospectively collected sinonasal tissue samples of patients failing medical therapy for CRS and undergoing primary FESS at the University of Pennsylvania or the Philadelphia Veterans Affairs Medical Center. Our medical therapy consisted of a minimum of two 3-week courses of antibiotic (culture-directed if available) with concurrent oral corticosteroid taper if medically acceptable. In addition, all patients were also placed on normal saline irrigations and topical nasal steroids. Finally, all patients underwent an allergy evaluation if an atopic history was present. Inclusion criteria included any patient 18 years or older of European descent. Exclusion criteria consisted of any patient with known autoimmune dysfunction, immune deficiency, primary ciliary dyskinesia, cystic fibrosis, history of radiation exposure to the paranasal sinuses, or history of sinonasal trauma.

Patients of European descent but not those of other ancestry were included in the statistical analysis because investigation of European descent of *TAS2R38* is best characterized both in the literature as well as in our control population. The decision to exclude other racial groups was justified because less data is available from other racial groups living in this metropolitan area to provide stable estimates of genotype frequency. In addition, although a larger population exists in the control population, we have included only biologically unrelated individuals. All subjects reported no sense of smell or taste abnormalities. Finally, subjects from both the patient and comparison sample with rare genotypes were excluded from the analysis.

Genomic DNA was isolated and each sample genotyped for *TAS2R38* as described.[18,21] Patient risk factors including asthma, allergies, nasal polyposis, aspirin sensitivity, diabetes, and smoking status were collected. We further compared the distribution of these known CRS risk factors between CRS patients with different T2R38 genotypes. This was to determine if the difference between T2R38 genotypes in CRS patients requiring FESS and the general population can be explained by the different distribution of known CRS risk factors among T2R38 genotypes. Statistical chi-square (χ^2) analysis was performed using Stata 10 (Statacorp, College Station, TX).

TABLE 1. Comparison of *TAS2R38* genotype frequencies between patients and geographic comparison sample[a]

Population observed	AVI/AVI	AVI/PAV	PAV/PAV	Total
Patients	26 (37)	38 (54)	6 (8.5)	70
Comparison group	100 (29)	177 (51)	70 (20)	347

[a]Values are n(%) except where indicated. The frequency of PAV/PAV genotype was significantly lower than expected, whereas the AVI/AVI genotype was significantly higher than expected based on comparison population ($\chi^2(2) = 6.526$, $p = 0.0383$).
AVI = alanine, valine, and isoleucine; PAV = proline, alanine, and valine.

Results

Seventy patients failing medical management for CRS and undergoing primary FESS who met the criteria were genotyped for *TAS2R38* from residual clinical material, and the genotype frequencies of the medically recalcitrant CRS cohort was compared to 347 individuals drawn from the general population of the Philadelphia metropolitan region (comparison sample).[22] The original study had 980 individuals but only those of European descent with biologically unrelated subjects were included. In addition, patients and individuals in the comparison sample with rare genotypes were excluded from the analysis (n = 3 patients; 1 AAV/AVI and 2 AAV/PAV; n = 280 in comparison sample; for individual genotypes see Mennella et al.[22]). The observed and expected genotype frequency between the patient and comparison cohorts was evaluated by chi-square analysis. As previously demonstrated in our pilot study, these results significantly confirm that the frequency of the AVI/AVI (nonfunctional) genotype is much higher and the PAV/PAV (protective) genotype is much lower in the medically recalcitrant CRS patient population than in the comparison (control) population ($\chi^2(2) = 6.526$, $p = 0.0383$) (Table 1).

We further compared the distribution of age, sex, asthma, allergies, polyp status, aspirin sensitivity, diabetes, and smoking status among different T2R38 genotypes in CRS patients requiring FESS (Table 2). In general, CRS patients with asthma, allergies, nasal polyposis, aspirin sensitivity, and diabetes seemed less likely to have the PAV/PAV (protective) genotype. Univariate analyses of the distribution of comorbidities by genotype did not demonstrate any statistical significance.

TABLE 2. Demographics and medical comorbidity distribution for each genotype[a]

Genotype	AVI/AVI	AVI/PAV	PAV/PAV	*p*
Patients	26 (37)	38 (54)	6 (8.5)	
Age, years	46	50	54	
Male gender	13 (50)	30 (79)	5 (67)	
Asthma	12 (46)	14 (37)	1 (17)	0.388
Allergies	16 (62)	21 (55)	3 (50)	0.825
Polyps	13 (50)	23 (60)	2 (33)	0.396
Aspirin sensitivity	0 (0)	2 (5)	0 (0)	0.420
Diabetes	1 (4)	5 (13)	0 (0)	0.313
Smoker	2 (7)	3 (8)	2 (33)	0.137

[a]Values are n (%) except where indicated. Univariate analyses of the distribution of comorbidities by genotype did not demonstrate any statistical significance.
AVI = alanine, valine, and isoleucine; PAV = proline, alanine, and valine.

Discussion

Substantial effort is ongoing to identify genetic bases for CRS.[13] Despite improved knowledge in our understanding of mucosal immunology and microbiology, common genetic factors contributing to CRS susceptibility remain poorly defined.[3] The majority of studies have focused on identification of polymorphisms in genes controlling important factors or regulatory elements that are part of known CRS mechanisms[5,23–25] or innate immune defenses in CRS.[26–28] Although this has led to a number of promising genetic contributions, no definitive genetic polymorphism(s) explaining CRS pathophysiology has been identified.[29]

We have recently identified expression of the bitter taste receptor T2R38 in human sinonasal ciliated epithelial cells, where it serves a novel role in mucosal innate defense as a sentinel against Gram-negative quorum-sensing molecules and thus protects against upper airway infection.[18] Within the context of the contribution of T2R38 to CRS, the focus of our work has not been on gene expression levels, but on genetic polymorphisms affecting the function of the receptor that may not affect the expression levels of gene. Thus, T2R38 may not have been identified in prior genetic searches using comparative genetic approaches such as microarray analysis. In upper respiratory defense, polymorphisms within the *TAS2R38* gene have both a functionally protective genotype (PAV/PAV) and a nonfunctional genotype (AVI/AVI) in response to AHLs with heterozygotes falling between the homozygote phenotypes.[18]

The polymorphisms within *TAS2R38* have been extensively studied as they relate to bitter taste perception in the oral cavity. We were able to draw upon these large population studies to compare the distribution of the polymorphisms within our CRS group to expected genotype distribution for our geographic region. We were able to compare our patient population of Caucasian patients predominately drawn from the greater Philadelphia metropolitan area with a baseline regional control group of 347 individuals that demonstrated a significant overrepresentation of the AVI/AVI nonfunctional genotype and an underrepresentation of the PAV/PAV functional genotype ($p = 0.0383$).

Our current study of 70 medically recalcitrant CRS patients undergoing primary FESS expanded and confirmed our initial pilot study of 28 patients demonstrating a similar skewed genetic distribution within this clinical cohort.[21] In our current study, we also evaluated a number of known

CRS risk factors and CRS-associated conditions. No other known CRS comorbidities were significantly associated with the *TAS2R38* genotype.

The T2R38 bitter taste receptor polymorphism is extremely common and may represent a genetic component leading to medically recalcitrant CRS. Interestingly, Endam et al.[30] recently presented a pooling-based genomewide association study of medically recalcitrant CRS and control patients identified the *TAS2R38* locus as a potential "hot spot" at the 2013 American Rhinological Society Annual Meeting.

Despite increasing evidence that polymorphisms in the T2R38 bitter taste receptor contribute to medically recalcitrant CRS, questions regarding this mechanism remain unanswered. The pathway identified for the T2R38 receptor is through Gram-negative quorum-sensing molecules. Currently, robust literature implicates *Staphylococcus aureus* in bacterial CRS,[31–34] thus making the contribution of T2R38 perplexing. Possible explanations include that CRS may in fact be more Gram-negative–driven than previously identified or additional yet-to-be-determined mechanisms of the T2R38 may aid in protection against other microbes such as Gram-positive microbes, leading to a decrease in recalcitrant CRS.

There are limitations to our current investigation. An inherent risk in identification of a specific gene includes the possibility of a linkage disequilibrium with another gene segregating with *TAS2R38* polymorphism that has yet to be identified.

In addition, the comparison population also has some limitations. The comparison population was drawn from a research investigation on taste and smell. Although the comparison population was from the same geographic area, that research investigation was not performed at the same institution where the surgical patients were identified. In addition, the original studies included multiple races as well as biologically related individuals and children. To control for this, only adult patients of European descent, with biologically unrelated individuals were included. Unfortunately, no information on comorbidities were available for this sample population to further support the independent association. Although there are limitations in this control population, we feel it serves as an adequate comparison group. We are currently collecting genotype and demographic data on a population presenting with nonrhinologic morbidities at our institution, where we will be able to improve on the control population selection methodology. Future investigation will also include evaluation of outcomes of the various *TAS2R38* genotypes following FESS, potentially identifying whether select genotypes (PAV/PAV) provide better outcomes after surgery vs the nonprotective genotype (AVI/AVI).

Conclusion

Our study confirms our pilot investigation[21] demonstrating that the nonfunctional *TAS2R38* genotype (AVI/AVI) is overrepresented in medically recalcitrant CRS patients whereas the functional genotype (PAV/PAV) is underrepresented. Furthermore, no other known risk factors associate with the *TAS2R38* polymorphism suggesting that the nonfunctional genotype is an independent risk factor for medically recalcitrant CRS.

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A chest physician's guide to mechanisms of sinonasal disease

V Hox,[1,2] T Maes,[3] W Huvenne,[4] C Van Drunen,[5] J A Vanoirbeek,[6] G Joos,[3] C Bachert,[4] W Fokkens,[5] J L Ceuppens,[2] B Nemery,[6] P W Hellings[1,2]

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[1]Clinical Division of Otorhinolaryngology-Head and Neck Surgery, University Hospitals Leuven, Leuven, Belgium
[2]Laboratory of Clinical Immunology, Department of Microbiology and Immunology, KU Leuven, Leuven, Belgium
[3]Laboratory for Translational Research in Obstructive Pulmonary Diseases, Department of Respiratory Medicine, Ghent University Hospital, Belgium
[4]Upper Airways Research Laboratory, Department of Otorhinolaryngology-Head and Neck Surgery, University of Ghent, Belgium
[5]Department of Otorhinolaryngology, Academic Medical Center, Amsterdam, The Netherlands
[6]Research Unit of Lung Toxicology, Department of Public Health, K U Leuven, Leuven, Belgium

Correspondence to
Dr Valerie Hox, Clinical Division of Otorhinolaryngology-Head and Neck Surgery, University Hospitals Leuven, Kapucijnenvoer 33, 3000 Leuven, Belgium; valeriehox@gmail.com

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ABSTRACT

The upper and lower airways are closely linked from an anatomical, histological and immunological point of view, with inflammation in one part of the airways influencing the other part. Despite the concept of global airway disease, the upper airways tend to be overlooked by respiratory physicians. We provide a clinical overview of the most important and recent insights in rhinitis and rhinosinusitis in relation to lower airway disease. We focus on the various exogenous and endogenous factors that play a role in the development and aggravation of chronic upper airway inflammation. In addition to the classical inhaled allergens or microorganisms with well-defined pathophysiological mechanisms in upper airway disease, environmental substances such as cigarette smoke, diesel exhaust particles and occupational agents affecting lower airway homeostasis have recently gained attention in upper airway research. We are only at the beginning of understanding the complex interplay between exogenous and endogenous factors like genetic, immunological and hormonal influences on chronic upper airway inflammation. From a clinical perspective, the involvement of upper and lower airway disease in one patient can only be fully appreciated by doctors capable of understanding the interplay between upper and lower airway inflammation.

INTRODUCTION

Due to its position at the entry of the airways, the nasal mucosa is continuously exposed to inhaled agents from the environment. In order to prevent continuous inflammation induced by exogenous stimuli, the nasal epithelium is armed with a variety of mechanisms contributing to mucosal homeostasis including nasal epithelial cells with tight junction molecules, mucus production and ciliary function. The environment in which we live and work contains pathogens, allergens and irritants that can lead to inflammation of the upper airway mucosa. However, endogenous factors also play a role in the manifestation of chronic upper airway inflammation.

The most common upper airway disease is rhinitis, which is defined as a symptomatic inflammation of the nasal mucosa.[1] Rhinosinusitis is defined as inflammation of the sinonasal mucosa which can present with or without nasal polyps.[2] Depending on the duration of symptoms, we distinguish acute rhinosinusitis (ARS; <12 weeks) and chronic rhinosinusitis (CRS; >12 weeks) (see additional information in online supplement).

The close link between upper and lower airway inflammation is well known in the context of 'global airway disease' referring to the common coexistence of upper and lower airway symptoms, especially in patients with asthma and chronic obstructive pulmonary disease (COPD).

This review (and the synopsis in table 1) focuses on both endogenous predisposing factors and exogenous triggers that may contribute to chronic upper airway disease and that can also impact lower airway disease.

ENDOGENOUS FACTORS ASSOCIATED WITH UPPER AIRWAY DISEASE

Genetic factors

Atopy is a strong hereditary predisposing factor for allergic rhinitis and allergic asthma. Additionally, polymorphisms in the interleukin 13 (IL-13) gene, one of the genes that has been most consistently associated with asthma, were also linked to allergic rhinitis to moulds in a large Korean study.[3] Patients with mutations in the transforming growth factor β (TGF-β) receptor gene are strongly predisposed to develop both allergic rhinitis and asthma.[4] Polymorphisms in the Toll-like receptor (TLR) 7 and 8 gene areas were also associated with allergic rhinitis in Swedish and Chinese populations.[5] Moreover, the same Swedish group identified 10 genes that were linked to non-allergic rhinitis.[6] Among these genes, *Cfos* (encoding a transcription factor activated by airway exposure to toxins and irritants) and *Cdc42* (encoding a GTPase implicated in the cell cycle) seem to be the most promising genes because they control and modulate genes or pathways that can be implicated in airway disease.

So far, 53 single nucleotide polymorphisms (SNPs) have been associated with CRS, with specific polymorphisms in genes involved in leukotriene and prostaglandin biosynthesis, nitric oxide synthase (NOS) 1[7] and production of cytokines such as IL-6, tumour necrosis factor α (TNFα), IL-1, IL-22 and IL-33.[2] Among patients with CRS requiring surgery, the bitter taste receptor *T2R38* genotype was different from the general population.[8] Recently, a replication study on genetic variants in CRS showed the highest consistency and significance for SNPs in *TGFB1*, *NOS1* and *PARS2* (an amino acid activator for protein synthesis).[9]

Immune deficiencies

Respiratory diseases have been linked to both primary and secondary immune deficiencies (PID/SID).

In Western countries, the most common PID is common variable immune deficiency (CVID), which is defined by a general impaired antibody production. Other humoral PIDs present as specific immunoglobulin (Ig) deficiencies. Among patients with CVID, 36–78% have CRS in addition to

Table 1 Summary of reported effect of endogenous and exogenous factors on either rhinitis or rhinosinusitis

	Rhinitis	Rhinosinusitis
Endogenous factors		
Genetic factors	*Allergic rhinitis*: SNPs in genes coding for leucotrienes, chemokines, chemokine receptors, cytokines, TLRs[4 5] *Non-allergic rhinitis*: SNPs in genes coding for Cfos and Cdc242[6]	CRS with nasal polyps: SNPs in genes coding for TGF-β1, iNOS, PARS2, IL-1α, IL-33, genes related to eosinophilia[2]
Immune deficiencies	*Primary humoral immune deficiencies*: increased prevalence of chronic upper airway disease (specific, common variable and SPAD)[2] *Secondary immune deficiencies*: difficult-to-treat rhinosinusitis with resistant or uncommon microorganisms[12]	
Hormones	Pregnancy rhinitis[18] Anecdotal reports linking rhinitis to hypothyroidism and acromegaly[20]	Anecdotal reports linking rhinosinusitis to hypothyroidism[20]
Systemic diseases	Sarcoidosis[25]	Difficult-to-treat CRS in Churg–Strauss syndrome[24] Granulomatosis with polyangiitis[22] Sarcoidosis[25]
Psychological factors	Increased prevalence of allergic rhinitis in persons who experienced stressful life events[26 27] Increased risk of developing upper airway infection in subjects with psychological stress[31]	
Exogenous factors		
Viruses	Common cold	ARS[2]
Bacteria	*Staphylococcus aureus* colonisation is increased in allergic rhinitis[47]	Superinfection of viral ARS[70] CRS with nasal polyps: increased colonisation with *S. aureus* and increased IgE towards *S. aureus* enterotoxins[47]
Fungi	Can cause allergic sensitisation	Mycetoma or fungal ball (one sinus) AFRS (multiple sinuses)[50] Granulomatous and chronic invasive FRS in immunocompromised patients[49]
Allergens	Cause of allergic rhinitis[1]	Increased prevalence of CRS in atopic patients[56]
Occupational agents	Allergic rhinitis to HMW allergens Allergic rhinitis to LMW sensitisers Irritant-induced rhinitis	Increased occupational exposure in FESS-requiring CRS patients[56]
Cigarette smoke	Active and passive smoking increase the risk of developing rhinitis[61]	Higher prevalence of CRS in smokers[62]
Pollution and DEP	DEP aggravate pre-existing rhinitis[68]	Weak association between pollution and prevalence of CRS[69]

ARS, acute rhinosinusitis; CRS, chronic rhinosinusitis; DEP, diesel exhaust particles; FESS, functional endoscopic sinus surgery; FRS, fungal rhinosinusitis; HMW, high molecular weight; IL, interleukin; iNOS, inducible nitric oxide synthase; LMW, low molecular weight; SNP, single nucleotide polymorphism; SPAD, specific polysaccharide antibody deficiency syndrome; TGF, transforming growth factor; TLR, Toll-like receptor.

having frequent episodes of bronchitis and pneumonia.[2] In a study involving 300 patients with refractory CRS, 21.8% showed a humoral immunodeficiency[2] and, in a comparable study including 74 patients with rhinosinusitis, 19% had low immunoglobulin levels, 31% had one or more IgG subclass deficiencies and 26% had low IgG3 levels.[2] However, the relevance of these findings is unclear since specific IgG subclass deficiencies are frequent in the general population. In addition, immunoglobulin treatment hardly provides benefit to patients with CRS.[2]

A distinct group of patients with PID shows a specific polysaccharide antibody deficiency syndrome (SPAD) characterised by a poor serological response to polysaccharide antigens despite normal levels of immunoglobulins. Although contradictory guidelines hamper correct diagnosis, patients with SPAD present with recurrent upper airway infections and seem to have an increased risk of developing allergic rhinitis.[10] Also, in patients with CRS requiring surgery, 11.6% were diagnosed with SPAD.[11]

Marked forms of cellular immune deficiencies such as defects in T cell function, cytokine or signalling defects are often associated with severe and atypical infections (with mycobacteria and fungi) of the upper airways. Information about deficiencies in the innate immune system is given in the online supplement.

In secondary immune deficiencies caused by HIV infection or chemotherapy and in transplant patients, upper airway disease is also a common complication. In HIV-positive patients a majority reported rhinitis (80%) and rhinosinusitis (54%).[12] In addition, secondary immunodeficient patients are at risk of developing a difficult-to-treat rhinosinusitis with resistant or uncommon microorganisms and fungi.

Mucociliary clearance dysfunction

Cystic fibrosis (CF) and primary ciliary dyskinesia (PCD) are both characterised by congenital defects in the mucociliary transport system leading to serious chronic upper and lower airway problems.

In patients with PCD, rhinitis is a lifetime problem[13] often from the first days of life onwards with impaired breast feeding due to nasal blockage. This should be an alarm sign to investigate ciliary dysfunction. Later in life, patients with PCD also suffer from CRS, generally in the absence of nasal polyps.[14] When this occurs in conjunction with atypical asthma, bronchiectasis, chronic productive cough and severe otitis media, the presence of PCD should be suspected.

Among patients with CF, up to 97% have CRS, often with massive nasal polyps,[15] and a correlation exists between the severity of upper and lower airway disease.[16] Interestingly, heterozygous carriers of the CF mutation appear to have an increased incidence of CRS, suggesting that this mutation might be associated with the development of CRS in the general population.[17]

Hormones

Imbalances in the hormonal system such as pregnancy have been associated with the development of rhinitis and rhinosinusitis. Pregnancy rhinitis, which has a cumulative incidence of 22%,[18] typically starts during the second month of pregnancy and usually disappears rapidly after delivery. Neither atopy nor asthma seem to be risk factors.[18] The pathogenesis remains largely unexplained, but a number of theories have been proposed. Oestrogens cause vasodilation by increasing nitric oxide

production,[19] have a proinflammatory effect (chemotaxis and maturation of mast cells)[E34] and increase the expression of histamine receptors on nasal epithelial and endothelial cells.[E35] Whether pregnancy rhinitis predisposes to rhinosinusitis is not clear, but two small studies indicate that the incidence of rhinosinusitis is not increased in pregnant women.

Although rhinitis as well as CRS have been described to occur with thyroid disease, evidence linking hypothyroidism directly with (sino)nasal pathology is limited.[20]

It has also been proposed that rhinitis occurs in acromegaly, however nasal congestion does not occur in response to low-dose recombinant growth hormone.[20]

Vasculitis and granulomatous disease

Systemic autoimmune diseases such as systemic lupus erythematosus, relapsing polychondritis and Sjögren syndrome may present with difficult-to-treat rhinosinusitis in addition to pulmonary problems. The most prevalent systemic diseases with upper airway involvement are Churg–Strauss syndrome (CSS) and granulomatosis with polyangiitis (GPA; previously Wegener's granulomatosis). Here, chronic rhinitis and recalcitrant rhinosinusitis are often initial manifestations before lower airway and systemic symptoms arise.

Over 75% of patients with GPA and CSS present with upper respiratory tract symptoms, usually nasal obstruction and chronic recurrent infections.[21] In a study from 2009, 61% of patients with GPA had CRS,[22] commonly manifested as bloody discharge, crusting and nasal obstruction.[23] In CSS, asthma is preceded by upper airway symptoms such as rhinitis or CRS with or without nasal polyps in about 75% of cases.[24] Compared with lesions seen in GPA, the nasal and sinus lesions of patients with CSS are typically non-erosive, although crusting and epistaxis can occur.

Sarcoidosis is a multiorgan disease with pulmonary involvement in >90% of cases. Although <5% of patients develop sarcoid of the nose and sinuses, at the time of presentation these patients are almost always symptomatic with nasal obstruction, rhinorrhoea or crusting.[25]

Psychological stress

It is well known that psychological stress can alter the immune homeostasis. The deteriorating role of psychological stress on asthma has been documented, but little is known on the relationship with upper airway disease. A large-scale Finnish study showed that severe emotional stress increased the risk of allergic rhinoconjunctivitis.[26] Perceived stress was even associated with atopic disorders in a dose-dependent manner, with a significantly increased prevalence of new onset rhinitis in adults who experienced more stressful events.[27] Stressful events during pregnancy were also associated with an increased prevalence of rhinitis in the mother's offspring,[28] as has been previously shown for asthma. Additionally, children with caregivers who experienced higher stress levels showed higher total serum IgE, a greater peripheral leucocytic allergen-specific response, as well as increased TNFα and decreased interferon γ (IFNγ) production.[29] In addition to stress, anxiety (but not depression) also seems to be associated with both rhinitis and asthma.[30] Whether stressful events increase the risk of developing airway problems or whether airway disease predisposes to stress and anxiety still remains to be elucidated.

Additionally, psychological stress has been shown to affect susceptibility to viral rhinitis. A large prospective study showed that the level of psychological stress was associated in a dose-dependent way with the risk of developing acute upper airway infection assessed by virus isolation in nasal lavage or antibody titres.[31]

The direct influence of stress on airway inflammation has only been investigated in the lower airways. One of these studies showed a lower expression of glucocorticoid receptors on peripheral leucocytes of children who experienced stress.[E36] Another study suggested activation of airway mast cells by corticotropin releasing hormone, a hormone that is secreted in the airways under stress conditions.[E37]

Although it is likely that psychological state and stress can influence the development and maintenance of rhinosinusitis, to our knowledge there are no published data discussing this relationship.

EXOGENOUS FACTORS ASSOCIATED WITH UPPER AIRWAY INFLAMMATION

Viruses in upper airway disease

Viruses are the major cause of acute infectious rhinitis and approximately 50% of common colds are caused by human rhinoviruses (HRV).[32] However, it is hard to distinguish a viral infection from viral-induced exacerbations of chronic airway disease, even at the molecular level.

Allergic patients seem to clear viral infections less effectively than healthy individuals, which is in agreement with the in vitro observation of an attenuated inflammatory response of airway epithelial cells to HRV after house dust mite exposure.[33] However, the functional relevance still remains unclear since allergy does not necessarily alter symptomatology or inflammation during a common cold[34] (see additional information in online supplement).

The relationship between viral rhinitis and exacerbations of asthma or COPD has been recognised for years.[35] Although asthmatic patients and those with COPD do not have more viral upper airway infections, they seem to have more severe and persistent symptoms in both upper and lower airways. The majority of asthma exacerbations follow viral upper respiratory tract infections, more than 50% of which are caused by HRV,[36] and HRV infection directly affects lung function in people with asthma.[37] Upper airway viruses are also detected in 22–57% of COPD exacerbations.[35] These findings have been attributed to an aberrant IFN response to viral infection, and hence insufficient clearance of HRV in patients with atopic asthma[38] and COPD,[39] although this remains debated.

Despite the frequency of viral rhinitis, the role of viral infections in CRS has not been well studied. Viruses may contribute to CRS exacerbations and also to the pathogenesis of CRS. Although patients often report that a cold preceded the development of CRS, robust data supporting this hypothesis are lacking. Mechanistically, viruses could contribution to CRS via polyclonal IgE activation,[40] induction of local immune responses[41] and facilitation of bacterial penetration through the epithelial barrier.[42] However, other data suggest that viral infections and antiviral responses do not differ between patients with CRS and healthy individuals.[43]

Bacteria

It is estimated that 0.5–2% of viral upper respiratory tract infections are complicated by bacterial infection. In acute sinusitis, cultures of sinus secretions obtained by sinus puncture predominantly grow *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*.

The contribution of bacterial infection to CRS remains unclear. Polymicrobial specimens have been isolated from both diseased and non-diseased sinuses in patients with CRS, suggesting that bacterial presence by itself is not the most significant cause of CRS.[44] Microbiome studies have confirmed that the sinuses of healthy people are inhabited by a rich and diverse

community of bacteria.[45] However, the sinonasal microbiome from patients with CRS may exhibit less diversity and the bacterial load might be different from healthy control subjects.[45 46] Interestingly, invasive bacterial infections are typically characterised by strong neutrophil-mediated inflammation whereas inflammation observed in the majority of Caucasian patients with CRS is eosinophilic (see additional information in online supplement).

Recently, the role of biofilms and superantigens in CRS has been intensively investigated. Bacteria are believed to use biofilms to chronically infect sinuses without tissue invasion; however, their role in disease pathogenesis remains controversial. Superantigens represent a growing family of bacterial and viral proteins that can induce massive immune activation, with *Staphylococcus aureus* enterotoxins (SAE) receiving the greatest attention. Patients with allergic rhinitis carry more *S. aureus* than control subjects,[47] but the most important findings were seen in CRS: patients with CRS with nasal polyps were more frequently colonised with *S. aureus* than control individuals and patients with CRS without nasal polyps.[47] IgE antibodies to SAE (SE-IgE) were significantly higher in patients with nasal polyps—especially in those with concomitant asthma—than control individuals and patients with CRS without nasal polyps. Additionally, the presence of SE-IgE was associated with an increased risk of developing comorbid asthma in patients with CRS with nasal polyps[47] and, in a recent study involving almost 3000 European subjects, nasal SE-IgE levels were associated with asthma in a concentration-dependent manner.[48] These findings suggest a role for SAE as upper airway disease modifiers, specifically in CRS with nasal polyps and, possibly, as a player in determining nasobronchial interactions.

Regarding the use of antibiotics for CRS treatment, only one randomised placebo-controlled trial using a macrolide antibiotic for several months showed efficacy.[2] A similarly designed study showed no improvement in the macrolide therapy arm compared with placebo,[2] although a retrospective study demonstrated a beneficial effect in recalcitrant CRS.[2] Moreover, a randomised placebo-controlled study showed a moderate beneficial effect of doxycycline in patients with CRS with nasal polyps.[2]

Fungi

Fungi can cause a variety of adverse health effects by both immunological and non-immunological mechanisms. Immunologically, moulds produce allergens that lead to allergic rhinitis in an estimated 3–20% of the world's population. Non-immunological effects of fungi include infection, irritation of mucous membranes and reactions to mycotoxins.[49]

Fungal disorders affecting the sinuses are classified into invasive and non-invasive diseases. The invasive diseases include acute or chronic invasive fungal rhinosinusitis (FRS) and granulomatous invasive FRS and they generally occur in immunocompromised hosts only. Non-invasive forms of FRS include sinus mycetoma (fungal ball), in general affecting only one sinus, and allergic FRS (AFRS), affecting multiple sinuses. AFRS is accepted as an immunologically distinct form of CRS and has several similarities with allergic bronchopulmonary aspergillosis (ABPA). Both are chronic inflammatory respiratory tract disorders driven by type I and III hypersensitivity towards fungi growing within eosinophilic mucin present in the paranasal sinuses or bronchi. Patients with AFRS typically have unilateral CRS symptoms, often with dark thick mucoid secretions.[50] The histopathology of ABPA and AFRS is very similar,[50] but the immunology of AFRS has been less extensively studied and the existence of AFRS without detectable fungal hyphae in sinuses or fungal sensitisation is troublesome.[51] Although ABPA and AFRS may coexist, epidemiological data are insufficient to state that they are presentations of a common allergic fungal airway disease.

For many years an IgE-mediated systemic fungal allergy has been thought to drive the pathological process characteristic of most forms of CRS. However, the finding that topical or systemic antifungal agents are not beneficial in patients with CRS pleads against this hypothesis.[49] Nevertheless, a disease-modifying role for fungi cannot be completely excluded.

Allergens

One of the best known causes of chronic rhinitis is allergy, affecting about 400 million people worldwide.[1] The sequence of events involving activation of Th2 cells and production of antigen-specific IgE leading to allergic rhinitis is well known and described in more depth in the online supplement.

In addition to the well-characterised activation of the adaptive immune system, several allergens (eg, *Der p* 1 and 9 in house dust mite) have proteolytic activity with the capacity of disrupting tight junctions, leading to disintegration of the epithelial barrier.[52] Some allergens can also activate epithelial cells directly, triggering an influx of innate immune cells and promoting Th2-polarised adaptive immune responses.[53] Possible mechanisms include direct co-activation of TLRs by allergenic proteins such as *Der p* 2[54] or increased epithelial production of IL-25, a potentiator of the Th2 response, upon exposure to allergen proteases.[55]

Allergic rhinitis is relatively easy to diagnose based on the combination of typical symptoms and positive skin prick tests (SPT) or antigen-specific IgEs in the serum. It has been suggested that some patients with negative SPT or serum IgEs against the suspected allergens may suffer from a 'locally mediated allergic rhinitis'. This is elaborated on in the online supplement.

Multiple studies have shown a higher prevalence of positive SPT in patients with CRS (50–80%) compared with the general population,[56] although this does not prove causality.

The link between allergic rhinitis and asthma has been studied extensively. Up to 90% of patients with asthma have allergic rhinitis and one-third of patients with allergic rhinitis have asthma.[57] Besides being linked anatomically, the nose and bronchi also communicate via indirect mechanisms such as neural and systemic pathways that are believed to be responsible for the nasobronchial interaction.[58]

Occupational agents

Many agents inhaled at work can harm the airways. Occupational rhinitis has been estimated to occur 2–4 times more often than occupational asthma and it generally precedes its development.

Inhaled occupational agents are classified into high molecular weight (HMW) and low molecular weight (LMW) compounds.[59] HMW agents are biological (glyco)proteins present in, for example, flour, mites, laboratory animals or latex, which can cause an allergic airway inflammation via the same mechanisms as described above for non-occupational aeroallergens. Some LMW chemicals can induce immune sensitisation by acting as haptens and, after an asymptomatic latency phase, they may cause airway symptoms upon repeated contact. A second group of LMW agents consists of irritants, and acute accidental exposure to high irritant concentrations causes injury to the respiratory mucosa which may lead to persistent respiratory symptoms.[59] As with irritant-induced asthma, evidence is now growing that repeated or long-term exposures to lower concentrations of irritants might also induce chronic dysfunction of the nasal mucosa. For example, cleaners, swimming pool workers

and competitive swimmers who are all chronically exposed to chlorination products suffer more from asthma and also from upper airway symptoms than controls. Similar findings have been reported in beverage processing plant workers chronically exposed to low levels of hydrogen peroxide[59] (see additional information in online supplement).

A recently proposed concept is that of 'occupational rhinosinusitis'. This was based on a large-scale retrospective assessment of occupational exposures in patients with rhinosinusitis requiring surgery which showed a higher prevalence of 'dirty jobs' among the patients with rhinosinusitis patients than controls.[56] Exposures that were most frequently mentioned in the study were chlorination products, inorganic dust, paints, cement, thinner, ammonia, white spirit and acetone. Interestingly, irritants were more frequently involved than sensitisers. This finding was supported by a Finnish study showing lower surgical satisfaction in patients reporting occupational exposures.[60]

Smoking

The impact of tobacco smoke has been less well studied on the upper airways than on the lungs. Nevertheless, several studies have shown that active as well as passive smoking increases the risk of developing chronic rhinitis and rhinosinutis.[61] A multicentre pan-European survey recently confirmed the strong association between smoking and CRS[62] with a dose-dependent relationship with pack-years of smoking. A Polish prospective study investigating 279 patients with CRS undergoing sinus surgery showed that revision surgery was significantly more frequent in smokers than non-smokers.[63]

In smokers, nasal and bronchial inflammation, characterised by infiltration of CD8+ lymphocytes, often coexist. However, different cytokine responses occur upon exposure of human nasal and bronchial epithelial cells to cigarette smoke extract.[64] The smoke components formaldehyde and acrolein act as local irritants on the upper airways and nicotine can influence physiological processes as well as cell transport systems of the nasal epithelium.[65] Cigarette smoke may aggravate pre-existing allergic rhinitis, as shown by an increased number of eosinophils in the nasal mucosa of patients with allergic rhinitis exposed to smoke compared with non-exposed patients.[66]

Ambient air pollution

Ambient air pollution consists of a mixture of gases (including sulphur dioxide and nitrogen dioxide) and particulate matter (PM) which is characterised according to size (eg, PM_{10} or $PM_{2.5}$ for particles $<10\,\mu m$ or $<2.5\,\mu m$, respectively). In industrially developed countries, diesel engines are a major source of air pollution. Duhme *et al*[67] demonstrated that adolescents living on streets with constant truck traffic were 71% more likely to report symptoms of rhinitis.

A direct causal role for diesel exhaust particles (DEP) in the induction of rhinitis has not yet been demonstrated, but DEP affects the nasal environment in many ways. In nasal provocation experiments it was shown that DEP enhances the expression of several cytokines (IL-2, IL-4, IL-5 IL-6, IL-13 and IFNγ), chemokines (RANTES, macrophage inflammatory protein-1α, monocyte chemotactic protein-3, but not eotaxin) as well as IgE levels in nasal lavage and numbers of IgE-secreting B cells in the nasal mucosa.[68] Nasal exposure of atopic subjects to DEP potentiated primary sensitisation towards a neo-allergen, suggesting that DEP can act as a mucosal adjuvant. Chronic exposure to diesel exhaust can also induce nasal epithelial changes with goblet cell hyperplasia and increased metaplastic and dysplastic epithelial cells.[68]

Exposure to DEP can also aggravate pre-existing allergic rhinitis, as shown for allergic asthma. Nasal challenge of patients with allergic rhinitis with a relevant allergen with or without DEP showed that DEP aggravated local histamine release and clinical symptoms and that lower allergen doses were required to trigger symptoms.[68] Combined exposure to ragweed and DEP also resulted in a strong induction of ragweed-specific IgE and IgG_4 in nasal lavage compared with ragweed alone.[68]

In vitro studies on human nasal epithelial cells demonstrated that DEP are phagocytised leading to the production of IL-8, granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-1β and induction of oxidative stress.[68] Additionally, DEP can upregulate histamine receptor mRNA and increase histamine-induced IL-8 and GM-CSF production in nasal epithelial and endothelial cells.[68]

Data on pollution and CRS are scarce. However, one German study demonstrated a weak but significant effect of raised urban air pollution levels on the prevalence of CRS.[69]

CONCLUSION

Chronic upper airway disease is one of the most important chronic disease entities in the Western world. Although current diagnostics in chronic upper airway disease mainly focus on infection and the detection of atopy, several other endogenous as well as exogenous factors can play a role in the development of the disease. Table 1 lists these factors and summarises their possible effects on upper airway function. Because of the well-known link between upper and lower airway disease and their reciprocal interference, we believe that knowledge of these factors is indispensable for the practising pulmonologist in order to fully evaluate a chronic airway problem. Awareness of these factors in patients with airway symptoms can result in a more individually-directed therapy and may represent a major step forward in the diagnostic and therapeutic approach in patients with chronic airway disease.

Contributors VH: conception, design, writing, revising. TM, WH, CVD, JAV, GJ, WF, CB and JLC: writing, revising, approval. BN: conception, design, writing, revising, approval. PWH: conception, design, writing, revising, approval.

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ORIGINAL ARTICLE

Familial risk of chronic rhinosinusitis with and without nasal polyposis: genetics or environment

Gretchen M. Oakley, MD[1], Karen Curtin, PhD[2,3], Quinn Orb, BA[1], Carole Schaefer, BACS[3], Richard R. Orlandi, MD[1] and Jeremiah A. Alt, MD, PhD[1]

Background: **Chronic rhinosinusitis (CRS) is a highly prevalent inflammatory condition, with significant effects on morbidity and quality of life, yet little is known about its pathogenesis. Preliminary evidence suggests there is a heritable component to the multifactorial etiology of CRS; however, our understanding of this genetic susceptibility is limited.**

Methods: **Using an extensive genealogical database linked to medical records, the risk of CRS with nasal polyps (CRSwNP) and without polyps (CRSsNP) was calculated for relatives and spouses of adult probands (1638 CRSwNP and 24,200 CRSsNP patients diagnosed between 1996 and 2011) and were compared to random population controls matched 5:1 on sex and birth year from Cox regression models.**

Results: **First-degree relatives (1stDRs) of CRSwNP patients demonstrated a 4.1-fold increased risk ($p < 10^{-3}$) of carrying the same diagnosis, whereas second-degree relatives (2ndDRs) demonstrated a 3.3-fold increased risk ($p < 0.004$), compared to controls. In CRSsNP patients, 1stDRs were at 2.4-fold increased risk ($p < 10^{-15}$), whereas 2ndDRs were at 1.4-fold increased risk ($p < 10^{-15}$) of the same diagnosis. Third-degree relatives (3rdDRs) had a slight increased risk at 1.1-fold ($p < 10^{-7}$). Spouses of CRSsNP patients, who likely share environmental circumstances, exhibited a 2-fold increased risk ($p < 10^{-15}$). No increased risk was observed in spouses of CRSwNP patients.**

Conclusion: **In the largest population study to date, a significant familial risk is confirmed in CRSwNP and CRSsNP, which may have a shared genetic and environmental component. Further understanding of the genetic basis of CRS and its interplay with environment factors could clarify disease etiology and lead to more effective targeted treatments.** © 2015 ARS-AAOA, LLC.

Key Words:
chronic rhinosinusitis; CRSwNP; CRSsNP; genetics; familiality; environment

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Despite the enormous impact on personal health and economic productivity of chronic rhinosinusitis (CRS), little is known about the pathophysiologic cause of CRS, limiting our ability to treat it definitively. The various presentations, associated diseases, and treatment responses of CRS indicate it likely has multiple etiologies. The role of genetics is minimally understood, but is supported by the prevalence of CRS in multiple inherited disorders, such as cystic fibrosis (CF) and Kartagener syndrome,[1,2] as well as its strong association with allergic rhinitis and asthma, both with known heritability.[3,4] Specifically, preliminary studies have reported that up to 14% of patients with CRS with nasal polyposis (CRSwNP) have positive family histories.[5] Furthermore, in a cohort of 174 patients with CRSwNP, 25% had 1 or more first-degree relatives with nasal polyps.[6] An investigation by Adappa et al.[7] demonstrated the association between the inheritance of the bitter taste receptor and CRS, implicating its potential role in predicting medical and surgical treatment outcomes in patients with CRS.

Although a genetic role has been implicated in the pathogenesis of CRSwNP and CRS without nasal polyposis

[1]*Division of Otolaryngology–Head and Neck Surgery, University of Utah School of Medicine, Salt Lake City, UT;* [2]*Department of Medicine, University of Utah, Salt Lake City, UT;* [3]*Pedigree and Population Resource, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*

Correspondence to: Jeremiah A. Alt, MD, PhD, University of Utah School of Medicine, Division of Otolaryngology–Head and Neck Surgery, 50 North Medical Drive, Room 3C120, Salt Lake City, UT 84132; e-mail: jeremiah.alt@hsc.utah.edu

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(CRSsNP), a Mendelian inheritance pattern is not supported, but rather a multifactorial etiology with both genetic and environmental influences. The complex nature of this pathogenesis necessitates a large-scale study to better elucidate familial patterns that may indicate potential for an underlying genetic susceptibility.

Our objective in this study was to determine whether relatives of patients with CRSwNP and CRSsNP are at an increased risk based on observed familial clustering in a unique population research database.

Subjects and methods

The Utah Population Database (UPDB) is a dynamic, shared resource located at the University of Utah and consists of computerized data records for over 7 million individuals. It is the only database of its kind in the United States and one of a few in the world; most families living in Utah are represented in the UPDB.[8] For example, of all individuals born in Utah in 1950, 79% have grandparent information and 67% have 5 or more previous generations documented in this resource. The UPDB includes statewide vital records and hospital inpatient and ambulatory facility data that are linked to individuals in multigenerational pedigrees.

Case population

We identified patients ages 18 years or older at index diagnosis with an International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM) diagnosis of CRS, defined as 1 or more of ICD-9-CM codes 473.x appearing in the medical record (any diagnostic position) from 1996 to 2011. Patients without a diagnosis of nasal polyps, defined as an absence of ICD-9-CM 471.x, were considered CRSsNP and those with this ICD-9-CM code were considered CRSwNP. Individuals with a history of CF (ICD-9-CM 277.0), inverted papilloma (ICD-9-CM 212.0), or head/facial trauma (ICD-9-CM 801.0–804.9) were excluded. We elected to also use as inclusion criteria Current Procedural Terminology (CPT) codes for diagnostic nasal endoscopy (CPT 31231) and sinus surgery CPT codes 31233, 31237 (nasal polypectomy), 31254, 31255, 31256, 31276, and 31287 to increase the probability of accurately identifying a clinical diagnosis of CRSwNP or CRSsNP based on medical claims data. The resulting case population included 1638 probands with CRSwNP and 24,200 probands with CRSsNP with genealogy in UPDB to examine familial risk.

Control population

Controls with no history of CRSwNP or CRSsNP were randomly selected from the Utah population and matched 5:1 to corresponding CRSwNP or CRSsNP cases on sex and birth year. To appropriately match exposure periods, a control had to have follow-up (known to reside in Utah) at least as long as the date of diagnosis for their respective case as described.[9]

Statistical analysis

Using a software suite developed specifically for the UPDB and in conjunction with the software package R (Rx64 2.14.2 Windows Server 2008),[10] the magnitude of familial risk was estimated by Cox regression in order to assess the relative risk of CRSwNP and CRSsNP for relatives and spouses of CRSwNP and CRSsNP cases diagnosed in Utah between 1996 and 2011 compared to matched controls.[11] Estimates of familial risk were based on a hazard rate ratio (HR) of familial recurrence. This represents the ratio of the hazard rate for the occurrence of CRSwNP and CRSsNP among relatives of the index cases with the comparable hazard rate among the relatives of the controls. Cox models included cases and controls with adequate follow-up in Utah, who linked to a UPDB pedigree comprising at least 2 generations. Model covariates included sex and birth year. As observations within families are non-independent, a Huber-White sandwich estimator of variance for clustered data was used.[10,12] This approach corrects for any families that were analyzed multiple times because of multiple CRSwNP or CRSsNP cases within the family. Analyses were performed separately in which specific groups of relatives of the cases were compared to the comparable relatives of the matched controls as follows: first-degree relatives (1stDRs), including parents, children, and siblings; second-degree relatives (2ndDRs), including grandparents, grandchildren, aunts/uncles, and nieces/nephews; third-degree relatives (3rdDRs), primarily first cousins; fourth-degree relatives (first cousins once removed); and fifth-degree relatives (second cousins). We also examined risk in spouses of probands to assess evidence of disease susceptibility from a shared environment. Spouses were defined as the married or unmarried co-parent of the index cases or controls who had children determined from UPDB records (77% and 71% of all CRSwNP cases or controls, respectively; 78% and 72% of all CRSsNP cases or controls, respectively).

Results

Verification of diagnosis

We randomly selected 81 patients from a total of 682 individuals treated in the University of Utah Healthcare system during 2008 to 2011 for whom we had access to electronic charts. This patient sample met our inclusion criteria based on the ICD-9 and CPT codes outlined in the Case population section and a chart review was performed to compare diagnoses based on ICD-9/CPT codes to the clinical record. We used criteria published in 2007 by Rosenfeld et al.,[13] which give cardinal symptoms for CRS and then require verification of the symptomatic diagnosis by either computed tomography (CT) or nasal endoscopy. Two electronic charts were unavailable, leaving 79 available for

review. Of these, 6 did not fulfill the CRS diagnostic criteria by symptoms. Two of these 6 did not have nasal endoscopy or CT evidence of CRS, whereas 4 who did not have qualifying symptoms nonetheless had CT evidence of CRS. These 4 patients with "negative" cardinal symptoms but "positive" CTs had the following profiles: 1 had silent sinus syndrome, 1 had facial pain with no other symptoms, 1 had a history of previous surgery elsewhere for CRS but was asymptomatic at the time of the visit in the database, and 1 had altered mental status due to intracranial complications of rhinosinusitis and symptoms could not be obtained. Of the remaining 73 patients with qualifying symptom profiles, 2 did not have a confirming endoscopy or CT. This review therefore resulted in 71 of 79 patients meeting the 2007 criteria by Rosenfeld et al.[13] for diagnosis of CRS, with a positive predictive value (PPV) of 90%.

The charts were then reviewed for presence/absence of polyps in the clinical record and compared to the coding results in the database for each patient. Of the 79 CRS charts available for review, 62 carried the ICD-9 diagnosis 473.x without 471.x and were considered CRSsNP, whereas 17 carried the ICD-9 diagnosis for CRSwNP, 471.x. Of the 62 putative CRSsNP from diagnosis codes, 48 were confirmed on chart review whereas the remaining 14 were determined to be clinical CRSwNP. Of the 17 putative CRSwNP from diagnosis codes, 8 were confirmed on chart review whereas the remaining 9 patients were determined to be CRSsNP. Thus, the accuracy of using billing codes available in the UPDB to identify CRSsNP or CRSwNP was 71% based on our chart review.

Demographic characteristics

The characteristics of 1638 CRSwNP and 24,200 CRSsNP adult cases in Utah and 5:1 matched population controls are shown in Table 1. Patients with CRSwNP and CRSsNP were similar in age, with a mean age at diagnosis of 44 years and 43 years, respectively. In contrast, CRSsNP probands were somewhat more likely to be female (52%), whereas the majority of CRSwNP probands were male (55%). This difference in gender percentage between CRSsNP and CRSwNP was statistically significant ($p < 0.0001$, chi-square analysis). Consistent with the Utah population and similar to other regions in the United States, cases and controls in our study were predominantly non-Hispanic Whites; however, the proportion of non-Whites was higher in controls compared to cases. The racial differences between cases and controls, which were solely selected on sex and birth year, were statistically significant for both CRSsNP and CRSwNP (both $p < 0.0001$, chi-square analysis).

Familial risk of CRS

The familial risk of CRSwNP and CRSsNP is shown in Table 2. First-degree relatives of case probands with CRSwNP had a 4.1-fold increased risk (95% confidence interval [CI], 1.8 to 9.4; $p < 10^{-3}$) of having the same diagnosis compared to population controls. Within this group, parents, siblings, and children contributed to the overall 1stDRs risk with similar HR estimates (data not shown). Second-degree relatives of CRSwNP probands had a 3.3-fold increased risk (95% CI, 1.5 to 7.5; $p = 0.004$). There was no significantly increased risk beyond 2ndDRs, although the HR in first cousins was suggestive of an increased risk in 3rdDR cases. We observed no increased risk in spouses of CRSwNP probands compared to controls.

In the CRSsNP group (Table 2), 1stDRs had a 2.4-fold increased risk (95% CI, 2.2 to 2.6; $p < 10^{-15}$) of carrying the same diagnosis compared to controls, 2ndDRs had a 1.4-fold increased risk (95% CI, 1.3 to 1.4; $p < 10^{-15}$), whereas 3rdDRs (first cousins) of cases exhibited a modest but significant increased risk at 1.1-fold (95% CI, 1.08 to 1.2; $p < 10^{-7}$; and 95% CI, 1.0 to 1.2; $p < 0.02$). More distant cousins of cases (fourth-degree and fifth-degree) also exhibited a slight increased risk of CRSsNP (HRs = 1.06; 95% CI, 1.03 to 1.08; $p < 10^{-12}$). In contrast to CRSwNP, spouses of CRSsNP probands carried a 2-fold increased risk of CRSsNP themselves (95% CI, 1.8 to 2.2; $p < 10^{-15}$).

We also calculated familial risk of CRSsNP in relatives of CRSwNP case probands, to examine if the risk of a non-polyposis phenotype was also elevated in their family members (Table 3). In 1stDRs of CRSwNP cases, we observed a 2.5-fold increased risk of CRSsNP (95% CI, 2.1 to 3.0; $p < 10^{-15}$), whereas the increased risk of CRSsNP in 2ndDRs of CRSwNP probands was 1.4-fold (95% CI, 1.2 to 1.7; $p < 0.001$). In the reverse comparison in which familial risk of CRSwNP in CRSsNP probands was calculated, similar risk estimates were observed.

Discussion

The complex nature of CRS has thus far limited our full understanding of the pathogenesis of this condition, and therefore our ability to treat it effectively and consistently. Not only is the etiology believed to be multifactorial, with both genetic and environmental influences, but it also presents as an array of various phenotypes or endotypes with associated comorbidities. Prior research into the genetics of CRS has targeted multiple levels of immunologic susceptibility and comorbid links, including multiple human leukocyte antigen (HLA) alleles, bitter taste receptor T2R38, Toll-like receptors (TLRs), and the cystic fibrosis transmembrane regulator (CFTR) locus.[2,4,14] Although these studies are promising, common limitations among them include small sample sizes, unclear causality, and difficulty replicating results.[4]

In an effort to take a broader look at the familiality of CRS, this population-based study assessed shared risk of CRSwNP and CRSsNP based on observed familial clustering compared to that expected in the population over a 16-year period. Although there are multiple studies that have analyzed the association between various single nucleotide polymorphisms (SNPs) and CRS in an effort to identify genetic links to the condition,[9,15–23] the clinical importance

TABLE 1. Characteristics of CRSwNP and CRSsNP case probands and 5:1 matched controls in Utah

	CRSwNP probands		CRSwNP controls (5:1)		CRSsNP probands		CRSsNP controls (5:1)	
Characteristic	n	(%)	n	(%)	n	(%)	n	(%)
Total	1,638	(100.0)	8,189	(100.0)	24,200	(100.0)	121,000	(100.0)
Men	897	(54.8)	4,485	(54.8)	11,570	(47.8)	57,850	(47.8)
Women	741	(45.2)	3,704	(45.2)	12,630	(52.2)	63,150	(52.2)
Race								
White	1,558	(95.1)	7,066	(86.3)	23,051	(95.3)	105,853	(87.5)
Non-White	80	(4.9)	1,123	(13.7)	1,149	(4.7)	15,147	(12.5)
Ethnicity								
Non-Hispanic/Latino	1,547	(94.4)	7,549	(92.2)	23,018	(95.1)	111,731	(92.3)
Hispanic or Latino	91	(5.6)	640	(7.8)	1,182	(4.9)	9,269	(7.7)
Age at diagnosis/selection, years, mean (SD)	44	(16)	44	(16)	43	(15)	43	(15)
Range	18–96		18–96			18–94		18–94
First-degree relatives per case/control	4.2		4.1		4.0		3.9	
Second-degree relatives per case/control	8.9		8.8		6.6		6.3	
First-cousin relatives per case/control	10.4		10.4		10.0		9.5	

CRSsNP = chronic rhinosinusitis without nasal polyposis; CRSwNP = chronic rhinosinusitis with nasal polyposis; SD = standard deviation.

TABLE 2. Familial risk of CRSwNP and CRSsNP in Utah*

	Relatives of probands		Relatives of controls				
Relationship	Affected	Unaffected	Affected	Unaffected	HR	95% CI	*p*
Risk of CRSwNP in relatives of 1638 CRSwNP probands (compared to 8189 controls)							
First-degree relatives	13	6,889	15	33,115	4.1	1.8–9.4	<0.001
Second-degree relatives	10	14,513	15	71,910	3.3	1.5–7.5	0.004
First cousins (third-degree)	14	16,973	44	84,907	1.6	0.9–2.9	0.14
Spouses	0	1,267	7	5,774	0	0	–
Risk of CRSsNP in relatives of 24,200 CRSsNP probands (compared to 121,000 matched controls)							
First-degree relatives	2,758	94,691	5,481	459,964	2.4	2.3–2.6	$<1 \times 10^{-15}$
Second-degree relatives	1,305	101,267	7,197	761,101	1.4	1.3–1.4	$<1 \times 10^{-15}$
Third-degree (first cousins)	1,756	132,294	13,812	1,138,399	1.1	1.1–1.2	$<1 \times 10^{-7}$
Spouses	542	18,376	1,282	86,370	2.0	1.8–2.2	$<1 \times 10^{-15}$

*Cases compared to controls matched 5:1 on sex and birth year.
CI = confidence interval; CRSsNP = chronic rhinosinusitis without nasal polyposis; CRSwNP = chronic rhinosinusitis with nasal polyposis; HR = hazard rate ratio from Cox model.

of these findings is unclear. In 2 prior studies that looked directly at the heritability of nasal polyposis in their patient population, 14% to 15% of patients with CRSwNP were reported to have at least 1 first-degree relative with the same diagnosis.[5,6] Consistent with these results, we also observed that CRSwNP demonstrates a high familial relative risk in 1stDRs, at 4.1-fold.

The strengths of our study include the use of a unique genealogical and research database with extensive data linked to medical records, making this the largest population study

TABLE 3. Familial risk of CRSsNP in CRSwNP probands and familial risk of CRSwNP in CRSsNP probands in Utah*

	Relatives of probands		Relatives of controls				
Relationship	Affected	Unaffected	Affected	Unaffected	HR	95% CI	*p*
Risk of CRSsNP in relatives of 1638 CRSwNP probands (compared to 8189 controls)							
First-degree relatives	174	6,149	334	29,585	2.5	2.1–3.0	$<1 \times 10^{-16}$
Second-degree relatives	134	10,161	474	50,275	1.4	1.2–1.7	<0.001
Third-degree relatives (first cousins)	189	15,081	931	74,235	1.0	0.9–1.2	0.93
Spouses	30	1,216	76	5,574	1.8	1.2–2.8	0.008
Risk of CRSwNP in relatives of 24,200 CRSsNP probands (compared to 121,000 matched controls)							
First-degree relatives	119	105,910	230	507,619	2.5	2.0–3.2	$<1 \times 10^{-14}$
Second-degree relatives	91	223,198	270	1,071,475	1.6	1.3–2.1	$<1 \times 10^{-4}$
Third-degree (first cousins)	117	266,523	607	1,271,208	0.9	0.7–1.1	0.41
Spouses	27	19,238	60	89,299	2.1	1.3–3.3	0.002

*Cases compared to controls matched 5:1 on sex and birth year.
CI = confidence interval; CRSsNP = chronic rhinosinusitis without nasal polyposis; CRSwNP = chronic rhinosinusitis with nasal polyposis; HR = hazard rate ratio from Cox model.

to date. Family relationships have been determined from genealogies and dynamically updated from vital records without reliance on self-reported data. There is no other study in the CRS literature that evaluates familial risk beyond first-degree relatives, whereas we have been able to assess risk in the CRSwNP and CRSsNP phenotypes in more distant family members and also in spouses. This affords us the advantage of investigating the familial nature of CRS with or without NP in distant relatives who share genes, but are less likely than close relatives (or spouses) to share in a common environment.

According to our findings for CRSsNP, an increased risk was demonstrated in 1stDRs, 2ndDRs, first-cousins, and more distant cousins of case probands, as well as in their spouses, compared to controls. This increased risk supports a multifactorial etiology to this disease; both genetic and environmental. Familial risk can be due to genetic or environmental factors, as the evidence of familiality in our study suggests. First-degree relatives (parents, children, and siblings) who share genetically are more likely to share a common household than more distant family members, and thus may be susceptible to the same environmental influences. On the other hand, second-degree relatives (grandparents, grandchildren, aunts/uncles, nieces/nephews) share genetically, but are less likely to share a common household. For this reason, familial risk of CRSwNP and CRSsNP may reflect a genetic susceptibility. Relatives of CRSwNP cases appear to have an increased risk of CRS without the presence of polyps, and conversely relatives of CRSsNP patients may also be at increased risk of nasal polyps.

Spouses may share the environmental risk of the proband, but do not share the genetic risk. We observed no risk of CRSwNP in spouses of CRSwNP probands; however, risk of CRSsNP in spouses of CRSsNP cases was nearly as high as in 1stDRs, which supports environmental influences. Given our findings, we conclude that familial risk of CRSwNP may be due more to underlying genetic susceptibility than familial risk of CRSsNP, which may be more environmentally influenced in addition to evidence of a genetic component. However, more research into environmental exposures such as tobacco smoke and comorbidities such as asthma and allergies is needed to evaluate familial risk patterns.

We acknowledge that the cases and controls linked to UPDB genealogies in order to assess familial risk of CRS may differ from subjects without pedigree information in the UPDB; individuals that link to the genealogies are more likely to be born in Utah, and to relocate outside of Utah less often. Despite this potential bias, our observations of increased risk in 1stDRs and 2ndDRs were highly significant and unlikely to represent chance findings. In the case of the UPDB, this relatively geographically stable population leads to more accurate and extensive data on subjects and their various relatives than could be collected otherwise. In addition, Utah has the highest fertility rate in the nation. This increased number of replicates for analysis can better reveal a genetic predisposition when one exists. As

reported, we observed that the proportion of non-Whites was higher in the controls than in the case probands. The randomly-selected controls are representative of the distribution of race in Utah whereas in the case population, fewer non-Whites may reflect a difference in access to healthcare and we acknowledge this may be a source of bias. However, as the Utah population is racially homogeneous (predominantly 86% White, based on the 2010 census) any bias reflected in our estimates is likely to be minimal. Although the racial composition in the state may provide less underlying genetic heterogeneity in future planned genetic studies of CRS, findings may not be generalizable to other populations, and future studies are needed to define CRS in non-White communities.

A major challenge in population-wide CRS research using medical records is the accuracy of CRS diagnoses from claims data, which may be questionable. Hsu et al.[24] demonstrated that accuracy of diagnosis in a study population compiled using billing codes generally associated with CRS can be as poor as 54%. However, accuracy was substantially improved when diagnostic criteria included otolaryngologic or allergy-immunology specialty evaluation, specific sinus surgery CPT codes, and the exclusion of CF diagnoses.[24] We therefore similarly used strict inclusion and exclusion criteria that portends a higher likelihood of specialty confirmation of diagnosis. We verified this through a chart review and found a high PPV based on stringent CRS diagnostic parameters. We recognize that requiring probands and families to have had surgery for their CRS to be included in the study population likely selects for more severe CRS phenotypes. By requiring surgery as an inclusion criterion, we may also be selecting for those with greater access to healthcare, although both major healthcare systems included in this database deliver a significant portion of their care as charity. Notwithstanding these drawbacks, we believe that improving the accuracy of diagnosis in cases and controls was of utmost importance and offsets the limitations.

Our sensitivity and specificity analysis demonstrates that in a database study of tens of thousands of patients, the presence or absence of coding for nasal polyposis (ICD-9-CM 417.x) has some inherent limitations in regards to accuracy. Although still relatively high (71%), diminished accuracy compared to our ability to correctly identify CRS (regardless of polyp status) may limit the validity of the CRSsNP and CRSwNP comparisons, yet the large sample size appears to have overcome any misclassification error in polyp diagnosis. The gender differences seen between CRSsNP and CRSwNP underscore the validity of our results inasmuch as they confirm previous studies.[25,26]

As we learn more about CRS, the differentiation into CRSsNP and CRSwNP may prove to be too simplistic and may even have significant overlap. More sophisticated CRS classifications based on inflammatory patterns or other molecular signatures may help us better differentiate this complex condition. For the years covered in this analysis, CRSsNP and CRSwNP were the "state of the art." We nonetheless recognize that as we move into a more prospective genetic analysis of CRSsNP versus CRSwNP, greater attention will need to be paid to accurately subclassifying CRS.

Conclusion

Although a clear understanding of the etiology of CRS still eludes us, this study firmly establishes a familial basis. These findings set the stage for future studies, in which high-risk pedigrees will be identified to further elucidate susceptibility genes, in conjunction with investigations of comorbid disease and environmental exposures. A better understanding of the genetic susceptibility of CRS could clarify the underlying pathophysiology and lead to the development of more effective, targeted treatments.

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Original Investigation

Importance of Tumor Grade in Esthesioneuroblastoma Survival
A Population-Based Analysis

Bobby A. Tajudeen, MD; Armin Arshi, BS; Jeffrey D. Suh, MD; Maie St John, MD, PhD; Marilene B. Wang, MD

IMPORTANCE There is a need for larger studies characterizing the effect of tumor grade on survival for patients with esthesioneuroblastoma.

OBJECTIVE To investigate prognostic factors for survival in patients diagnosed with esthesioneuroblastoma, including emphasis on tumor grade.

DESIGN, SETTING, AND PARTICIPANTS Retrospective, population-based cohort study of patients in the Surveillance, Epidemiology, and End Results (SEER) tumor registry who were diagnosed with esthesioneuroblastoma from January 1, 1973, to January 1, 2010. The last date of survival follow-up was 2013.

MAIN OUTCOMES AND MEASURES Overall and disease-specific survival.

RESULTS The cohort included 281 patients with a mean age of 52 years. There were 154 males (54.8%) and 127 females (45.2%). Kaplan-Meier analysis demonstrated an overall and disease-specific survival rate of 61% and 70% at 5 years and 50% and 64% at 10 years, respectively. Multivariable Cox regression analysis showed that advanced tumor grade and modified Kadish stage (hazard ratio, 4.930; 95% CI, 2.635-9.223; $P = .001$) portended worse disease-specific survival, and radiation therapy (hazard ratio, 0.499; 95% CI, 0.272-0.916; $P = .03$) improved disease-specific survival. Patients with low-grade tumors (grades I and II) demonstrated an overall and disease-specific survival rate of 84% and 92% at 5 years and 67% and 87% at 10 years, respectively. Multivariable analysis of low-grade tumors only revealed receiving surgery ($P = .004$) as an independent positive predictor of disease-specific survival. High-grade tumors (grades III and IV) demonstrated overall and disease-specific survival of 40% and 50% at 5 years and 34% and 43% at 10 years, respectively. Multivariable analysis of high-grade tumors showed modified Kadish stage (hazard ratio, 2.025; 95% CI, 1.430-2.866; $P < .001$) predicted worse disease-specific survival, and radiation therapy (hazard ratio, 0.433; 95% CI, 0.228-0.864; $P = .02$) independently predicted improved disease-specific survival.

CONCLUSIONS AND RELEVANCE Here, to our knowledge, we report the largest study investigating prognostic factors for survival, with the inclusion of tumor grade, in patients diagnosed with esthesioneuroblastoma. Patients with high-grade tumors had substantially worse survival rates than patients with low-grade tumors. Multivariable analysis revealed only receiving surgery as an independent predictor of disease-specific survival for patients with low-grade tumors, while modified Kadish stage and postoperative radiation therapy were significant factors in predicting disease-specific survival in patients with high-grade tumors. This study highlights the growing evidence that tumor grade should be a key factor in predicting survival in patients with esthesioneuroblastoma, and that adjuvant radiation therapy improves survival rates among patients with high-grade, but not low-grade, tumors.

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Author Affiliations: Department of Head and Neck Surgery, David Geffen School of Medicine at UCLA (University of California, Los Angeles) (Tajudeen, Arshi, Suh, St John, Wang); Jonsson Comprehensive Cancer Center, David Geffen School of Medicine at UCLA, Los Angeles (Tajudeen, St John, Wang); Head and Neck Cancer Program, David Geffen School of Medicine at UCLA, Los Angeles (Tajudeen, Suh, St John, Wang).

Corresponding Author: Marilene B. Wang, MD, Department of Head and Neck Surgery, David Geffen School of Medicine at UCLA, 200 UCLA Medical Plaza, Ste 550, Los Angeles, CA 90095 (mbwang@ucla.edu).

Esthesioneuroblastoma, also known as olfactory neuroblastoma (ONB), is a rare tumor thought to originate from the olfactory neuroepithelium in the superior nasal vault. Because of its rarity, to our knowledge, there have been no prospective, randomized clinical trials investigating optimal treatment regimens. Therefore, treatment guidelines must be extrapolated from grouped institutional experiences or population-based tumor registries. Current treatment guidelines recommend wide local excision via open or endoscopic craniofacial resection with postoperative radiation therapy.[1-5] The role of chemotherapy is less studied, but is generally reserved for advanced disease in the neoadjuvant or adjuvant setting.[6]

Experiences from many institutions have begun to highlight the distinct clinical behavior of high- and low-grade ONB. Our series (although the results are not shown) and the experiences of other institutions[7,8] have begun to highlight the distinct clinical behavior of high- and low-grade ONB. Here, to our knowledge, we report results of the largest population-based study investigating the importance of tumor grade on outcome in ONB and aim to identify distinct prognostic factors for survival between high- and low-grade ONB.

Methods

A retrospective study was performed using the Surveillance, Epidemiology, and End Results (SEER) tumor registry database.[9] The National Cancer Institute does not require institutional review board approval for this deidentified registry. The public-use database from the SEER 18 (1973-2010) registry was used to extract appropriate cases. The SEER database is composed of cancer registries that are thought to include approximately 10% of the US population and is the primary source of national estimates of cancer incidence and survival. Use of the database has been validated for clinical outcomes research.[10]

The SEER database codes information regarding the primary site and extent of disease. All patients diagnosed with ONB from January 1, 1973, through January 1, 2010, were identified using histologic feature code 9522. Site-specific codes were used to confirm that the tumor originated in the nasal cavity or paranasal sinuses. Cases with a histologic ONB code that were located at sites outside the nasal cavity or paranasal sinuses were considered a coding error and excluded from analysis. The addition of tumor grade to ONB in the SEER database has only been consistently reported in the last 2 decades. Therefore, only patients with information regarding tumor grade were included in this study. Tumor grade is reported on a scale from I to IV in the SEER database and, for the purposes of this study, low-grade tumors included grades I and II and high-grade tumors represented grades III and IV.

No specific staging information such as Dulguerov-Calcaterra or modified Kadish staging was available for these cases; however, related disease information, including SEER historic stage, collaborative stage extension, extent of disease, and primary site, allowed for deduction of modified Kadish staging. This method of modified Kadish stage derivation has been used previously for SEER studies pertaining to ONB.[2] Briefly, the modified Kadish stage was derived for each case using the extent of disease and collaborative staging data sets available through the SEER database case-listing search. Extent of disease and collaborative staging extent codes for anatomic involvement of primary tumors were grouped and correlated with the appropriate modified Kadish stage as follows: confined to the nasal cavity (stage A), extension to the paranasal sinuses (stage B), extension beyond the nasal cavity and sinuses, including the cribriform plate and base of skull (stage C), and lymph node and distant metastases (stage D). Cases with unknown or ambiguous extent of disease and collaborative staging extent codes were not assigned a stage according to the modified Kadish system and were excluded from analysis.

Primary outcomes included overall survival (OS) and disease-specific survival (DSS), with the last date of survival follow-up in 2013. *Overall survival* was defined as the time from initial treatment to death from any cause. *Disease-specific survival* was defined as the time to death directly attributable to the primary malignant tumor, as reported in the SEER database. Kaplan-Meier curves were constructed to visualize OS and DSS rates between groups. The differences were formally tested for using the log-rank test. Covariates were assessed for predictive performance with univariable and multivariable Cox proportional hazards regression models with regard to OS and DSS. Comparisons between groups were deemed statistically significant at $P < .05$. Covariates were chosen for multivariable analysis based on factors identified as significant or near significant on univariable analysis ($P < .20$; log-rank test). This method was chosen to minimize the total number of covariates, thus improving the generalizability of the findings and minimizing instability in the model. As a default, age and sex were included in all multivariable models. Using this method, there were no less than 10 events per covariate for each model. Statistical analyses were performed in SPSS, version 21 (IBM Corporation).

Results

A total of 705 patient records were initially extracted from the SEER database, including those of patients with ONB diagnosed from January 1, 1973, through January 1, 2010. Information regarding tumor grade has only been consistently reported in the SEER database in the last decade. This resulted in 291 patients with information regarding tumor grade. A total of 281 patients had sufficient clinical data to apply the modified Kadish staging system (**Table 1**). Therefore, the final study cohort included 281 patients, of which 154 (54.8%) were male and 127 (45.2%) were female. The mean age was 52 years (range, 3-88 years). The median follow-up time was 40 months (range, 0-330 months). A total of 81.5% of patients were white, 9.6% were African American, and 8.8% were of another race or ethnicity. Fifty patients' tumors (17.8%) were Kadish stage A, 50 (17.8%) were stage B, 75 (26.7%) were stage C, and 106 (37.7%) were stage D. A total of 135 patients (48.0%) had low-grade tumors and 146 (52.0%) had high-grade tumors. Information re-

Table 1. Patient Demographics, Tumor Characteristics, and Treatment Modality

Characteristic	Value[a]
Sex	
Female	127 (45.2)
Male	154 (54.8)
Age, y	
Mean	52
Median (range)	52 (3-88)
Race	
White	229 (81.5)
African American	27 (9.6)
Asian	17 (6.0)
Native Hawaiian/Pacific Islander	4 (1.4)
American Indian	2 (0.7)
Other	2 (0.7)
Kadish stage	
A	50 (17.8)
B	50 (17.8)
C	75 (26.7)
D	106 (37.7)
Tumor grade	
Low	135 (48.0)
High	146 (52.0)
Lymph node involvement	
Positive	26 (9.3)
Negative	199 (70.8)
Unknown	56 (19.9)
Received surgery	
Yes	230 (81.9)
No	49 (17.4)
Unknown	2 (0.7)
Received radiation therapy	
Yes	122 (43.4)
No	169 (56.6)

[a] Values are expressed as number (percentage) unless otherwise specified.

garding lymph node status at diagnosis was available for 225 patients, of whom 26 (9.3%) had presence of neck disease and 199 (70.8%) did not. A total of 230 patients (81.9%) received surgery while 49 (17.4%) did not. A total of 122 patients (43.4%) received radiation therapy either postoperatively or primarily while 159 (56.6%) did not.

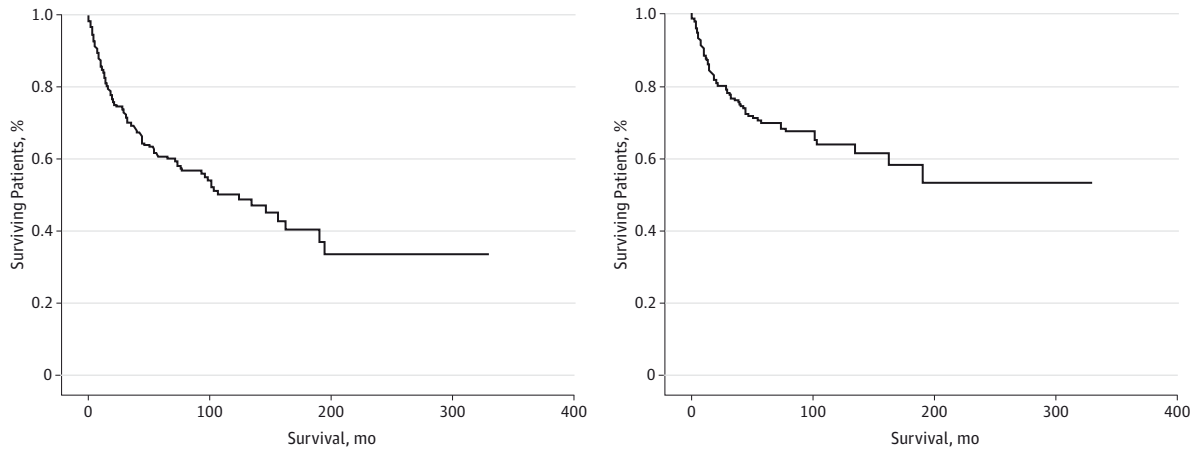
Factors Predicting Survival

Kaplan-Meier analysis demonstrated OS and DSS of 61% and 70% at 5 years and 50% and 64% at 10 years, respectively (**Figure 1**). Univariable analysis of the entire cohort revealed race (P = .02; log-rank test), sex (P = .001; log-rank test), presence of neck disease (P < .001; log-rank test), radiation therapy (P = .01; log-rank test), receiving surgery (P < .001; log-rank test), tumor grade (P < .001; log-rank test), and modified Kadish stage (P < .001; log-rank test) to be predictors of OS. Sex (P = .02; log-rank test), presence of neck disease (P < .001; log-rank test), radiation therapy (P < .001; log-rank test), receiving surgery (P < .001; log-rank test), tumor grade (P < .001; log-rank test), and Kadish stage (P < .001; log-rank test) were predictors of DSS. Multivariable Cox regression analysis (**Table 2**) revealed advanced age, tumor grade, and modified Kadish stage to be independent negative predictors of OS while female sex independently predicted better OS. Advanced tumor grade and modified Kadish stage independently predicted worse DSS. Radiation therapy independently predicted better DSS.

Factors Predicting Survival With Low-Grade Tumors

Analysis of low-grade tumors (n = 135) by univariable analysis revealed sex (P = .01; log-rank test) and surgery (P = .04; log-rank test) to be predictors of OS, and presence of neck disease (P = .01; log-rank test) and receiving surgery (P < .001; log-rank test) to be predictors of DSS. Multivariable analysis (incorporating age, sex, presence of neck disease, and receiving surgery as covariates) revealed age (hazard ratio, 1.062; 95% CI, 1.030-1.094; P < .001), receiving surgery (hazard ratio, 0.244; 95% CI, 0.080-0.747; P = .01), and sex (hazard ratio, 0.277; 95%

Figure 1. Overall and Disease-Specific Survival for Cohort



A, Kaplan-Meier estimates of overall survival. B, Kaplan-Meier estimates of disease-specific survival.

Table 2. Multivariable Cox-Regression Analysis of Factors Affecting Overall and Disease-Specific Survival

Factor	Overall Survival[a]	*P* Value	Disease-Specific Survival[a]	*P* Value
Age	1.024 (1.012-1.037)	.001	1.013 (0.999-1.029)	.07
Sex	0.576 (0.387-0.856)	.006	0.689 (0.431-1.102)	.12
Race	0.950 (0.727-1.241)	.71	0.764 (0.272-0.916)	.16
Presence of neck disease	1.194 (0.967-1.474)	.10	1.106 (0.849-1.442)	.46
Received radiation	0.701 (0.433-1.136)	.15	0.499 (0.272-0.916)	.03
Received surgery	0.885 (0.510-1.535)	.66	0.779 (0.415-1.460)	.44
Tumor grade	3.144 (2.018-4.899)	.001	4.930 (2.635-9.223)	.001
Kadish stage	1.436 (1.115-1.786)	.001	1.905 (1.411-2.572)	.001

[a] Values are presented as hazard ratio (95% CI).

CI, 0.117-0.656; *P* = .04) to be independent predictors of OS. Multivariable analysis of low-grade tumors (incorporating modified Kadish stage, presence of neck disease, receiving surgery, age, and sex as covariates) only revealed receiving surgery (hazard ratio, 0.135; 95% CI, 0.035-0.521; *P* = .004) to be an independent predictor of DSS.

Factors Predicting Survival With High-Grade Tumors

Univariable analysis of high-grade tumors (n = 146) revealed presence of neck disease (*P* = .001; log-rank test), receiving surgery (*P* = .02; log-rank test), and modified Kadish stage (*P* < .001; log-rank test) as predictors of OS, and presence of neck disease (*P* < .001; log-rank test), radiation therapy (*P* = .02; log-rank test), receiving surgery (*P* = .006; log-rank test) and modified Kadish stage (*P* = .001; log-rank test) to be predictors of DSS. Multivariable analysis (incorporating age, sex, race, presence of neck disease, radiation therapy, receiving surgery, and modified Kadish stage as covariates) revealed age (hazard ratio, 1.016; 95% CI, 1.003-1.029; *P* = .02) and modified Kadish stage (hazard ratio, 1.710; 95% CI, 1.286-2.274; *P* < .001) to be independent predictors of OS and modified Kadish stage (hazard ratio, 2.025; 95% CI, 1.430-2.866; *P* < .001) and radiation therapy (hazard ratio, 0.433; 95% CI, 0.228-0.864; *P* = .02) to be independent predictors of DSS.

Discussion

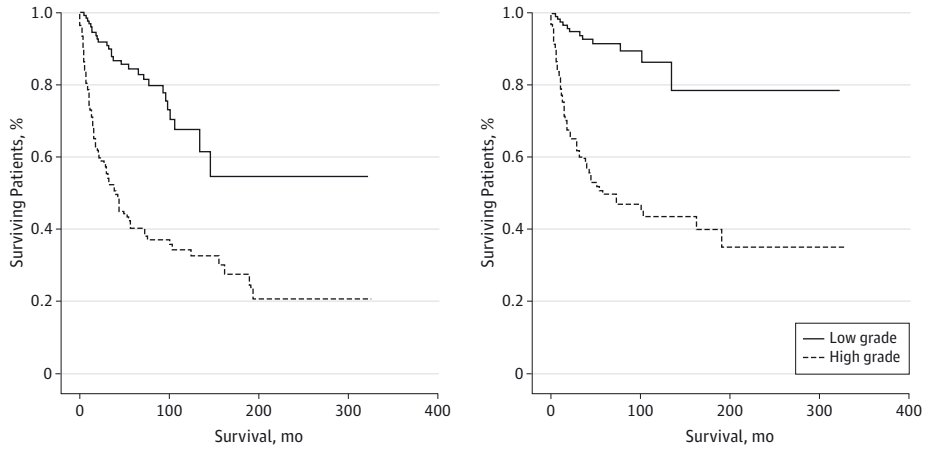
Esthesioneuroblastoma is a rare malignant tumor of the superior nasal vault. Treatment guidelines are constantly evolving owing to innovation in surgical access and improvement in pathologic evaluation. A particular area of controversy is the prognostic significance of tumor grade in ONB outcome. This article represents, to our knowledge, the largest population-based study evaluating prognostic factors for survival in patients with ONB with the inclusion of tumor grade.

Numerous studies have attempted to identify prognostic factors for survival for patients with ONB. One of the largest series[5] was an international collaborative study involving 151 patients that investigated outcomes after craniofacial surgery for ONB. Using multivariable analysis, intracranial extension and positive surgical margins were identified to be independent predictors of worse overall, disease-specific, and recurrence-free survival. Other studies have identified the Kadish system, T staging of Dulguerov-Calcaterra, tumor grade, nodal involvement, and radiation dose to also be factors.[3,4,11] In this study, multivariable Cox regression analysis revealed advanced age, tumor grade, and modified Kadish stage to be negative independent predictors of OS, while female sex independently predicted better OS. The effect of age and sex on all-cause survival is expected in this analysis because the OS rate includes extraneous deaths from expected age-related mortality. This issue is circumvented when reporting DSS. In this study, advanced tumor grade and modified Kadish stage independently predicted worse DSS, while radiation therapy independently predicted better DSS. Age and sex had no influence on DSS. These findings agree with prior published studies.[3-5]

Pathologic grading of ONB is by Hyams criteria, which groups tumors on a scale of I to IV based on histologic features that roughly represent a spectrum of benign to malignant behavior. Briefly, Hyams grade I tumors display preserved lobular architecture, zero mitotic index, no nuclear polymorphisms, prominent fibrillary matrix, no evidence of necrosis, and cells loosely organized around a central fibrillar eosinophilic material (Homer-Wright pseudorosettes). Hyams grade II tumors have similar findings to grade I but have evidence of low levels of mitoses and nuclear polymorphisms. Hyams grade III tumors begin to have reduced lobular architecture, a moderate mitotic index with moderate levels of nuclear polymorphisms, and a reduction in fibrillary matrix. Flexner-Wintersteiner rosettes, which are true rosettes with cells arranged around an empty space, may be present in Hyams grade III tumors. Hyams grade IV tumors show a high mitotic index and nuclear polymorphism, no fibrillary matrix and rosettes, and frequent necrosis.[7]

Because of the low power of institutional articles, prognostication by tumor grade has provided varied results.[12,13] Kane et al[14] performed a systematic review of 956 patients from 205 studies that reported ONB outcomes. Using univariable analysis, their investigation revealed worse survival in patients with Kadish stage C tumors and Hyams grade III or IV tumors, and in patients older than 65 years. Multivariable analysis demonstrated that Hyams grade III or IV tumors carried significant risk (hazard ratio, 4.83; *P* < .001). In addition, they concluded that the biological behavior of ONB could be summarized as representing 2 patterns: low grade (Hyams grade I or II) and high grade (Hyams grade III or IV). This hypothesis was supported in a follow-up study[7] that investigated 20 patients with Kadish stage C tumors in which patients with low-grade tumors demonstrated improved 2-year

Figure 2. Overall and Disease-Specific Survival by Tumor Grade



A, Kaplan-Meier estimates of overall survival for low- and high-grade tumors. B, Kaplan-Meier estimates of disease-specific survival for low- and high-grade tumors. $P < .001$; log-rank test.

progression-free survival compared with patients with high-grade tumors (86% vs 49%). Furthermore, the authors concluded that tumor grade appeared to be the best method to select patients for adjuvant radiotherapy among patients with Kadish stage C tumors. One of the largest institutional studies,[8] which included 109 patients, also supported distinct natural history for low- and high-grade ONB tumors. In addition to reporting worse OS for patients with high-grade pathologic features, they showed that high-grade tumors correlated with more advanced localized disease as well as regional neck metastasis.

The large sample size in our study provided sufficient power to more thoroughly understand the natural history of low- and high-grade lesions. In addition, multivariable analysis was able to statistically assess the effect of treatment modality and adjuvant therapy. Our study confirms prior findings and reports substantially worse OS and DSS for high-grade tumors (**Figure 2**). A powerful addition to the literature is the divergent prognostic factors for survival identified between low- and high-grade lesions in this study. As reported in this study, multivariable analysis of high-grade tumors revealed advanced modified Kadish stage (hazard ratio, 2.025; $P < .001$) to be a negative independent predictor of DSS, and radiation therapy (hazard ratio, 0.433; $P = .02$) to be a positive independent predictor of DSS. This finding supports the current impression that high-grade pathologic features should warrant combination therapy.[7] In contrast with high-grade tumors, multivariable analysis of low-grade tumors only revealed receiving surgery (hazard ratio, 0.135; $P = .004$) to be a positive independent predictor for DSS, while radiation therapy had no effect on OS and DSS for low-grade tumors ($P = .22$ and .23, respectively; log-rank test). This suggests that, for low-grade tumors, surgical resection with negative margins may suffice as the optimal treatment, and the morbidity of adjuvant radiation therapy may be avoided. However, care should be taken with this approach because it has been shown that radiation therapy is crucial for local control.[15] Further research is needed to ascertain whether radiation therapy for low-grade lesions provides improved local control.

There are inherent weaknesses in this study that should be acknowledged when reviewing our results, because use of the SEER database is not without its own limitations. First, surgical intervention, as defined by the SEER database, does not provide further details of the extent of resection, nor does it provide a time reference with respect to other treatments, such as radiation. In addition, detailed radiation therapy data are not provided, and there is an inability to differentiate neoadjuvant, concurrent, adjuvant, and palliative radiation therapy. Finally, tumor grade is reported on a scale from I to IV in the SEER database, with grade I designated as well differentiated, grade II as moderately differentiated, grade III as poorly differentiated, and grade IV as undifferentiated. This grading scheme roughly corresponds to the Hyams grading scale and may not be interpreted as a true Hyams grade. Nonetheless, the results are still novel, and variability was minimized in this study by grouping patients into low- and high-grade tumor groups. It is expected that these results will provide the early evidence for multi-institutional series.

Conclusions

The management of esthesioneuroblastoma is constantly evolving because of advances in surgical technique and histopathologic analysis. Here, to our knowledge, we report the largest study confirming a distinct natural history between low- and high-grade esthesioneuroblastoma, with unique prognostic factors for survival. Patients with low-grade lesions had significantly improved survival. Surgery alone predicted improved DSS while radiation therapy had no effect on survival. In contrast, patients with high-grade tumors had improved survival with the addition of radiation therapy.

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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Tajudeen, Arshi, Suh, Wang.
Critical revision of the manuscript for important intellectual content: Tajudeen, Suh, St John, Wang.
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ORIGINAL ARTICLE

The fate of chronic rhinosinusitis sufferers after maximal medical therapy

Campbell Baguley, MD[1,2], Amanda Brownlow, MD[2], Kaye Yeung, BSc[2,3], Ellie Pratt, BA, BSc[2], Raymond Sacks, MD[2,4] and Richard Harvey, MD[2]

Background: **Many chronic rhinosinusitis (CRS) treatment regimes revolve around "one-off" maximal medical therapy (MMT) protocols, and although many patients initially respond, long-term control is unpredictable. The value of imaging, endoscopy, and patient progress after MMT for CRS is assessed.**

Methods: **Symptomatic CRS patients with computed tomography (CT)-confirmed disease were recruited at a tertiary rhinology clinic. All patients received at least a 3-week oral prednisone course as part of their MMT. Pretreatment and posttreatment nasal symptoms scores (NSS), quality of life (22-item SinoNasal Outcomes Test [SNOT-22]), and CT (Lund-Mackay [LM]) scores were recorded along with post-MMT endoscopy status.**

Results: **A total of 86 patients (38% female, age 46 ± 13 years) met inclusion criteria. Pre-MMT and post-MMT LM scores were 10.9 ± 5.3 and 8.3 ± 5.5 (change 2.6 ± 3.8, $p < 0.001$). Median follow-up after their initial post-MMT assessment was 6.3 (interquartile range [IQR] 17) months. At initial post-MMT review, 43 (50%) were symptomatic with persistent radiologic disease ("symptomatic CRS"), 12 (14%) were asymptomatic with no radiologic disease ("resolved CRS"), 21 (24%) were asymptomatic with persistent radiologic disease ("asymptomatic CRS"), and 10 (12%) were symptomatic with no radiologic disease ("alternate diagnosis"). Pre-MMT NSS and SNOT-22 were similar among groups. The "asymptomatic CRS" group had the highest age (52 ± 11 years, $p = 0.07$). The "alternate diagnosis" group had the lowest initial LM scores (5.2 ± 2.9, $p = 0.001$). Of the "asymptomatic CRS" patients, 43% relapsed between 3 and 23 months (median 6; IQR 4.4 months) post-MMT and 29% eventually underwent surgery.**

Conclusion: **Although MMT for CRS achieved symptomatic relief in 38% patients, objective evidence of disease was associated with clinical relapse. The concepts of "response" to medical therapy and the need to "control" long-term inflammatory burden need to be balanced.** © 2014 ARS-AAOA, LLC.

Key Words:
sinusitis; treatment; imaging; endoscopy; recurrence

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Many descriptions of response to medical therapy for chronic rhinosinusitis (CRS) imply an endpoint is reached with a number of patients avoiding surgery. Subsequent progress is less well studied. CRS cases present along a spectrum of chronic airway disease with relapses, much like asthma, and are managed initially by combinations of topical and sometimes systemic therapy.

The reported response to a round of maximal medical therapy (MMT) varies between patient groups. This is from 37.5% at a tertiary rhinology clinic[1] to as much as 90% of patients treated through an asthma center with Lund-Mackay (LM) scores of 10.9 ± 4.8.[2]

Considering the variable chronicity of inflammation of the airway, more recent publications, such as the European Position Paper on Rhinosinusitis, discuss the management of CRS as a condition to be "controlled" with ongoing medical therapy, similar to other chronic lower airway diseases.[3] Simple intranasal corticosteroids and saline irrigations, with intermittent systemic therapy, often form the basis of ongoing therapy. This presents a clinical conundrum, as the philosophy suggests that a period of MMT will have an endpoint of symptom relief for an unspecified duration of time, rather than a cure. For many CRS patients

[1]*Dept of Otolaryngology, Wellington Hospital, Wellington, New Zealand;* [2]*Applied Medical Research Centre, St. Vincent's Hospital, Sydney, Australia;* [3]*Faculty of Medicine, University of NSW, Sydney, Australia;* [4]*Australian School of Advanced Medicine, Macquarie University, Sydney, Australia*

Correspondence to: Campbell Baguley, MD, Wellington Hospital, Riddiford St, Newtown, Wellington 6021, New Zealand; e-mail: campbell.baguley@ccdhb.org.nz

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post-MMT, the presence of residual radiological and/or endoscopic disease despite symptomatic control may increase risk of symptom relapse.[4] The presence or degree of disease burden post-MMT may play a critical role in determining chronicity and whether further treatment is required, independent of symptom status. The influence of post-MMT symptoms and their correlation to radiological appearance post-MMT are assessed.

Patients and methods

A retrospective cohort of patients treated at a tertiary rhinology clinic was assessed. All data were collected prospectively. The study had prior institutional ethics review approval from St Vincent's Hospital.

Population

Inclusion criteria were radiologic confirmation of diffuse mucosal disease and a history consistent with major or minor CRS symptoms[5] or fulfilling the current European Position Paper <on Rhinosinusitis and Nasal Polyps (EPOS) classification.[3] Atopic status (by history or blood/skin prick test), history of asthma, smoking, previous surgery, and aspirin-sensitive airways disease (ASAD) were recorded. Patients with suspected comorbidities such as migraine, atypical facial pain, and allergic rhinitis were included as long as they met the inclusion criteria of both radiologically confirmed mucosal changes and CRS symptoms. Patients with clear indications for surgery, such as mucoceles, extensive fungal disease, and uncinate atelectasis, and those with isolated sinus disease (eg, sphenoid or odontogenic sinusitis) were excluded. Patients who had recently had prednisone courses and remained symptomatic and requested surgery rather than further medical treatment were also excluded.

MMT

MMT consisted of oral prednisone for 3 weeks (1 week each of 25 mg/day, 12.5 mg/day, and 5 mg/day), topical steroids in spray or irrigation form, and saline irrigation. Antibiotics were given whenever discolored discharge from the middle meatus was observed and in these cases swabs were taken from the middle meatus with endoscopic guidance. Amoxicillin/clavulanic acid was prescribed for 20 days and the antibiotic was altered if indicated by subsequent culture. Atopic patients were not offered oral antihistamines or antileukotrienes. For the included group follow-up was arranged in 4 to 6 weeks (later if requested by the patient) to assess response to medical therapy.

Clinical outcomes

Patient-reported outcomes consisted of nasal symptom scores (NSS), and disease specific quality of life (QOL) scores (22-item SinoNasal Outcomes Test [SNOT-22]).[6] Nasal symptoms were nasal obstruction, rhinorrhea, postnasal discharge, loss of smell, and facial pain/pressure, each scored on a scale of 0 to 5. SNOT-22 scores were tallied both initially and post-MMT and reported as means.

Clinically reported status of CRS post-MMT was defined as "controlled" if symptoms had resolved or were not bothersome.[3] This was recorded post-MMT only because all patients were symptomatic for CRS initially.

Endoscopic outcomes

Endoscopic images were captured digitally at both pre-MMT and post-MMT visits with archived images from the latter visits assessed using the Lund-Kennedy scoring system as well as EPOS 2012 definitions of "positive endoscopy."[3,7]

Radiological outcomes

CT scans were performed with a Xoran miniCAT™ low-dose cone-beam scanner (Xoran Technologies Inc., Ann Arbor, MI), which delivers an equivalent radiation dose of 0.17 mSv per sinus CT series. CT scans were scored as described by Lund and Mackay[8] and were given a clinician-assigned category of "resolved" or "persistent inflammation." Mucosal cysts and minor isolated thickening of the maxillary sinus floor were considered neither to represent CRS nor to influence the LM scores.

Patients were thus grouped according to the presence or absence of both ongoing symptoms and objective evidence of inflammation (see Fig. 1, results).

Patients were followed as required to assist with ongoing therapy and asked to represent should symptoms recur after discharge.

Statistical analysis

Data were analyzed using IBM SPSS Statistics v20 (IBM Corp., Chicago, IL). Descriptive data are presented as percentages with mean ± standard deviation (SD) for parametric data and median and interquartile range (IQR) for nonparametric data. Chi-square tests were used for categorical variables with the Fisher exact test for cell counts <5. Parametric data were compared with 1-way analysis of variance (ANOVA) and nonparametric data with the Mann-Whitney U test or Kruskal-Wallis test for 3 or more independent samples. Statistical significance was reported for alpha of 0.05.

Results

A total of 86 patients (38% female, age 46 ± 13 years) met inclusion criteria and had post-MMT CT scans available for review. Nasal polyposis was evident in 31%, allergy/atopy in 37%, asthma in 28%, and ASAD in 2%; 13% were smokers and 10% had undergone previous sinus surgery.

MMT consisted of a 3-week course of prednisone with daily intranasal corticosteroids and saline irrigation for all patients with antibiotic treatment given to 53% patients, usually amoxicillin/clavulanic acid for 20 days. The median

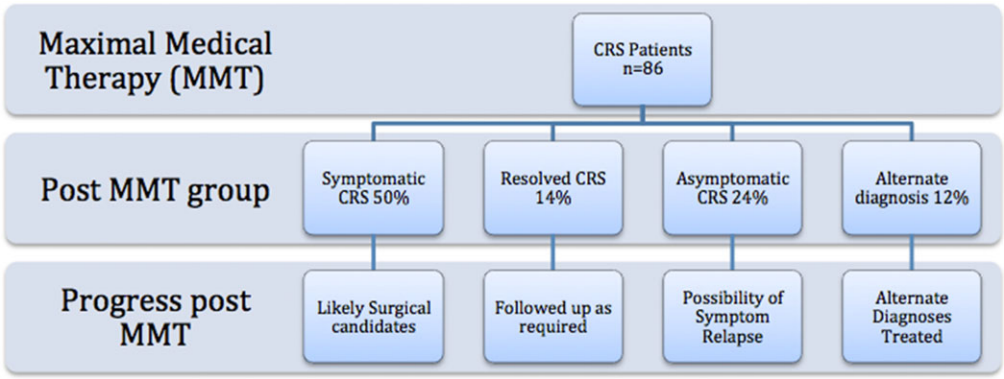

FIGURE 1. Allocation of patient groups after MMT. MMT = maximal medical therapy.

TABLE 1. Characteristics of post-MMT groups

Post MMT group	n	Age (years)	Gender (%F)	CRSwNP	Pre-NSS	Pre-SNOT-22	Post-NSS	Post-SNOT-22	Pre-CT	Post-CT	Symptom relapse
Symptomatic CRS	43	45 ± 12	26%	33%	2.5 ± 0.9	1.9 ± 0.9	1.9 ± 1.0	1.4 ± 0.8	11.6 ± 5.2	10.5 ± 4.5	n/a
Resolved CRS	12	42 ± 11	58%	17%	2.0 ± 1.0	1.7 ± 0.9	0.6 ± 0.3	0.5 ± 0.3	8.2 ± 3.9	2.75 ± 2.0	0
Asymptomatic CRS	21	52 ± 11	43%	52%	2.7 ± 1.1	2.2 ± 1.1	1.1 ± 0.9	0.8 ± 0.7	12.1 ± 6.3	11.1 ± 3.5	9
Alternate diagnosis	10	42 ± 20	60%	0%	2.2 ± 1.1	1.9 ± 0.8	1.9 ± 1.3	1.7 ± 1.0	5.2 ± 2.9	0.7 ± 1.6	0
p[a]		0.07	0.07	**0.02**	0.42	0.54	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**

[a]Bold values are significant.
CRS = chronic rhinosinusitis; CT = computed tomography; MMT = maximal medical therapy; NSS = nasal symptom scores; pre/post CT = Lund-Mackay CT scores before/after MMT; n/a = not applicable; SNOT-22 = 22-item SinoNasal Outcome Test.

time of MMT was 46 days (IQR 24) and did not differ between the patient groups outlined in the next paragraph ($p = 0.94$). Although the post-MMT CT scan was always performed at the post-MMT visit, there was variation in the interval between the 2 scans being compared (median 63 days, IQR 78).

At the post-MMT visit, patients were categorized into 4 groups: 43 (50%) were symptomatic with persistent radiologic disease ("symptomatic CRS"); 12 (14%) were asymptomatic with no radiologic disease ("resolved CRS"); 21 (24%) were asymptomatic with persistent radiologic disease ("asymptomatic CRS"); and 10 (12%) were symptomatic with no radiologic disease ("alternate diagnosis") (Fig. 1).

Pretreatment factors affecting response to MMT

Age was highest in the "asymptomatic CRS" group (52 ± 11 years, $p = 0.07$) (Table 1). The proportion of patients with nasal polyposis was highest in the "symptomatic CRS" (33%) and "asymptomatic CRS" groups (52%), and lowest among those with alternate diagnoses (0%, $p = 0.018$). Table 2 shows percentages of patients within each group, when separated for CRS phenotype (with vs without polyps).

There were 2 patients with ASAD. One ended up with "symptomatic CRS" and 1 with "asymptomatic CRS." Previously operated patients (n = 9) were fairly evenly split between the "symptomatic CRS" (4) and "asymptomatic CRS" groups (5), with none of these patients having resolution of CT changes after MMT (χ^2 7.26, $p = 0.06$).

TABLE 2. Post-MMT groups and CRS phenotype

CRS phenotype	Post-MMT groups			
	Symptomatic CRS	Resolved CRS	Asymptomatic CRS	Alternate diagnosis
With polyps (n = 27)	52%	7%	41%	0%
Without polyps (n = 59)	49%	17%	17%	17%

CRS = chronic rhinosinusitis; MMT = maximal medical therapy.

Pre-MMT NSS and SNOT-22 were similar across the 4 groups. This included pre-MMT facial pain scores ($p = 0.64$). Pre-MMT and post-MMT LM scores for the entire study group were 10.9 ± 5.3 and 8.3 ± 5.5 (change 2.6 ± 3.8, $p < 0.001$). The interval between pretreatment and posttreatment scans did not differ significantly between groups ($p = 0.82$). The "alternate diagnosis" group had the lowest LM scores initially ($p = 0.001$, Fig. 2) and was more likely to score facial pain highly after treatment ($p = 0.028$). This group had other reasons for their persistent symptoms, such as migraine, rhinitis, mucus recirculation, postviral hyposmia, and postviral cough, despite having evidence of CRS on radiology at initial assessment.

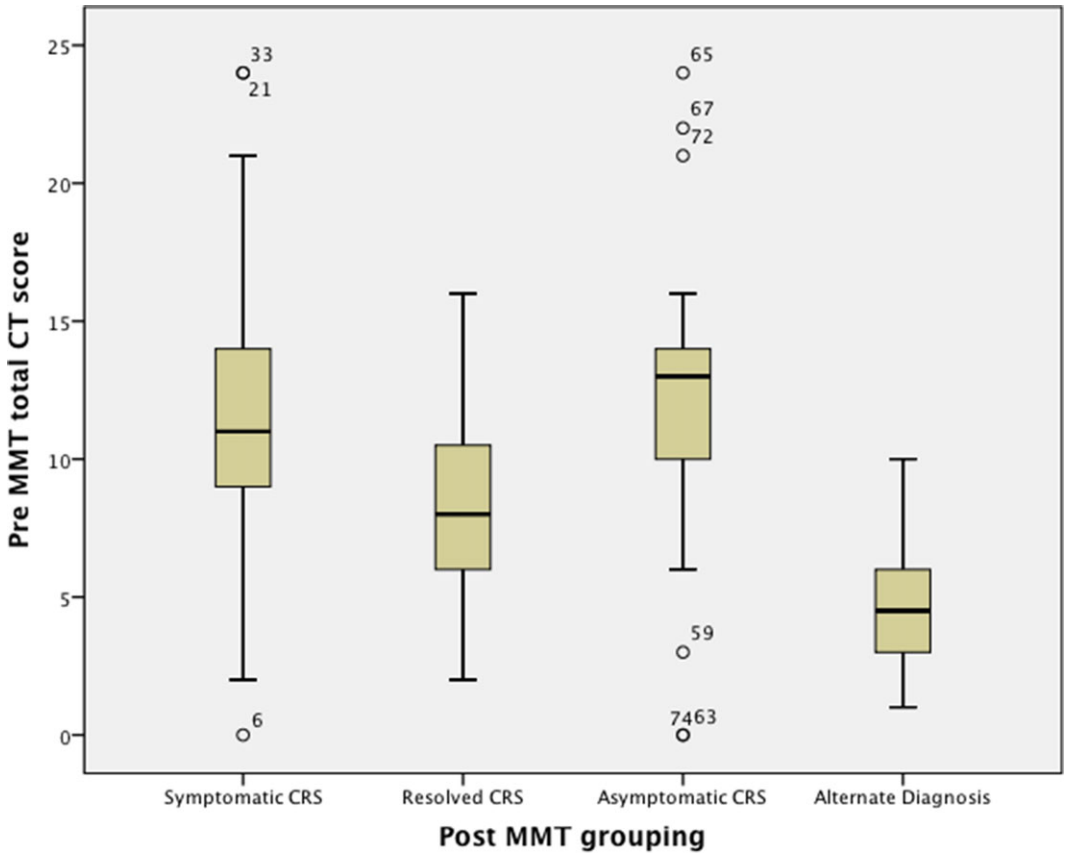

FIGURE 2. Pretreatment CT scores within patient groups. CT = computed tomography.

The presence of purulent secretions and hence antibiotic prescription did not differ significantly between groups (χ^2 2.42, $p = 0.49$).

Subgroup analysis for patients with and without polyps

The groups of patients with and without polyps had different baseline characteristics. Although age, gender, and asthma/allergy history were not statistically different ($p =$ 0.80, 0.11, 0.08, 0.28, respectively) the CRSwP group had higher pretreatment CT scores (14.4 vs 8.7, $p < 0.01$), higher rates of previous surgery (29% vs 6%, $p = 0.053$), and were less likely to receive antibiotics (for purulent nasal secretions; 41% vs 64%, $p = 0.04$).

Factors at post-MMT assessment determining response

Post-MMT mean NSS differed as expected given that groups were assigned based on patient-reported symptomatic progress ($p = 0.002$) (Table 1). These scores were the same however among "symptomatic CRS" patients, whether there was radiological disease or not (mean NSS 1.9, 1.9, $p = 0.98$). Similarly for patients who reported good symptom control, the mean NSS were similar whether radiologic disease persisted or not ($p = 0.37$, Fig. 3).

Clinical progress subsequent to post-MMT visit

Median follow-up after the post-MMT visit for all patients was 6.3 months (IQR 17) with case files last being reviewed at 24 months (IQR 19). Follow-up differed across groups, being shortest for those with "resolved CRS" ($p = 0.006$). Most of these 12 patients were discharged with advice to represent should symptoms recur. No known CRS recurrence has occurred in a minimum of 11 months since the post-MMT visit for this group.

Of the 43 patients considered surgical candidates, 84% had endoscopic sinus surgery (ESS) scheduled, with others opting for further medical treatment.

Symptomatic patients with normal CT scans (n = 10) were further assessed as required and treated for alternate diagnoses as described above. One underwent ESS for mucus recirculation.

The fate of patients with radiological mucosal disease but symptom control after 1 course of MMT

All "asymptomatic CRS" patients were followed at 3- or 6-month intervals and offered topical steroid sprays and saline irrigations. Nine of 21 patients (43%) suffered symptom relapse between 3 and 23 months (median 6, IQR 4.4 months) post-MMT and 6 (29%)

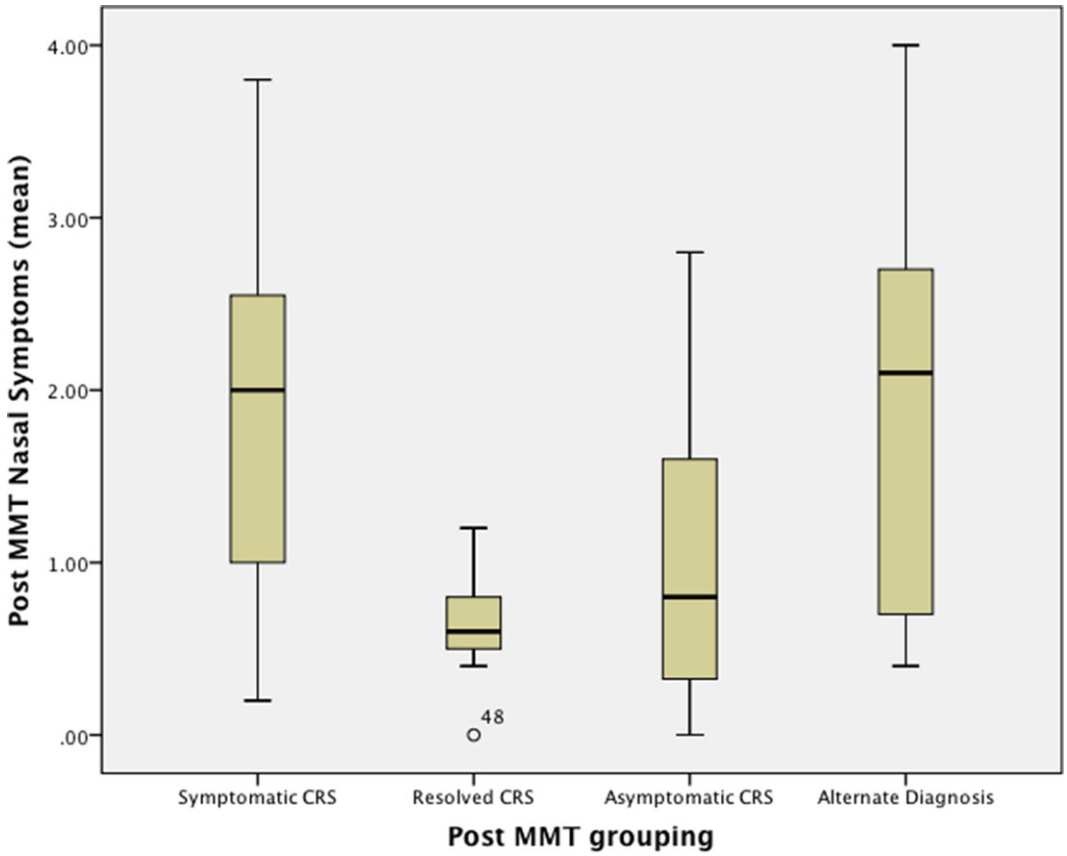

FIGURE 3. Posttreatment mean nasal symptom scores within patient groups.

TABLE 3. Endoscopic findings within post-MMT groups

	Post-MMT groups				Total
	Symptomatic CRS	Resolved CRS	Asymptomatic CRS	Alternate diagnosis	
Post-MMT endoscopic examination					
No evidence of sinus inflammation	13	9	5	9	36
Evidence of sinus inflammation	29	2	15	1	47
Total	42	11	20	10	83

CRS = chronic rhinosinusitis; MMT = maximal medical therapy.

underwent surgery. Three were managed with further prednisone courses and one with more intensive topical therapy (Fig. 4).

Symptom relapse was not related to gender (χ^2 0.016, $p = 0.90$), age (t test, $p = 0.28$) atopic status (χ^2 0.28, $p = 0.60$), history of asthma (χ^2 0.30, $p = 0.58$) or presence of polyps (χ^2 0.064, $p = 0.80$). It was also not related to pre-MMT SNOT 22 ($p = 0.89$) or NSS ($p = 0.71$), or post-MMT SNOT-22 ($p = 0.37$) or NSS ($p = 0.07$). Pre-MMT and post-MMT CT scores were not related ($p = 0.42$ and 0.31, respectively) and neither was history of previous ESS ($p = 1.0$).

Predictive value of endoscopy

Post-MMT endoscopy was considered positive for inflammation in 47 of 86 patients (57%) and was significantly correlated with post MMT radiologic inflammation ($p = 0.001$) (Table 3). When compared with CT scanning, endoscopy had a positive predictive value (PPV) of 94% and a negative predictive value (NPV) of 50%, with sensitivity 71% and specificity 86%. Among symptomatic patients (n = 52) PPV was 97% and NPV 41% (sensitivity 69%, specificity 90%, Table 3). Among symptomatic patients with facial pain scores ≥3 (n = 12) the NPV was 100% (5/5).

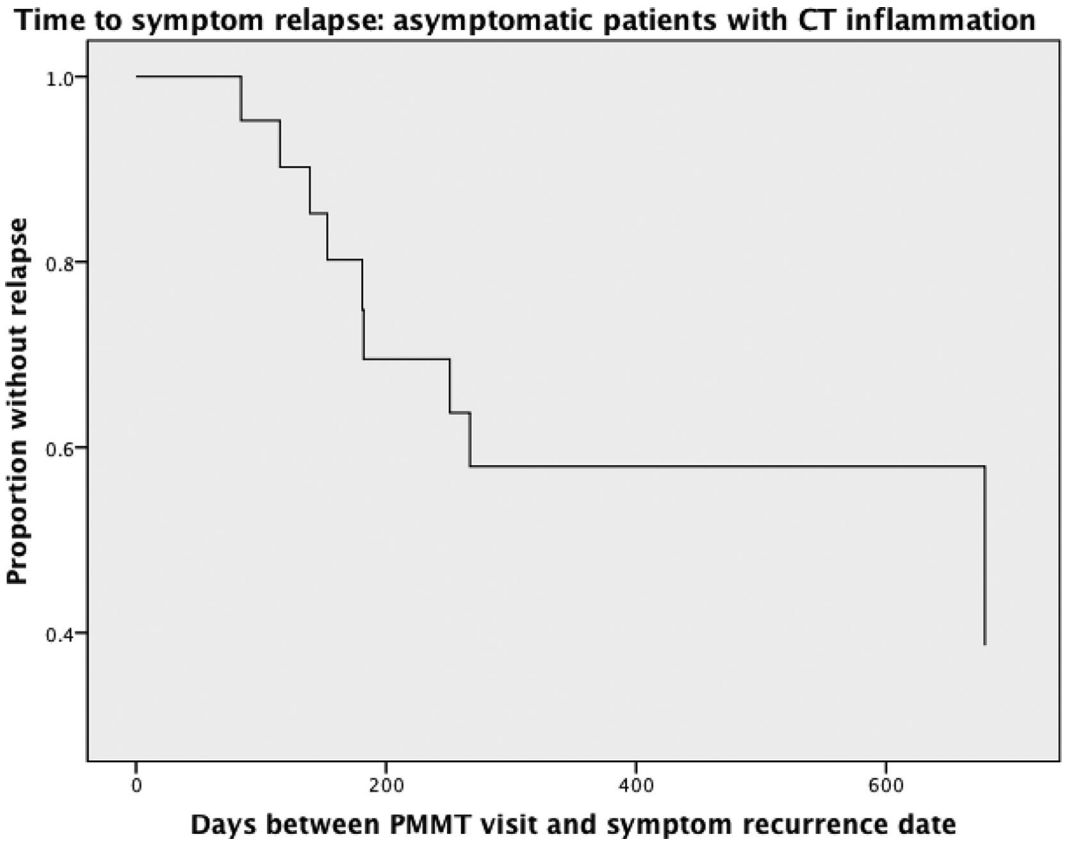

FIGURE 4. Time to symptom relapse among asymptomatic patients with CT inflammation. CT = computed tomography.

TABLE 4. Progress after MMT and endoscopy for patients with "asymptomatic CRS"

	CRS symptoms relapsed after MMT		
	No	Yes	Total
Post-MMT endoscopic examination			
No evidence of sinus inflammation	5	0	5
Evidence of sinus inflammation	7	8	15
Total	12	8	20

CRS = chronic rhinosinusitis; MMT = maximal medical therapy.

Within the group with "asymptomatic CRS" (with radiologic evidence of CRS), none of the 5 patients with negative endoscopy suffered symptom relapse before the most recent clinic visit (median 8, IQR 21 months after post-MMT visit) whereas 8 of 15 (53%) did if their endoscopy was abnormal ($p = 0.035$, Table 4).

Discussion

Among the challenging aspects of CRS patient management are the difficulties correlating patient symptoms with objective measures of inflammation and predicting early and long-term response to medical therapy. The current study has shown that the knowledge of both the radiologic and endoscopic status of the sinuses after medical therapy can help with management decisions, potentially avoiding unnecessary surgery for some patients and predicting the likelihood of symptomatic relapse for other patients.

MMT included the use of saline irrigation and topical steroid sprays, as is well supported by evidence.[3,9,10] Most patients were prescribed mometasone 100 μg twice daily to both nostrils. Patients with some open sinus ostia after previous surgery were prescribed high-volume steroid irrigation, using either betamethasone 1 mg or budesonide 1 mg, per 240-mL bottle, daily.[11] Specific details of compliance were not recorded. Our practice is to offer all CRS patients (with and without polyps) systemic steroids provided there are no contraindications. We accept that the evidence supporting their use for CRS without nasal polyposis (CRSsP) patients is weaker than for CRS with nasal polyposis (CRSwP).[12] However, the systemic route guarantees some delivery to the sinuses compared to simple nasal sprays. Culture-directed antibiotics were used only when purulence was observed endoscopically rather than longer term antibiotics alone that may have specific anti-inflammatory actions.[13–15]

CT scanning has a well-established role in confirming the diagnosis of CRS when symptoms are persistent after

medical treatment, assessing disease extent, ruling out other pathologies, and assessing anatomy prior to surgery. Patients in this study frequently presented after some form of medical therapy, with CT scans. Others underwent imaging at the initial visit to clarify the presence and extent of disease, given the availability of a low-radiation-dose in-office scanner. CT is less well studied as a tool to monitor response to medical therapy.

Imaging was with an in-office scanner with a low radiation dose of 0.17 mSv per scan. This compares with 0.96 mSv for a conventional sinus CT scan[16] and around 2 mSv for a standard head CT. Even the higher radiation dose associated with head CT appears not to have any cataractogenic effect, based on an Australian study of patients undergoing detailed eye examinations.[17] The findings of this study were in contrast with a prior report that found a moderate positive association between head CT scan history (conventional scanner) and cataract presence.[18] For this and other reasons protocols should always exist to prevent indiscriminate CT scan use and thus radiation exposure.

Changes in CT findings have previously been reported after medical treatment of CRS. In a group of patients with nasal polyps and higher initial LM scores (mean 18.2), Benitez et al.[19] found that oral prednisone followed by topical budesonide achieved a reduction in LM scores of around 3. These authors point out that the improvement in CT scores compared with symptoms is small and follow-up CT is probably not indicated in nonsurgical patients. Subramanian et al.[2] reported that mean LM scores improved from 10.9 to 5.4 after prednisone and antibiotics plus topical therapy and 90% of their patients achieved symptom control after MMT. This study also evaluated symptom relapse. It occurred in 14 of 40 patients, up to 8 weeks after medical treatment. There was a positive association between symptom relapse and the presence of nasal polyps and a history of previous surgery, but not persistent ostiomeatal unit (OMU) obstruction on CT. The higher response in this group to medical therapy may relate to the treatment setting (allergy center as opposed to tertiary rhinology clinic). Finally Wei et al.[20] assessed the effectiveness of once-daily saline and antibiotic irrigation in the treatment of pediatric CRS and found that both saline and topical antibiotic irrigation led to an improvement in CT LM scores of around 8 on average.

Our data revealed an average improvement in LM score of 2.6 after medical therapy. One-half of the patients were surgical candidates after MMT. Only 14% percent were successfully treated in terms of symptomatic and radiologic response with none re-presenting with CRS. Importantly, 24% were not bothered by their symptoms but had persistent CT changes and these patients were likely (43%) to suffer symptom relapse, usually within 9 months. Although repeat imaging may not be necessary in every case, knowledge of the radiologic status of a patient's sinuses after initial response to MMT has some prognostic value and can help guide ongoing treatment. The value of endoscopy in this setting is discussed below.

Other diagnoses to explain nasal symptoms existed in 12% of patients, who despite remaining symptomatic had no persistent disease on CT scans. Careful analysis of patient symptoms and their response to systemic steroids along with endoscopic findings often alerts the clinician to alternate diagnoses to CRS. Some still require imaging for clarification given the generally poor correlation between symptomatology and CT findings.[21,22]

Endoscopy as an objective measure of inflammation has previously been compared with CT and its role recently summarized.[23–26] Although generally specific (76–95%) for confirming the presence of radiologic inflammation in symptomatic patients, most studies including ours demonstrate a poor NPV for endoscopy (50–70%). This information, along with our data, suggest that repeat imaging could be avoided for some who appear to be clear surgical candidates with abnormal endoscopy after medical treatment, assuming the extent of residual radiologic disease will not influence the extent of ESS performed. For many others though follow-up CT scans provide additional useful information.

Endoscopy may provide prognostic information in addition to CT scanning. More severe endoscopic changes have been associated with failure of medical therapy.[27] In the current study, asymptomatic patients with persistent radiologic changes post-MMT and with abnormal endoscopy were more likely to suffer symptom relapse than those with normal endoscopy (53% vs 0%, $p = 0.035$). The potential of endoscopy to define the "active" state of mucosal inflammation as opposed to radiologic mucosal thickening/edema might better define those at risk of relapse.

Conclusion

Although MMT achieved symptomatic control of CRS for 38% patients, over one-half of this number had persistent radiologic disease, which was frequently associated with symptom relapse. Twelve percent, although still symptomatic, had normal scans and other diagnoses to explain their symptoms. Future discussions of "response" to medical therapy should acknowledge the chronicity of this condition, the behavior of which relates in part to the underlying inflammatory burden within the sinuses.

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ORIGINAL ARTICLE

Investigation of change in cardinal symptoms of chronic rhinosinusitis after surgical or ongoing medical management

Adam S. DeConde, MD[1], Jess C. Mace, MPH, CCRP[2], Jeremiah A. Alt, MD, PhD[3], Zachary M. Soler, MD, MSc[4], Richard R. Orlandi, MD[3] and Timothy L. Smith, MD, MPH[2]

Background: **Chronic rhinosinusitis (CRS) has been defined as inflammation of the paranasal sinuses lasting at least 12 weeks with corresponding 2 or more "cardinal symptoms" that include: (1) nasal obstruction; (2) thick nasal discharge; (3) facial pain/pressure; and (4) reduction or loss of sense of smell. Although prior studies have investigated symptoms of CRS after sinus surgery, none have compared the outcomes of these specific symptoms to ongoing medical therapy.**

Methods: **Patients with CRS were prospectively enrolled into a multi-institutional, comparative effectiveness, cohort study. Subjects elected either continued medical management or endoscopic sinus surgery (ESS). Baseline characteristics and objective clinical findings were collected. Cardinal symptoms of CRS were operationalized by 4 questions on the 22-item Sino-Nasal Outcome Test (SNOT-22). Symptom improvement was evaluated in subjects with at least 6-month follow-up.**

Results: **A total of 342 subjects were enrolled, with 69 (20.2%) electing continued medical management, whereas 273 (79.8%) elected ESS. Subjects electing surgical therapy were more likely to have a higher baseline aggregate SNOT-22 score (44.3 (18.9) vs 53.6 (18.8); $p < 0.001$). All subjects improved across all cardinal symptoms; however, subjects undergoing ESS were significantly more likely ($p \leq 0.013$) to experience improvement in thick nasal discharge (odds ratio [OR] = 4.36), facial pain/pressure (OR = 3.56), and blockage/congestion of nose (OR = 2.76). Subjects with nasal polyposis were significantly more likely to report complete resolution of smell/taste following ESS compare to medical management (23.8% vs 4.0%; $p = 0.026$).**

Conclusion: **Across a large population, surgical management is more effective at resolving the cardinal symptoms of CRS than ongoing medical management with the exception of sense of smell/taste.** © 2014 ARS-AAOA, LLC.

Key Words:
Sinusitis; diagnosis; quality of life; endoscopy; therapy

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Chronic rhinosinusitis (CRS) is defined in the 2007 Adult Sinusitis Clinical Practice Guidelines[1] and the 2012 European Position Paper on Rhinosinusitis[2] as inflammation of the nose and paranasal sinuses manifesting with 2 or more "cardinal" symptoms for 12 weeks with

[1]*Department of Surgery, Division of Otolaryngology–Head and Neck Surgery, University of California San Diego, San Diego, CA;* [2]*Department of Otolaryngology–Head and Neck Surgery, Division of Rhinology, Oregon Health and Science University, Portland, OR;* [3]*Division of Head and Neck Surgery, Rhinology–Sinus and Skull Base Surgery Program, Department of Surgery, University of Utah, Salt Lake City, UT;* [4]*Department of Otolaryngology–Head and Neck Surgery, Division of Rhinology and Sinus Surgery, Medical University of South Carolina, Charleston, SC*

Correspondence to: Timothy L. Smith, MD, MPH, Oregon Health and Science University, Department of Otolaryngology–Head and Neck Surgery, Division of Rhinology and Sinus/Skull Base Surgery, Oregon Sinus Center, 3181 SW Sam Jackson Park Road, PV-01, Portland, OR 97239; e-mail: smithtim@ohsu.edu

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endoscopic and/or computed tomography (CT) signs of disease. The cardinal symptoms include nasal obstruction, thick nasal discharge, facial pain/pressure, and reduction or loss of sense of smell. These guidelines are designed to aid clinicians in the diagnosis and management of CRS. These cardinal symptoms were chosen because they are the most common symptoms of CRS[1] and are used clinically because they are well understood by both patients and clinicians.

The impact of endoscopic sinus surgery (ESS) on CRS is well documented using a variety of quality-of-life (QOL) measures.[3,4] QOL instrument measures are often reported in aggregate (eg, 22-item Sino-Nasal Outcome Test [SNOT-22])[5] or broken down by domain scores (eg, Rhinosinusitis Disability Index [RSDI], Chronic Sinusitis Survey [CSS]).[3,6] Aggregate and domain scores are effective means to provide a complete view of the impact of ESS, but do not translate well for clinical use and patient-centered decision-making. Aggregate scores may also obfuscate improvements or lack of improvements in specific symptoms[7] concealing specific symptomatic changes that may be weighed as more important to each individual patient.

Patients with CRS report interval improvement across all cardinal symptoms following ESS.[8] However, specific symptom outcomes have not been compared to a medical cohort, which limits our ability to counsel patients between sinus surgery and continued medical management. The goal of this investigation was to specifically evaluate changes in cardinal symptoms after both continued medical management and sinus surgery.

Patients and methods

Patient population and inclusion criteria

Adult patients (≥18 years of age) with a current diagnosis of medically refractory CRS were prospectively enrolled into an ongoing, North American, multi-institutional, observational, cohort study between February 2011 and January 2014 to compare the effectiveness of treatment outcomes for this chronic disease process. Preliminary findings from this cohort have been previously described.[9–12] A current diagnosis of CRS was defined by the 2007 Adult Sinusitis Guideline, endorsed by the American Academy of Otolaryngology–Head and Neck Surgery,[1] with subsequent previous treatment with oral, broad-spectrum, or culture-directed antibiotics (≥2-week duration) and either topical nasal corticosteroid sprays (≥3-week duration) or a 5-day trial of systemic steroid therapy during the year prior to enrollment. Enrollment sites consisted of 4 academic, tertiary care rhinology practices as part of the Oregon Health and Science University (OHSU, Portland, OR), the Medical University of South Carolina (Charleston, SC), Stanford University (Stanford, CA), and the University of Calgary (Calgary, Alberta, Canada). The Institutional Review Board at each enrollment location provided oversight and annual review the informed consent process and all investigational protocols, whereas central review and coordination services were conducted at OHSU (eIRB #7198). Study participation did not change the medical therapy regimen or follow-up schedule required for any patient.

Study participants elected 1 of 2 treatment options during the preliminary enrollment meeting as their standard of care. Participants either elected to continue medical management for control of symptoms associated with CRS or ESS procedures based on individual disease processes and intraoperative clinical judgment of the enrolling physician at each site. Surgical procedures consisted of either unilateral or bilateral maxillary antrostomy, partial or total ethmoidectomy, sphenoidotomy, middle or inferior turbinate reduction, frontal sinus procedures (Draf I, IIa/b, or III), or septoplasty. Participants were either primary or revision surgery cases in both treatment groups.

Exclusion criteria

Study participants diagnosed with a current exacerbation of either recurrent acute sinusitis or ciliary dyskinesia were excluded from the final study cohort due to the heterogeneity of those disease processes. Participants were also excluded from final analyses if they failed to complete all required baseline study evaluations or had not yet entered into the follow-up appointment time window. Subjects originally electing continued medical management and changed treatment course to include ESS during the study period ("crossed over") were also excluded due to the heterogeneity of the treatment protocols.

Clinical disease severity measures

During the initial clinical/enrollment visit, all study subjects completed a medical history, head and neck clinical examinations, sinonasal endoscopy, and computed tomography (CT) imaging as part of their standard care. Endoscopic examinations were scored using the Lund-Kennedy endoscopy scoring system, where higher scores represent worse disease severity (total score range, 0 to 20).[13] This staging system grades bilateral, visual pathologic states within the paranasal sinuses including polyposis, discharge, edema, scarring, and crusting. CT images were evaluated and staged in accordance with the Lund-Mackay bilateral scoring system, where higher scores represent higher severity of disease (total score range, 0 to 24).[14] This scoring system quantifies the degree of image opacification in the maxillary, ethmoidal, sphenoidal, ostiomeatal complex, and frontal sinus regions. All visualizations were subjectively scored by the enrolling physician at each site at the time of enrollment.

Cardinal symptom evaluations

To operationalize the cardinal symptoms associated with confirmatory diagnosis of CRS, study participants were asked to complete items included on the 22-item Sinonasal Outcome Test (SNOT-22; Table 1).[5] The SNOT-22 is a validated, 22-item treatment outcome measure applicable to chronic sinonasal conditions (Washington University,

TABLE 1. Survey items on SNOT-22 instrument used to operationalize cardinal symptoms of CRS

SNOT-22 survey items	Symptom
Item #6	"Thick nasal discharge"
Item #10	"Facial pain/pressure"
Item #21	"Sense of smell/taste"
Item #22	"Blockage/congestion of nose"

CRS = chronic rhinosinusitis; SNOT-22 = 22-item Sino-Nasal Outcome Test.

St. Louis, MO). Higher scores on the SNOT-22 survey items suggest worse patient functioning or symptom severity (total score range, 0 to 110). Individual item scores are recorded using patient selected responses on a Likert scale (0 to 5), where higher scores represent worse symptom severity.

Participants were asked to complete the SNOT-22 survey items at both baseline appointments and at least 6 months after continued medical therapy or ESS procedures when possible, with the assistance of a research coordinator at each site. Patients were lost to follow-up if they did not complete any survey evaluations within 18 months after enrollment. The last available follow-up collected for study subjects (at least 6 months) was used to determine interval change in cardinal symptoms. Physicians at each site were blinded to all patient-based survey responses for the study duration.

Study data collection

Study participants were required to complete all necessary baseline surveys and informed consent in English. Participants were asked to provide demographic, social, and medical history cofactors including, but not limited to: age, gender, race, ethnicity, education (years), insurance status, nasal polyposis, history of prior sinus surgery, asthma, acetylsalicylic acid (ASA) intolerance, chronic obstructive pulmonary disorder (COPD), current tobacco use, alcohol consumption, depression, known allergies (reported by patient history or confirmed skin prick or radioallergosorbent testing), ciliary dyskinesia/cystic fibrosis, and asthma/sinusitis–related steroid dependency. All study data was collected at each site using standardized clinical research forms, deidentified, and manually transferred to a centralized, relational database (Access 2007; Microsoft Inc., Redmond, WA).

Data management and statistical analysis

All statistical analysis was performed using a commercially available statistical software program (SPSS v.22.0; IBM Corp., Armonk, NY). Sample size determination were completed assuming a minimum 1.0 mean difference on SNOT-22 item responses between independent treatment modalities, corresponding to a discernible shift in Likert scale responses for each cardinal symptom. Using a conservative

TABLE 2. Sample size estimations for mean changes in SNOT-22 scores between treatment groups

SNOT-22 mean score difference	Treatment group ratio	Total sample size
0.5	1:4	200
1.0	1:4	52
1.5	1:4	24
2.0	1:4	16
2.5	1:4	12
3.0	1:4	8

SNOT-22 = 22-item Sino-Nasal Outcome Test.

1:4 allocation ratio of patients electing medical therapy to ESS, 2-sided t testing used 80% $1-\beta$ error probability (power), 0.050 alpha level, and an assumed equal variance of 1.0 for both treatment group values (Table 2). Complete descriptive analysis of clinical disease severity measures, demographics, clinical characteristics, and cardinal symptom survey scores were evaluated for distribution and assumptions of normality where appropriate. Comparisons between study participant characteristics were completed using either 2-tailed independent t tests or chi-square (χ^2) analysis for measures of comorbidity and baseline disease severity. The percentage (%) of relative improvement was calculated for each treatment cohort using the formula: [(mean follow-up score − mean baseline score)/mean baseline score] × 100. Differences over time between baseline and follow-up cardinal symptom scores were compared using Wilcoxon signed-rank tests. Baseline and follow-up score distributions were evaluated for all symptom item scores to identify potential floor or ceiling effects. Binary logistic regression was used to identify whether treatment modality was a significant predictor of treatment outcome for each cardinal symptom score before and after adjustment for other independent cofactors. Primary model outcomes were considered to be patient-reported indications of complete symptom resolution of cardinal symptom (eg, SNOT-22 item score of "0" at follow-up evaluation) after removal of subjects reporting "0" at both baseline and follow-up assessments to eliminate potential survey floor effects A total of 23 additional cofactors, including baseline SNOT-22 item scores, were screened for preliminary entry into each of four predictive models at the 0.250 level of significance. Final models were selected using a manual, step-wise procedure with forward inclusion ($p \leq 0.100$) and backward elimination ($p \leq 0.050$) process. Crude and adjusted odds ratios (ORs) with 95% confidence intervals are reported. Predictive model goodness-of-fit was evaluated using the Hosmer and Lemeshow χ^2 test.[15] Statistical associations were set at the 0.050 level of significance.

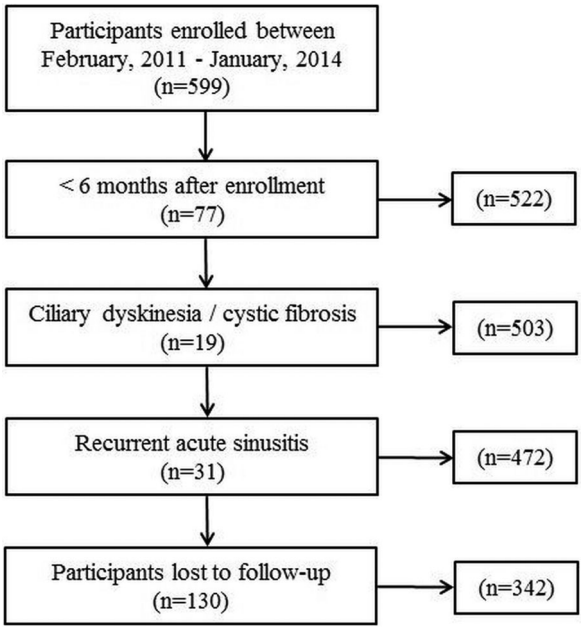

FIGURE 1. Final cohort selection after inclusion and exclusion criteria.

Results

Final study population

The application of inclusion and exclusion criteria allowed for a total of 342 participants with follow-up in the final analysis enrolled between February 2011 and January 2014 (Fig. 1). A total of 69 (20.2%) participants elected continued medical management, whereas 273 (79.8%) elected ESS. Both medical and surgical cohorts were found to have similar prevalence of follow-up (70.4% vs 73.0%; $p = 0.610$). Baseline demographics, clinical characteristics, and clinical disease severity measures were compared between treatment modality for participants with follow-up (Table 3). No significant differences between treatment modalities were noted with the exception of average years of education, the prevalence of deviated septum, and SNOT-22 total scores.

A total of 130 subjects (medical management, n = 29; sinus surgery, n = 101) were either lost to follow-up or had not entered the first 6 month follow-up evaluation period at study inception. Compared to subjects with at least 6 month follow-up evaluations, patients without follow-up were significantly younger (47.6 (14.2) vs 52.1 (14.4) years; $p = 0.003$), reported a higher prevalence of tobacco use (10.8% vs 4.7%; $p = 0.015$) and were found to have slightly lower baseline CT scores (11.2 (3.8) vs 12.5 (6.0); $p = 0.048$). No other statistical differences were found for other demographics, clinical characteristics, or measures of disease severity.

Total improvement in cardinal symptom scores

Overall improvement over time between mean baseline and follow-up scores for each cardinal symptom item on the SNOT-22 was evaluated (Table 4). Significant improvement for all cardinal symptoms was reported for both the total cohort and for each treatment modality. On average, participants electing sinus surgery reported significantly greater improvement compared to participants who continued with ongoing medical management (Table 5). Additionally, the total cumulative percentages of cardinal symptom item scores between baseline and follow-up evaluations for both treatment cohorts are described in Figures 2 through 5.

Prevalence of reported symptom resolution

Participants reporting no indications (eg, score of "0") of each separate cardinal symptom item at both baseline and follow-up assessments were removed due to the potential for healthy user bias. As the primary outcome of interest, the frequency of remaining participants describing complete symptom resolution for each cardinal symptom were compared between medical and surgical modalities, as well as between subjects with and without nasal polyposis (Table 6). Overall, participants electing ESS reported a significantly higher frequency of complete symptom resolution in three of four cardinal symptoms, with the exception of improved sense of smell and/or taste.

Binary logistic regression

Four multivariate logistic regression models were then performed to assess the predictive ability of treatment modality type (main independent exposure variable) on reported complete symptom resolution (primary outcome measure). Crude and adjusted OR values are listed for each model, with corresponding 95% confidence intervals and p values (Table 7). After removal of participants reporting "No problem" at baseline for each separate model the odds of subjects reporting complete symptom resolution for "Thick nasal discharge" are 4.36× better for subjects undergoing ESS than for participants electing continued medical management after adjustment for significant cofactors. Similarly, the odds of participants reporting symptom resolution for "Facial pain and/or pressure" are 3.56× better for subjects undergoing ESS compared to participants electing continued medical management. Treatment modality was not found to be a significant predictor of symptom resolution associated with "Sense of smell/taste" after adjustment for several independent predictive factors (OR = 1.50; $p = 0.306$). Last, the odds of subject reporting complete resolution for "Blockage/congestion of the nose" are 2.76× higher for subjects electing ESS compared to continued medical management.

Discussion

This study describes the impact of both medical and surgical management on the cardinal symptoms of CRS. Subjects in both the medical and surgical cohorts improved across all the cardinal symptoms; however, subjects

TABLE 3. Baseline characteristics of subjects with follow-up by treatment modality

	Medical management (n = 69)		Endoscopic sinus surgery (n = 273)		
Demographics	Mean (SD)	n (%)	Mean (SD)	n (%)	*p*
Follow-up duration (months)	12.8 (5.6)		13.4 (5.6)		0.398
Age (years)	52.0 (13.8)		52.2 (14.6)		0.937
Males		28 (40.6)		127 (46.5)	—
Females		41 (59.4)		146 (53.5)	0.376
White/Caucasian		58 (84.1)		231 (84.6)	0.909
Hispanic/Latino		1 (1.4)		16 (5.9)	0.213
Education (years)	15.9 (2.6)		15.0 (2.8)		0.014
Clinical characteristics					
Asthma		21 (30.4)		101 (37.0)	0.309
Allergies (skin prick/RAST confirmed)		27 (39.1)		102 (37.4)	0.787
ASA sensitivity		8 (11.6)		23 (8.4)	0.413
Depression		13 (18.8)		48 (17.6)	0.807
Tobacco use/current smoker		1 (1.4)		15 (5.5)	0.211
Alcohol consumption		36 (52.2)		123 (45.1)	0.289
COPD		3 (4.3)		13 (4.8)	>0.999
Steroid dependency		3 (4.3)		19 (7.0)	0.587
Previous sinus surgery		40 (58.0)		142 (52.0)	0.376
Nasal polyposis		27 (39.1)		105 (38.5)	0.919
Septal deviation		15 (21.7)		119 (43.6)	0.001
Hypertrophy turbinate		5 (7.2)		42 (15.4)	0.115
Clinical disease severity measures					
SNOT-22 total score	44.3 (18.9)		53.6 (18.8)		<0.001
Computed tomography score	13.3 (6.0)		12.3 (6.0)		0.265
Endoscopy score	6.6 (4.0)		6.2 (3.8)		0.426

ASA = acetylsalicylic acid; COPD = chronic obstructive pulmonary disease; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test; RAST = radioallergosorbent.

electing surgical therapy experienced greater mean gains in all cardinal symptoms except for olfaction. A subgroup analysis of the total cohort, though, highlights a treatment differential in the subgroup of subjects with CRS with nasal polyposis (CRSwNP) with more improvement in smell and taste after surgery in contrast to subjects without nasal polyposis (CRSsNP). The frequency that subjects experience complete resolution of each cardinal symptom is greater in the surgical cohort with the exception of olfaction. Subjects undergoing surgical intervention are 3 to 4 times more likely to experience complete resolution of thick nasal discharge, facial pain/pressure, and blockage/congestion of the nose when compared to subjects undergoing continued medical management.

Defining clinically significant improvement in symptoms is a critical step in translating QOL research to clinical care. One-half of an SD from baseline symptoms has been deemed a universally detectable change in symptoms across disease processes and has been applied to CRS QOL investigations.[4,16] This definition allows for building logistic models and defining research outcomes, but is challenging to articulate to patients. Other studies have found that 0.8 in a single symptom on the SNOT-20[17] or 10 points on the total SNOT-22 score[5] represents a minimally clinically detectable change based on comparisons to patient-reported transition scales. We elected to define "success" as complete resolution of symptoms to avoid any concern over establishing what is meant by "clinically" meaningful. Our

TABLE 4. Improvement in mean cardinal symptom scores over time*

Cardinal symptoms	Baseline	Follow-up	Improvement	*p*
Total cohort (n = 342)				
"Thick nasal discharge"	3.0 (1.5)	1.6 (1.5)	−1.4 (1.7)	<0.001
"Facial pain/pressure"	2.6 (1.5)	1.3 (1.4)	−1.3 (1.5)	<0.001
"Sense of smell/taste"	2.8 (1.8)	1.9 (1.7)	−1.0 (1.8)	<0.001
"Blockage/congestion of nose"	3.5 (1.4)	1.8 (1.5)	−1.7 (1.9)	<0.001
Medical management (n = 69)				
"Thick nasal discharge"	2.9 (1.5)	2.2 (1.6)	−0.6 (1.4)	0.001
"Facial pain/pressure"	2.3 (1.7)	1.8 (1.7)	−0.5 (1.2)	0.002
"Sense of smell/taste"	2.8 (1.8)	2.3 (1.9)	−0.5 (1.9)	0.044
"Blockage/congestion of nose"	3.2 (1.5)	2.6 (1.6)	−0.6 (1.8)	0.009
Endoscopic sinus surgery (n = 273)				
"Thick nasal discharge"	3.0 (1.4)	1.5 (1.5)	−1.6 (1.7)	<0.001
"Facial pain/pressure"	2.7 (1.5)	1.2 (1.4)	−1.5 (1.5)	<0.001
"Sense of smell/taste"	2.9 (1.8)	1.8 (1.7)	−1.1 (1.8)	<0.001
"Blockage/congestion of nose"	3.6 (1.3)	1.6 (1.4)	−2.0 (1.7)	<0.001

*Values are mean (SD).
SD = standard deviation.

TABLE 5. Comparison of average and relative score improvement between treatment modalities

	Medical management (n = 69)		Endoscopic sinus surgery (n = 273)		
Cardinal symptoms	Improvement mean (SD)	Relative improvement (%)	Improvement mean (SD)	Relative improvement (%)	*p*
"Thick nasal discharge"	−0.6 (1.4)	24.1	−1.6 (1.7)	50.0	<0.001
"Facial pain/pressure"	−0.5 (1.2)	21.7	−1.5 (1.5)	55.6	<0.001
"Sense of smell/taste"	−0.5 (1.9)	17.9	−1.1 (1.8)	37.9	0.007
"Blockage/congestion of nose"	−0.6 (1.8)	18.8	−2.0 (1.7)	55.6	<0.001

SD = standard deviation.

standard of complete resolution of symptoms, although an extremely high standard, carries no ambiguity, and allows for determination of OR between treatment modalities (Table 7). These ORs are easily articulated to patients and help translate CRS outcomes research to clinical care when counseling patients with CRS. An important caveat to these ORs is that they were derived from a sampling of patients spanning several academic referral centers and care should be taken when applying these findings to individual patients. Furthermore, our regression models were built to isolate the impact of treatment modality on outcomes, not to identify other clinical factors which could potentially skew the probability of success for an individual.

The present study represents the largest prospective cohort study to investigate the impact of different therapies on the cardinal symptoms of CRS. The current available literature investigating individual symptom scores is dominated by smaller cohort studies at single institutions. A meta-analysis of these prior studies demonstrated that ESS successfully improves all cardinal symptoms.[8] Interestingly, patient-reported olfactory dysfunction improved less than the other cardinal symptoms. The shortcomings of available interventions for olfaction may result from an irreversible olfactory neuron end-organ damage that has been described in the presence of long-standing inflammation.[18] Recovering durable olfactory function may require more than just control of inflammation in patients with impaired olfaction using available treatment modalities. The focus of this study was to investigate patient-based clinical responses to different treatment modalities because quantifiable, objective measures of olfaction are cost prohibitive and rarely employed in standard clinical practice for this patient population. Additionally, subjectively measured olfaction correlates only weakly with objective measures of olfaction

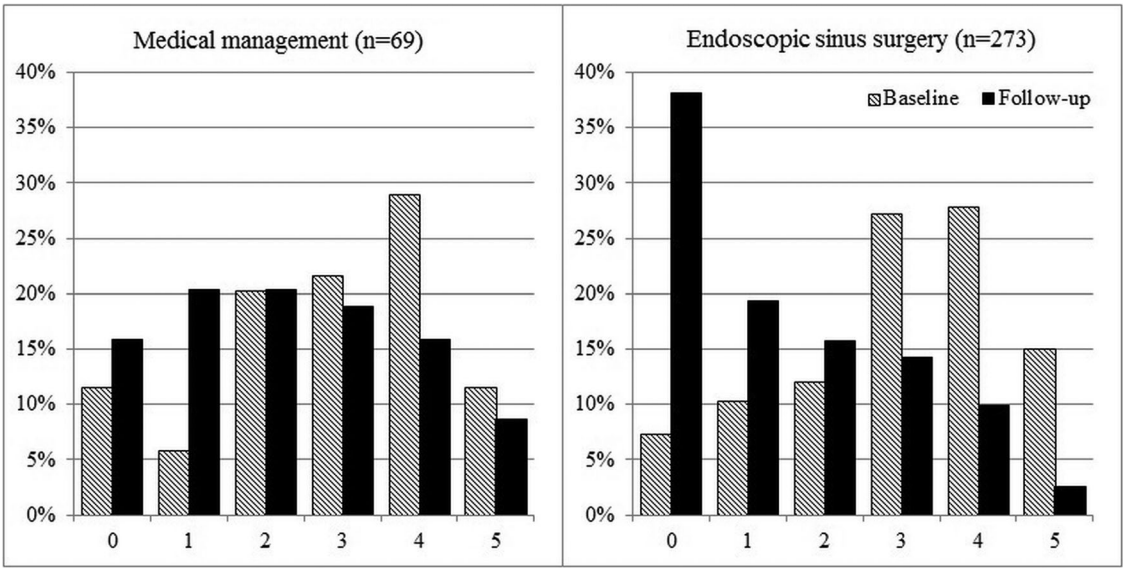

FIGURE 2. Frequency of symptom scores for SNOT-22 item "Thick nasal discharge."

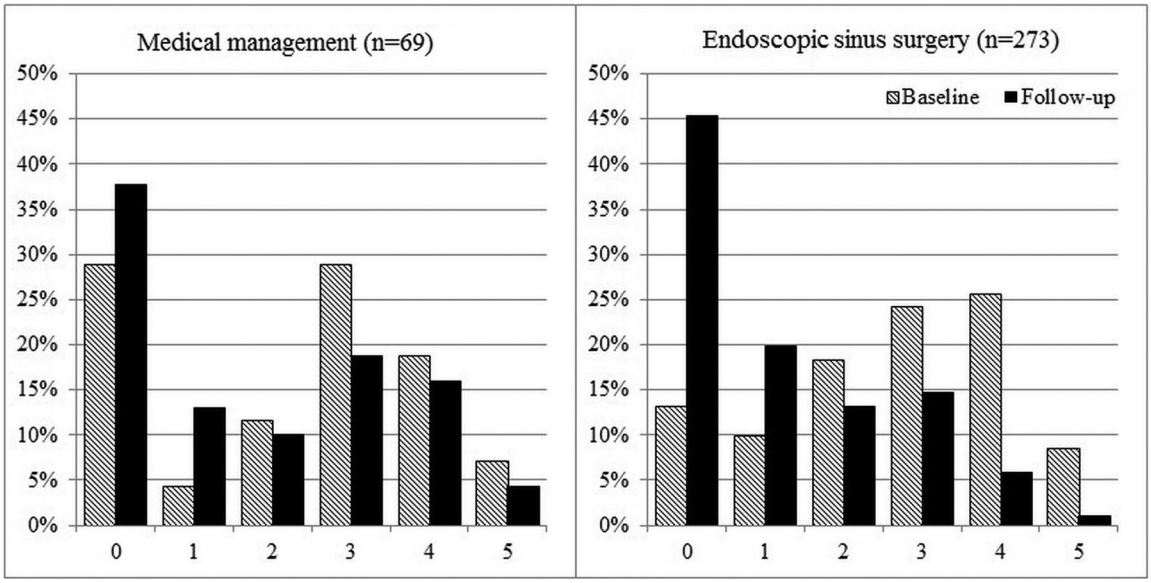

FIGURE 3. Frequency of symptom scores for SNOT-22 item "Facial pain/pressure."

and is neither highly sensitive nor specific in detecting olfactory loss when compared to subjective olfaction.[19] Prior evaluation of objective olfactory outcomes, in a subset of the present cohort, found that only about 40% of subjects regain olfaction.[12] Similarly, subjects with CRSwNP were more likely to regain sense of smell and taste, which may reflect the impairment of odorant conduction in this subgroup. Prior study has also demonstrated that nasal polyposis is associated with greater olfactory gains.[19] Patients with CRS should have cautious expectations about recovering olfactory function after either medical or surgical management.

Prior study has identified that baseline QOL scores can be a significant predictor of patient-elected treatment modality.[9] In fact, baseline QOL scores predicts treatment selection better than perceived social support, patient personality profile, and physician-patient relationship. Patients are driven by symptoms to elect surgical management yet we do not understand the differential effects of medical and surgical therapy on symptom-specific scores and if these differentials in treatment efficacy parallel the symptoms driving patients to elect surgery. The concern would be that a patient electing surgical therapy over ongoing medical therapy in the hopes of improving a particular symptom might assume that all CRS patients have the same likelihood of improving. Indeed, subjective improvement of smell/taste is no more likely to improve with ESS than continued medical management. Although there is great convenience and value to comparing aggregate scores at a population level, a greater degree of transparency adds important clinical

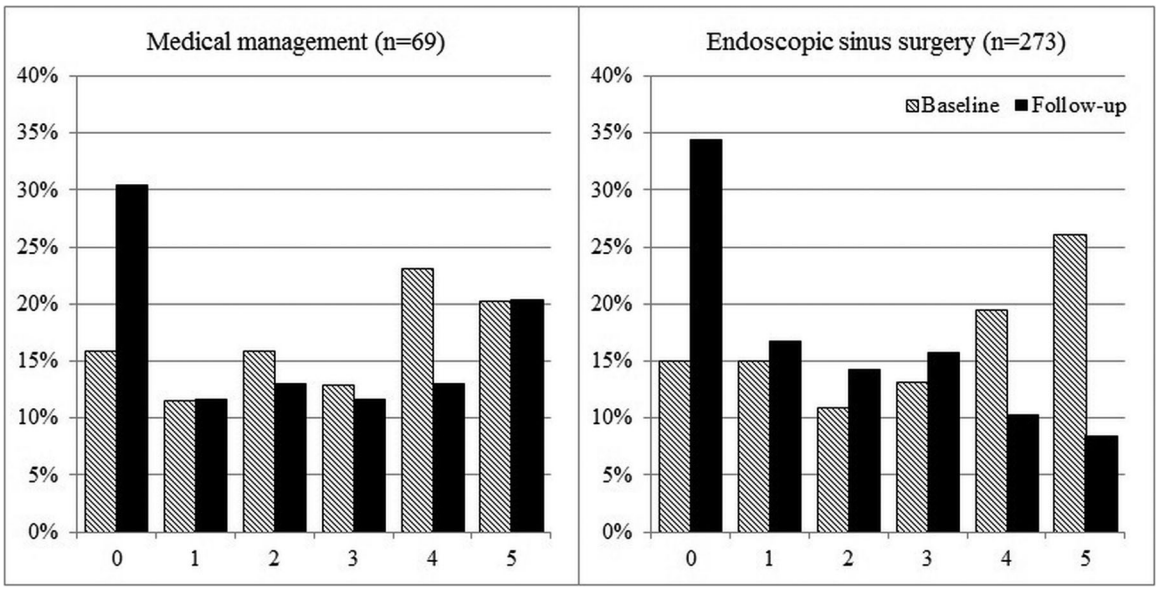

FIGURE 4. Frequency of symptom scores for SNOT-22 item "Sense of smell/taste."

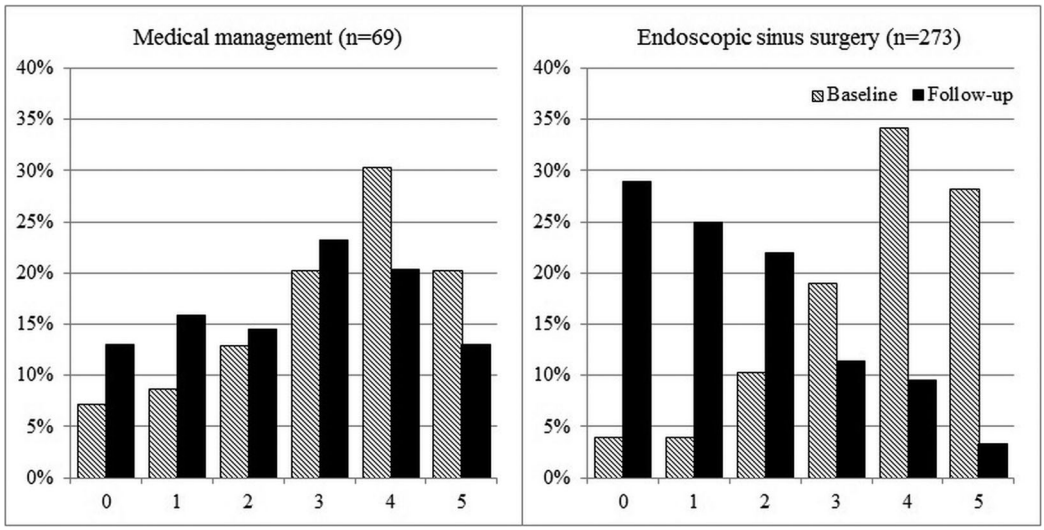

FIGURE 5. Frequency of symptom scores for SNOT-22 item "Blockage/congestion of nose."

value. We elected to examine the cardinal symptoms of CRS because current guidelines[1] have highlighted these as diagnostic criteria; however, future studies illuminating other symptoms associated with treatment selection and differential improvement after treatment would similarly add value to clinical decision-making.

The present study has some important limitations that warrant discussion. The ability of patients to self-select ongoing medical therapy or surgical intervention, with physician guidance, introduces a possible source of treatment selection bias. This is inherent to the study design and ideally would be avoided through a strict randomization process. There are some important factors that preclude randomizing study participants that have been discussed elsewhere.[20] In short, after failing typical medical management many patients may be reluctant to enroll in a study where chance alone would determine if a surgical procedure is performed. The differential enrollment rate (20.2% vs 79.8%) between treatment cohorts reflects this potential bias with study subjects having already failed "maximal" medical management. Despite the lack of randomization, we were able to identify and account for significant confounders between the 2 cohorts through regression modeling procedures. Additionally, a subset of the originally enrolled medical cohort elected to cross over from medical therapy to surgical treatment. These subjects likely crossed over to surgical management because of a failure to achieve QOL gains; therefore, by excluding crossover subjects from analysis in the medical cohort there is an introduction of bias that favors medical therapy. Regardless, the data favor surgical management; thus we did not pursue further analysis of the crossover cohort. Finally, the observational nature

TABLE 6. Comparison of complete symptom resolution frequency between treatment modalities*

	Medical management	Endoscopic sinus surgery	*p*
Total cohort			
"Thick nasal discharge" (n = 324)	8 (12.1)	89 (34.5)	<0.001
"Facial pain/pressure" (n = 292)	8 (15.7)	92 (38.2)	0.002
"Sense of smell/taste" (n = 305)	12 (20.0)	66 (26.9)	0.270
"Blockage/congestion of nose" (n = 333)	8 (11.8)	71 (26.8)	0.009
CRSwNP			
"Thick nasal discharge"	3 (11.5)	35 (34.3)	0.029
"Facial pain/pressure"	2 (6.9)	41 (47.1)	0.004
"Sense of smell/taste"	1 (4.0)	24 (23.8)	0.026
"Blockage/congestion of nose"	3 (11.1)	33 (32.0)	0.032
CRSsNP			
"Thick nasal discharge"	5 (12.5)	54 (34.6)	0.006
"Facial pain/pressure"	6 (18.8)	51 (33.1)	0.109
"Sense of smell/taste"	11 (31.4)	42 (29.2)	0.793
"Blockage/congestion of nose"	5 (12.2)	38 (23.5)	0.137

*Values are n (%).
CRSsNP = chronic rhinosinusitis without nasal polyposis; CRSwNP = chronic rhinosinusitis with nasal polyposis.

TABLE 7. Logistic regression findings for endoscopic sinus surgery to result in resolution of cardinal symptoms compared to continued medical management

Cardinal symptom resolution	Unadjusted OR	Adjusted OR	95% CI	*p*	H-L χ^2
"Thick nasal discharge"	3.82	4.36[a]	1.90–10.04	0.001	3.03*
"Facial pain/pressure"	3.32	3.56[b]	1.48–8.55	0.005	8.00*
"Sense of smell/taste"	1.48	1.50[c]	0.69–3.24	0.306	10.70*
"Blockage/congestion of nose"	2.75	2.76[d]	1.24–6.13	0.013	12.24*

[a]Adjusted for significant independent predictors ($p < 0.050$) including: age, enrollment site, previous sinus surgery, and baseline SNOT-22 item score.
[b]Adjusted for significant independent predictors ($p < 0.050$) including: enrollment site, previous sinus surgery, nasal polyposis, COPD, and baseline SNOT-22 item score.
[c]Adjusted for significant independent predictors ($p < 0.050$) including: enrollment site, previous sinus surgery, and baseline CT score.
[d]Adjusted for significant independent predictors ($p < 0.050$) including: age, previous sinus surgery, and nasal polyposis.
*H-L χ^2 tests indicate adequate goodness-of-fit for all models ($p > 0.050$).
CI = confidence interval; COPD = chronic obstructive pulmonary disease; CT = computed tomography; H-L = Hosmer-Lemeshow test statistic; OR = odds ratio; SNOT-22 = 22-item Sino-Nasal Outcome Test.

of the study precludes tight control over medical therapies and surgical philosophies between sites and patients. By allowing for this heterogeneity this data reflects a more "real world" milieu providing greater external validity of these findings to other tertiary referral centers.

Conclusion

Surgical intervention was found to be more effective at resolving thick nasal discharge, nasal obstruction, and facial pain/pressure than continued medical therapy in patients with CRS. Patient-reported sense of smell/taste showed no differential improvement between medical and surgical cohorts with the exception of the CRSwNP subjects on subgroup analysis. Subjects electing surgical intervention were more likely to have worse aggregate baseline QOL scores than subjects electing continued medical management. Further investigation into which symptoms motivate patients to elect surgical therapy would help elucidate which symptoms patients are trying to resolve by electing surgical interventions. Coupled with further study of the other symptoms classically associated with CRS, a profile of what symptoms are best treated surgically could help guide both physicians and patients in selecting the ideal treatment modality.

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Does time to endoscopic sinus surgery impact outcomes in Chronic Rhinosinusitis? Prospective findings from the National Comparative Audit of Surgery for Nasal Polyposis and Chronic Rhinosinusitis*

C. Hopkins[1], J. Rimmer[2], V.J. Lund[2]

[1] ENT Dept., Guy's and St Thomas' Hospitals, London, United Kingdom
[2] Royal National Throat, Nose and Ear Hospital, London, United Kingdom

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Abstract

Objectives: Patients with chronic rhinosinusitis refractory to medical management undergo elective surgery. The time from initial diagnosis to surgery varies considerably. The impact of this delay on surgical success has never previously been evaluated.

Design: First-time patients within the National Comparative Audit of Surgery for Nasal Polyposis and Chronic Rhinosinusitis were grouped based on time to surgery: 1) Early cohort: < 12 months; 2) Mid cohort: 12-60 months; and 3) Late cohort: > 60 months. Co-morbidities and preoperative CT scores were analysed for all patients.

Main outcome measures: The 22-item Sino-Nasal Outcome Test scores (SNOT-22) were collected at 0, 3, 12 and 60-months. Absolute and relative SNOT-22 changes from baseline were evaluated.

Results: Asthma and allergies were significantly more prevalent in the Late versus the Early and Mid-cohorts. In addition, patients in the Late cohort had greater symptom burden on the SNOT-22 and more extensive preoperative radiographic disease as determined by Lund-Mackay (LM) scores. SNOT-22 scores demonstrated greater percentage improvements in the Early versus the Mid- and Late cohorts, at all time points after surgery. At 12 and 60 months after surgery, significantly more patients in the Early group achieved a clinically important change in SNOT-22 scores compared with the other groups. These differences were maintained when cohorts were matched for preoperative co-morbidities.

Conclusion: Patients with asthma and/or allergies are more likely to experience delayed surgical intervention versus other patients. Overall, patients with delayed surgery reported less improvement in SNOT-22 scores than patients treated at earlier time points, regardless of co-morbid status. Delaying surgical intervention may worsen long term clinical outcomes.

Key words: sinusitis, outcomes, sinus surgery

Introduction

Chronic rhinosinusitis (CRS) is a common condition with a prevalence estimated at 10.9% (range 6.9 – 27.1%)[1]. It has significant impact on quality of life [2] and socio-economic burden, with costs per year in the US estimated to be between $4.3 and $5.8 billion [3]. Widely held consensus mandates a trial of maximum medical therapy as the first line of treatment, with surgical intervention reserved only for cases refractory to medical management. The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) suggests a number of therapies, including steroid (topical or oral), antibiotics and/or saline irrigation, for at least 12 weeks [4]. Failure of medical therapy may thereafter lead

to surgery. However, there is little in the literature to inform on the optimum timing of surgical intervention beyond that failed three-month time window.

Smith et al. [5, 6] in a prospective, non-randomized multi-centered cohort study, offered CRS patients refractory to medical therapy either continued medical management or endoscopic sinus surgery according to patient and surgeon preference. While this inherently introduces bias to the study, this design provides an appropriate reflection on the decision-making process that patients and surgeons may face at time of failed medical therapy. 34% of the medical management arm did not improve and further worsened within three months of entering the study, and then crossed over into the surgical treatment arm. While these patients experienced significant improvements in patient rated symptom scores, at 12 months' follow-up they had failed to achieve the same level of symptomatic improvement as the cohort who had undergone surgery ab initio. Perhaps delaying surgical intervention may adversely affect outcome in refractory patients. We hypothesise that untreated chronic sinusitis is a progressive disease, and with time patients may develop irreversible changes within the sinus mucosa [7]. Early successful treatment may prevent the development of such adverse prognostic characteristics.

In this study, we evaluated whether the duration of symptoms of chronic rhinosinusitis prior to timing of surgical intervention has any impact on the effectiveness of surgery, in terms of symptomatic outcomes. Our hypothesis was that patients with CRS ongoing over a long period of time would be less responsive to surgery than patients treated early on in the natural history of the disease, in terms of a reduction in self-reported outcomes scores.

We could find no evidence in the published literature regarding either the symptomatic or cost effectiveness of surgical interventions at different times after the development of symptoms, and thus performed this study to address these questions. We evaluated patient-reported symptomatic improvements that had been collected prospectively from the National Comparative Audit of Surgery for Nasal Polyposis and Chronic Rhinosinusitis, grouping patients undergoing primary surgery at different time points during the course of their disease. The study methodology and overall results from the Comparative Audit have been previously described [8]. However, analysis of results based on patient time to surgery is shown here for the first time.

Materials and methods

Study design

The National Comparative Audit of Surgery for Nasal Polyposis and Chronic Rhinosinusitis – a prospective, observational cohort study of 3,128 patients undergoing sinus surgery for CRS in 87 NHS Trusts in England and Wales – has been previously described [8] and included data of patients who underwent mostly maxillary and anterior ethmoidal surgery. The main outcome measure was the Sino-Nasal Outcome Test 22 (SNOT-22), a validated patient reported outcome measure [9]. Patients completed the SNOT-22 surveys preoperatively on the day of surgery (baseline) and at 3, 12 and 60 months after surgery.

Setting

All 156 NHS Trusts in England and Wales were invited to participate to the Audit. A total of 87 centres contributed patients to the study.

Patient inclusion and cohorts

Patient eligibility criteria and overall selection was described previously [8]. For this analysis, only patients undergoing primary surgery were considered, and therefore 1606 patients (51%) with a prior history of surgery were excluded. Remaining patients who had completed a pre-operative SNOT-22 score were included in this analysis (29 patients were excluded as the baseline SNOT-22 score was missing). Patients were asked to report "How long ago did your nose/sinus symptoms begin". Three cohorts of patients were defined, based on the length of time from onset of sinus symptoms to surgery, as reported by the patient: Early cohort - less than 12 months; Mid cohort - 12-60 months; and Late cohort - more than 60 months of symptoms.

Analyses

Patient demographics were analysed for each group to identify any potential confounding factors. Disease severity was estimated based on average preoperative Lund Mackay (LM) scores, for all cases where computed tomography (CT) scans were available.

Variables

Average SNOT-22 scores at each time point were obtained from all patients as previously described, and were calculated and compared to baseline. As rates of asthma were found to be higher in the Late cohort, calculations were repeated after excluding patients with asthma across all groups, to test for a potential confounding effect of this co-morbidity. Similarly, allergies were overly preresented in mid and late cohorts, and calculations were repeated having further excluded patients reporting allergies. The minimally clinically important difference (MCID) in SNOT-22 has been shown to be 8.9. This was used to dichotomise the cohort into two groups; those with improvement in SNOT-22 greater than 8.9, and those failing to achieve this. The percentage of patients achieving the MCID was calculated for each group. Finally, a multiple linear regression was performed to simultaneously control for other demographic

and operative variables (pre-operative SNOT-22, LM score, age, gender, asthma, allergy and extent of surgery) on the SNOT-22 end point at 60 months.

Statistical analyses

All statistical analyses were performed on STATA (StataCorp. 2003. Stata Statistical Software: Release 8. College Station, TX: StataCorp LP). Paired t-tests were used to analyse difference in pre- and post-operative scores within groups (significance $\alpha = 0.05$). One-way analysis of variance (ANOVA) (unequally sized groups) was used to calculate p values of the differences in absolute pre- and post-operative SNOT-22 scores, at all post-operative time points and between all 3 groups. Chi-squared tests of association were used to analyse dichotomized variables.

Results

A total of 1,493 patients were included in the evaluation, 172 in the Early cohort, 750 in the Mid cohort and 571 in the Late cohort. Response rates declined at each follow-up point. Complete SNOT-22 surveys were available for 80% of patients at 3 months, 78% at 12 months, and 49% at 60 months (Table 1). Patient demographics and clinical presentation at baseline are shown in Table 2. There was a possible association between duration of symptoms and disease severity with patients in the Late cohort showing greater LM scores versus patients in the Early cohort (Late cohort 11.1; Early cohort 9.6; $p = 0.05$). Similarly the SNOT-22 scores of patients in the late cohort were also significantly greater than that of patients in the Early cohort (Late cohort 40.8; Early cohort 35.8; $p < 0.006$). There was also a significantly greater percentage of patients with asthma and allergies in the Late cohort compared to the Early cohort (Asthma: Late cohort 36.6%, Early cohort 20.1%, $p = 0.02$; Allergies: Late cohort 39.2%, Early cohort 23.1%, $p < 0.001$).

Table 1. Response rates for cohort and by duration of symptoms.

Follow-up \ Cohort	All patients	Early Cohort: < 12 months	Mid Cohort: 12 – 60 months	Late Cohort: > 60 months
Baseline n	1493	172	750	571
3 months n (% baseline)	1200 (80.4)	144 (83.7)	602 (80.3)	454 (79.6)
12 months n (% baseline)	1177 (78.9)	130 (75.6)	594 (79.2)	453 (79.3)
60 months n (% baseline)	734 (49.2)	81 (47.1)	375 (50)	278 (48.7)

Table 2. Patient demographics by duration of symptoms (CRSwNP – CRS with nasal polyps).

	Early Cohort: < 12 months	Mid Cohort: 12 – 60 months	Late Cohort: > 60 months
Age	52.0	48.6	49.8
% Male	64.5	59.8	59.9
% asthmatic	20.1	28.8	36.6
% smokers	22.6	22.4	17.9
% patient reported allergies	23.1	33.1	39.2
% aspirin sensitivity	0.6	1.6	1.4
% CRSwNP	67.1	60.9	68.4
Polyp grade (%)			
1	20.9	28.4	25.3
2	51.3	38.9	44.3
3	27.8	32.7	30.4
Mean Lund-Mackay Score	9.6	10.2	11.1
Mean SNOT-22	35.8	39.7	40.8

All patient groups demonstrated improvement in SNOT-22 scores at all time points post-operatively. The average SNOT-22 by time point and cohort and the percentage changes in SNOT-22 are shown in Table 3.

Preoperatively, the average SNOT-22 scores ranged from 35.3 (all patients) or 33.7 (patients with asthma excluded) in the Early group to 40.8 (all patients) or 40.6 (patients with asthma excluded) in the Late group. Post-operatively, there was a significant decrease in average SNOT-22 scores across all patient groups (paired T test, $p < 0.001$ for each group compared to baseline at each time point). Mean SNOT-22 scores were lowest at all time points in the Early cohort versus the Mid and Late cohorts (Table 3). To determine whether changes were simply a reflection of preoperative status, absolute and percentage change from baseline were also calculated. The range of absolute score changes from baseline across all three cohorts was surprisingly narrow, from an average 18.6 points in the Early group to 17.3 in the Late group, with no significant difference between groups. This range remained narrow at 12 months post-operatively but broadened at 60 months, with the Late cohort showing signs of increasing SNOT-22 scores (mean absolute score change 16.8 for Early Cohort and 11.7 for Late Cohort). Percentage changes from baseline were greater for the Early cohort than the Late cohort at all time points. This reached statistical significance ($p < 0.005$)

Table 3. Absolute values for SNOT-22 at each time point, actual change in SNOT-22 score from baseline, and percentage change from baseline, by duration of symptoms. Repeated analysis after excluding asthmatic patients shown in italics. One way analysis of variance used to test for difference between groups for total value and absolute change in score. (Change score calculated only for patients with paired data, and therefore differs slightly from simple difference in means at each time point. Percentage change calculated for each individual – mean percentage change is then reported, not the percentage change of the difference in means).

Duration of symptoms before surgery	n	Mean Pre-op SNOT-22 (SE)	Mean 3 month SNOT-22 (SE)	Mean 12 month SNOT-22 (SE)	Mean 60 month SNOT-22 (SE)	Mean Change in SNOT-22 at 3 months (SE)	Change in SNOT-22 at 12 months	Change in SNOT-22 at 60 months	% Change in SNOT-22 at 3 months (SE)	% Change in SNOT-22 at 12 months	% Change in SNOT-22 at 60 months
< 12 months	172	35.3 (0.7)	18.0 (1.6)	19.5 (1.8)	19.7 (2.2)	18.6 (1.8)	17.2 (1.8)	17.3 (2.1)	43.5 (5.7)	43.3 (6.0)	46.1 (5.9)
	139	*33.7*	*18.2*	*19.9*	*17.3*	*17.2*	*15.7*	*18.2*			
12 – 60 months	750	39.7 (0.8)	22.9 (0.8)	24.9 (0.9)	25.0 (1.0)	17.3 (0.8)	15.2 (0.9)	13.6 (1.1)	39.4 (2.2)	34.1 (2.4)	28.2 (3.3)
	567	*38.7*	*21.7*	*23.0*	*23.5*	*17.4*	*15.7*	*13.9*			
> 60 months	571	40.8 (0.5)	24.4 (0.9)	26.3 (1.0)	28.2 (1.2)	17.3 (0.9)	14.5 (0.9)	11.7 (1.3)	37.0 (3.1)	30.8 (4.3)	16.6 (5.6)
	406	*40.6*	*24.8*	*25.9*	*28.4*	*17.2*	*14.7*	*11.9*			
One-way ANOVA		F = 5.2 p< 0.006	F = 5.9 p< 0.003	F = 5.1 p< 0.006	F = 6.0 p< 0.002	F = 0.27 p = 0.64	F = 0.90 p = 0.29	F = 2.37 p = 0.49	F = 0.66 p = 0.5	F = 1.42 p = 0.24	F = 5.18 p< 0.005

at 60 months (Early 46.1%, Mid 28.2%, Late 16.6%). While improvements were maintained from 12 to 60 months in the Early cohort, a progressive deterioration of symptom scores findings are shown visually in Figure 1, which demonstrates increasing divergence as the follow-up period after surgery increases.

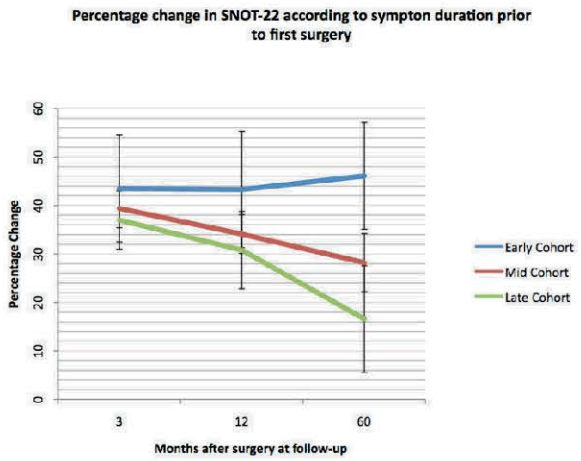

Figure 1. Percentage change in SNOT-22 for each cohort at 3,12 and 60 months (95% confidence intervals shown).

Repeating the analyses above but excluding asthmatic patients demonstrated the same pattern of results, suggesting that the higher rates of asthmatic patients in the Late cohort did not confound the results (Table 3, results shown in italics). Further exclusion of patients with allergies did not result in a change in the pattern of results. At 60 months there was a 59.0% improvement in SNOT-22 score from baseline in the early group, 35.6% in the Mid Cohort, and 31.6% in the late cohort.

The percentage of patients achieving at least an 8.9-point difference in SNOT-22 score from preoperative to post-operative time points (the MCID) is shown in Table 4. At 3 months post-operatively, 75.0%, 74.5% and 75.4% of patients in the Early, Mid and Late cohorts reached the MCID, respectively (p = 0.971). At 12 months, however, 78.0% of the Early cohort maintained a MCID in pre-post SNOT-22 scores versus 70.8% and 70.5% in the Mid and Late cohorts respectively, and by 60 months, 71.5% of the Early cohort versus 57.3% of the Mid and 53.0% of the Late cohort reached the MCID – this difference was significant (p = 0.028).

Multivariate regression confirmed that duration of symptoms to surgery remained an important predictor of post-operative outcomes when other demographic factors (pre-operative

Table 4. Percentage of patients achieving MCID by symptom duration.

Cohort / Follow-up	Chi² test for difference between groups	Early Cohort: < 12 months	Mid Cohort: 12 – 60 months	Late Cohort: > 60 months
		% patients achieving MCID of 8.9		
3 months	p = 0.971	75.0	74.5	75.4
12 months	p = 0.05	78.0	70.8	70.5
60 months	p = 0.028	71.2	57.3	53.0

SNOT-22, LM score, age, gender, asthma and allergy) and extent of surgery were controlled for (at 12 months post-operatively $\beta = 2.67$, $p = 0.03$; at 60 months post-operatively $\beta = 3.59$, $p = 0.05$).

Discussion

With austerity measures becoming widespread, there is a drive to manage referral pathways, with the potential to restrict access to secondary care and surgical management. This is likely to both reduce and delay referrals, with many commissioning guidelines insisting on prolonged trials of medical therapy in primary care. While these measures may have an immediate budgetary impact, it is important to carefully consider the consequences of such decisions on patients' quality of life and future treatment success, as long-term treatment costs and lost productivity may outweigh short-term gains.

In this study, we evaluated whether the clinical benefits of sinus surgery varied according to the duration of CRS symptoms prior to surgery in patients treated either within 12 months of symptom onset (Early cohort), between 12-60 months of symptoms (Mid cohort) or more than 60 months from first symptoms (Late cohort). Clinical benefits were calculated based on post-operative quality of life outcome scores, using a validated instrument for sinusitis (SNOT-22 scores). Our results indicate that absolute SNOT-22 scores were significantly lower in the Early cohort at all pre- and post-operative time points versus those of the Mid and Late cohorts. Percentage changes in scores between groups from preoperative to post-operative time points demonstrated a significant trend of greater change for patients in the Early cohort as duration of follow-up increased. In addition, when analysing the percentage of patients reaching the MCID for SNOT-22, there was a significantly greater proportion of patients in the Early and Mid cohorts reaching the MCID compared with the Late cohort at 12 and 60 months post-operatively. Our results therefore suggest that intervention within 12 months of the onset of symptoms may yield better clinical outcomes in terms of patient-reported quality of life, at least as far as 5 years post-surgery.

Recent guidelines recommend that surgery should be considered if a 3 month trial of medical treatment fails to bring about adequate improvement in symptom levels [4]. However, based on the National Comparative Audit data analysed herein, in the UK 88.2% of patients have symptoms for one year or more prior to first-time surgery, and 38.2% of the cohort are symptomatic for more than 5 years. We do not know for how long these patients have been receiving medical treatment for their sinusitis, but it is likely that the 3-month period recommended by the EPOS 2012 Guidelines [4] for medical management is far exceeded in the vast majority of cases.

Preoperatively, patients in the Early cohort had statistically, but not clinically, lower average SNOT-22 scores compared to the Mid and Late cohorts. The average difference in SNOT-22 scores between the Early and Late cohort was 5.0 points and as described previously, the MCID for SNOT-22 is 8.9 points. Therefore, while the Early cohort may have scored lower on the SNOT-22, their perception of symptoms was not clinically different from that of patients in the Mid and Late cohorts. Patients in the Early cohort also had less severe radiological disease, as shown by the LM score. While the LM score does not necessarily correlate with subjective, patient-reported symptoms, it is a meaningful indicator of disease severity and has been shown to be associated with post-operative outcome [10]. There is little published regarding the natural history of CRS, but our results, demonstrating increasing preoperative SNOT-22 and LM scores from the Early to Mid and Late cohorts, suggest that both radiological and symptomatic disease severity increases with prolonged duration of symptoms.

Following surgery, all patients experienced significant symptomatic improvement as shown by the SNOT-22. This finding is consistent with other recent studies demonstrating the effectiveness of sinus surgery [6]. Patients treated within 12 months of symptom onset had, on average, statistically lower post-operative SNOT-22 scores versus the other cohorts, at all post-operative time points. In addition, the procedure was found to have a durable effect, especially in the Early cohort where more than 70% of patients maintained a clinically significant improvement from baseline as far as 60 months post-operatively. In the Late cohort, although 75% of patients obtained a clinically significant improvement from surgery as determined 3 months post-operatively, this number gradually decreased to 53% at 60 months post-operatively. These findings suggest that early intervention may increase durability of the treatment.

Limitations of this study include general methodology limitati-

ons as expected with any audit or registry, i.e. no randomisation was done to ensure that probability of prognosis was equal across all three groups. Therefore, and as discussed above, differences in comorbidity rates across groups need to be considered. We are reliant upon patient reported duration of symptoms, and it is possible that some patients were unable to differentiate symptoms of co-existing allergic rhinitis from those of CRS, both before and after surgery. We have attempted to control for this by repeating our analysis having excluded thise with asthma and allergies, and by performing a multivariate analysis, but some bias may persist. An additional limitation may be related to the outcomes tool; patient-reported outcomes, even validated ones, may have some intrinsic variability and, while still one of the best predictors of patient well being, may differ from clinical or radiographic outcomes. Finally, and as with most observational cohort studies, there was a progressive loss of respondents with time. This is due in part to general loss to follow-up despite 2 attempts with postal questionnaires as well as, in a small number of cases, withdrawal of consent to further contact. However, a nearly 80% response rate was achieved at 12 months, with no difference in drop-out rates between the groups of interest. The greatest differences between groups were found at 60 months, when response rates were at their lowest. There is therefore a risk of bias due to loss to follow-up. Accepting the limitations of this current study, we therefore plan to test the same hypothesis using a second independent patient cohort, the Clinical Practice Research Datalink (CPRD) database.

It is interesting that there were much higher rates of asthma and allergy in the Late cohort. While endoscopic sinus surgery is aimed at relieving sinonasal symptoms, it has also been shown to improve bronchial symptoms and reduce medication use for asthma [11-13], and therefore this group may potentially benefit even more from surgical intervention if medical treatment has failed, when compared with non-asthmatic patients. It is unclear why surgery was delayed in a large proportion of these patients: all patients were considered to be at an American Society of Anaesthesiology (ASA) Physical Status Score grade 2 or less at the time of the surgery so these patients did not have an increased surgical risk. We repeated all analyses without the asthmatic patients, to identify any confounding effects. Not surprisingly, analyses showed similar trends irrespective of whether asthmatic patients were included or excluded. This may be due to the fact that, while asthmatic patients may experience greater healthcare needs and general morbidity, their self-reported perceptions of disease symptoms and benefits from surgery was shown in prior research to be similar to that of non-asthmatic patients [14].

In the consolidated 3,128-patient audit results, pre-operative SNOT-22 scores were found to be the greatest predictor of post-operative outcomes, as patients with higher scores achieved greater absolute reductions in SNOT-22 scores – on average, a halving of their pre-operative score. In our study, however, when patients were subdivided into 3 cohorts based on the preoperative duration of symptoms, the opposite was observed: the Early cohort achieved greater absolute and relative reductions in symptom scores than both the Mid and Late cohorts, despite starting with lower scores. Moreover, the Early cohort's post-operative symptom scores remained low and constant over the entire 5-year post-operative period, whereas progressive decline in improvements was noticed in the other groups, particularly the Late cohort. These results suggest that the maximum and most persistent benefit from endoscopic sinus surgery occurs in patients undergoing surgery at an early stage in their history of CRS disease, in keeping with current guidelines. The multivariable regression analysis further confirmed that preoperative duration of symptoms was an important predictor of surgical outcome. Delays in surgical intervention, where it is indicated, may therefore adversely affect outcome.

There are many possible reasons why earlier surgical intervention improves outcome. Surgery leads to improved ventilation of the sinuses and allows better irrigation and instillation of topical steroids.; it may therefore be that earlier surgery simply allows medical therapy to be more effective. However, surgery may help by removing factors that adversely affect outcome. Bacterial biofilms are known to be associated with CRS, and are thought to contribute to the persistent inflammatory state [15]. Endoscopic sinus surgery has been shown to significantly reduce biofilm density, with associated improvements in QOL and objective outcome measures [16]. Osteitis is associated with more severe inflammation and worse disease severity scores. The natural history of osteitis in CRS in not known, but its presence is associated with an increase in the number of surgical procedures undertaken; further studies are needed to identify whether earlier surgical intervention and removal of diseased bone may prevent disease progression [17]. There is also increasing evidence that irreversible mucosal changes may occur in CRS, in direct correlation to the duration of the disease [18]. Whilst steroids, due to their anti-inflammatory properties, have some effect on this remodeling process, it has been proposed that early surgical intervention to reduce the inflammatory load may be beneficial in preventing disease progression [7].

Whilst we suggest that ongoing untreated sinusitis leads to disease progression with mucosal remodelling and accumulation of adverse features such as biofilms and osteitis, it is possible that prolonged use of topical or systemic medications may also be detrimental to long term outcomes. It is beyond the scope of

the current study to identify the mechanisms behind the differences in outcome; future studies will be needed if our findings are replicated in independent cohorts.

Attempts to reduce healthcare expenditure by restricting access to secondary care should therefore be carefully considered, as such measures may have a negative and lasting impact on patients' ability to experience meaningful improvements from CRS symptoms. While there is a clear ethical consideration in denying relief to these patients, the societal impact of CRS should also be considered against any potential short-term cost-saving measure. Recurrent disease incurs direct costs from ongoing health care utilisation. Indirect costs are likely to be far greater; productivity analyses of patients suffering from CRS have recently been evaluated and shown to be more than 30% lower than that of patients without CRS [19]. In patients with CRS, productivity at work improved by approximately 76% after surgery. Prompt referral allowing correct diagnosis to be reached and a subsequent trial of maximum medical therapy will allow surgical candidates to be identified at an earlier stage than we currently achieve. Improving outcomes from surgery will reduce both direct and indirect long term costs of CRS.

Conclusion

Maximum medical therapy should form the first-line of care for patients with CRS, but both our results and those of Smith et al. [5,6] suggest that when this approach has failed, surgery is best considered without significant further delay. In addition, our study indicates that delaying surgical intervention may reduce both the extent of symptomatic benefit from surgery, and significantly reduce the percentage of CRS patients who experience sustained clinical improvements. Clinical improvement as defined by SNOT-22 was stable in patients treated early on, for at least the 60 months post-operative period reported herein. This is the first published evidence suggesting that delaying endoscopic sinus surgery in CRS patients refractory to medical management may lead to worse clinical outcomes than when surgery is offered at an earlier stage in the history of the disease.

Timely assessment, an appropriate trial of medical therapy and evaluation of the response to treatment will allow us to treat our patients in the time frame recommended by current guidelines [20], while delays in this pathway may be detrimental to long term outcomes.

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Authorship contribution

CH: study design, data analysis, preparation of manuscript
JR: Preparation of manuscript
VJL: study design, editorial input

Conflicts of Interest

None reported

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Claire Hopkins, BM BCh MA (Oxon)
DM FRCS (ORL-HNS)
ENT Dept, Guy's Hospital
London SE1 9RT
United Kingdom

Tel: +44 -20-7188 2215
Fax: +44-20-7188 2206
E-mail address:
clairehopkins@yahoo.com

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ORIGINAL ARTICLE

Health utility outcomes in patients undergoing medical management for chronic rhinosinusitis: a prospective multiinstitutional study

Lauren J. Luk, MD[1], Toby O. Steele, MD[1], Jess C. Mace, MPH[1], Zachary M. Soler, MD[2], Luke Rudmik, MD, MSc[3] and Timothy L. Smith, MD, MPH[1]

Background: **A health utility value represents an individual's preference for living in a specific health state and is used in cost-utility analyses. This study investigates the impact of continuing medical therapy on health utility outcomes in patients with chronic rhinosinusitis (CRS).**

Methods: **The Medical Outcomes Study Short Form-6D (SF-6D) questionnaire was administered to patients prospectively enrolled in a longitudinal study examining treatment outcomes for CRS. Patients were prescribed robust, initial medical therapy and then elected to continue with medical therapy (n = 40) or undergo endoscopic sinus surgery (ESS), followed by medical therapy (n = 152). Patients observed through treatment crossover to ESS were also evaluated (n = 20). Health utility values (SF-6D) were generated at baseline, 6-months, and 12-months follow-up for both cohorts and evaluated using repeated measures analysis of variance (ANOVA).**

Results: **Treatment crossover patients were found to have a significantly higher prevalence of previous sinus surgery compared to medical management ($\chi^2 = 6.91$; $p = 0.009$) and surgical intervention ($\chi^2 = 8.11$; $p = 0.004$) subgroups. Mean baseline utility value for the medical therapy cohort was significantly better compared to the ESS cohort (mean ± standard deviation; 0.76 ± 0.12 vs 0.70 ± 0.15; $p = 0.023$). Significant improvement in health utility was reported in the ESS cohort ($F_{(2)} = 37.69$; $p < 0.001$), whereas values remained stable, without significant improvement, in both the medical therapy cohort ($F_{(2)} = 0.03$; $p = 0.967$) and treatment crossover cohort ($F_{(2)} = 2.36$; $p = 0.115$).**

Conclusion: **Patients electing continued medical management report better baseline health utility compared to patients electing ESS. Patients electing ESS show significant improvement in health utility, whereas those electing continued medical management demonstrate stable health utility over 12 months.** © 2015 ARS-AAOA, LLC.

Key Words:
sinusitis; endoscopy; chronic disease; quality of life; therapeutics; medication therapy management; utility; health utility; cost-effectiveness

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One of the primary factors driving health reform in the United States is the unsustainable yearly increase in healthcare expenditure, currently estimated to be 4%

[1]*Division of Rhinology and Sinus/Skull Base Surgery, Oregon Sinus Center, Department of Otolaryngology–Head and Neck Surgery, Oregon Health and Science University, Portland, OR;* [2]*Division of Rhinology and Sinus Surgery, Department of Otolaryngology–Head and Neck Surgery, Medical University of South Carolina, Charleston, SC;* [3]*Division of Otolaryngology–Head and Neck Surgery, Department of Surgery, University of Calgary, Calgary, Alberta, Canada*

Correspondence to: Timothy L. Smith, MD, MPH, Oregon Health and Science University, Department of Otolaryngology–Head and Neck Surgery, Division of Rhinology and Sinus/Skull Base Surgery, Oregon Sinus Center, 3181 SW Sam Jackson Park Road, PV-01, Portland, OR. 97239; e-mail: smiththtim@ohsu.edu

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of the gross domestic product.[1] In this climate, healthcare providers are challenged to critically evaluate the risk and cost effectiveness of medical and surgical interventions. Economic analyses of quality of life (QOL) outcomes can help decision-makers best allocate limited healthcare resources toward those who would most benefit.

A health state utility value quantifies an individual's perception of his or her current health. These values are used in identifying optimal cost-effective treatments for the management of chronic disease.[2,3] Utility values are useful because they allow the impacts of different diseases to be compared using a common metric.[4] Prior studies have shown patients with chronic rhinosinusitis (CRS) report baseline utility values similar to patients with end-stage renal disease on hemodialysis and moderate asthma.[5,6]

Up to 50% of patients with CRS will fail to improve after initial medical management and will be faced with a decision: to continue with medical therapy or to pursue endoscopic sinus surgery (ESS).[7,8] This decision represents a balance of possible benefits, risks, and monetary concerns. Previous studies show improved health utility in patients with refractory CRS after ESS.[6,9] The literature also supports the long-term cost-effectiveness of ESS over continued medical management in these patients.[1,5] However, no prior studies have reported the specific trend of health utility values in patients with CRS who elect continued medical management instead of surgical intervention. An improved understanding of the longitudinal health state utility outcomes in patients choosing to continue with medical therapy would aid in decision-making.

The primary purpose of this study is to measure baseline and follow-up utility values using the Medical Outcomes Study Short Form-6D (SF-6D) instrument in patients with CRS who elect continued medical management. Data for patients who elected surgical management was also collected for comparison. We hypothesize that patients who elect continued medical management for CRS have higher baseline health utility when compared to patients who elect surgical management for CRS. This study expands on previously published data to characterize health utility in patients electing medical management for CRS and provides a basis for future economic modeling in cost-effectiveness research.

Patients and methods

Patient population

Study patients (≥18 years of age) were recruited from the Oregon Sinus Center at Oregon Health and Science University (OHSU, Portland, OR), Stanford University (Palo Alto, CA), the Medical University of South Carolina (MUSC, Charleston, SC), and the University of Calgary (Calgary, Alberta, Canada) as part of a continuing, observational, prospective cohort investigation to assess outcomes of various treatment modalities for CRS. Preliminary findings from this cohort study are readily available through published literature.[10–14] All patients were diagnosed with medically refractory CRS and met criteria endorsed by the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS2012) and the American Academy of Otolaryngology.[15,16] Refractory CRS was defined as patients having persistent symptoms of CRS despite maximal medical therapy and were considered candidates for ESS. For this study, maximal medical therapy included at least 1 course (>14 days) of broad-spectrum or culture-directed antibiotic therapy and at least 1 course of topical corticosteroid (>21 days) or a 5-day course of systemic corticosteroid therapy.

Patients were interviewed during an initial enrollment meeting and considered study participants after providing informed consent in English and agreeing to complete all baseline study evaluations. The Institutional Review Board at each academic enrollment site granted study approval and annual review of protocol safety, potential adverse events, and enrollment progression. Central study coordination was conducted at OHSU (eIRB #7198) by the Principal Investigator (T.L.S.). Participants were assured study involvement was completely voluntary and in no way altered the standard of care for their chosen treatment modality. Study participants were followed for 12-month duration with observational, follow-up evaluations at 6-month intervals, either during routine, physician-directed clinical appointments or via follow-up mailings using the U.S. Postal Service with self-addressed return envelopes.

Exclusion criteria

Because of differences in disease etiologies and potential variability in medical treatment regimens, study participants with exacerbations of other comorbid conditions, including recurrent acute rhinosinusitis, cystic fibrosis/ciliary dyskinesia, autoimmune disorders, or steroid dependency (eg, asthma, sinusitis), were excluded. Study participants were also excluded if they had not yet entered the initial follow-up appointment window (≤6 months) or completed baseline and follow-up evaluations at the appropriate time intervals.

Treatment modality

Prior to any study enrollment meeting and following physician-directed counseling, patients self-selected subsequent treatment. Patients elected to either continue physician-directed medical management or to pursue ESS directed by the intraoperative clinical judgment of the enrolling physician at each site. Study patients were categorized into 1 of 3 treatment arms including a medical management cohort, surgical treatment cohort, and a treatment crossover cohort of patients initially electing medical therapy who elected to change treatment modality to include ESS at some point during the duration of the study period. Surgical intervention consisted of either unilateral or bilateral maxillary antrostomy, partial or total ethmoidectomy, sphenoidotomy, middle turbinate resection or

inferior turbinate reduction, septoplasty, or frontal sinusotomy procedures with judicious use of image guidance.

Clinical measures of disease severity

Standard clinical measures of disease severity, collected during initial clinical evaluations, were used simultaneously for investigational purposes. High-resolution computed tomography (CT) with bone and tissue windows was used to evaluate sinonasal disease severity using 1.0-mm contiguous images in both sagittal and coronal planes. Images were also staged by each enrolling physician in accordance with the semiquantitative Lund-Mackay bilateral scoring system (score range, 0–24) that quantifies the severity of image opacification in the maxillary, ethmoidal, sphenoidal, ostiomeatal complex, and frontal sinus regions using a Likert scale.[17] Follow-up CT evaluations were not routinely collected per the standard of care.

The paranasal sinuses were also evaluated bilaterally using rigid, fiber optic endoscopes (SCB Xenon 175; Karl Storz, Tuttlingen, Germany) by each enrolling physician. Endoscopic exams were staged by the enrolling physician using the bilateral Lund-Kennedy scoring system (score range, 0–20) that quantifies pathologic states within the paranasal sinuses including the severity of polyposis, discharge, edema, scarring, and crusting on a Likert scale.[18] Endoscopic examinations were collected during concurrent 6-month intervals when feasible during standard clinic follow-up visitations. Higher scores on both staging systems reflect worse disease severity. Enrolling physicians were blinded to all survey responses during the study duration.

Health state utility values

Study participants completed the SF-6D during each study evaluation time point as part of a larger total battery of evaluative instruments. The SF-6D is a subset of questions extracted from the longer SF-36 survey and includes general-health survey inquiries measuring physical functioning, role limitations, social functioning, bodily pain, mental health, and vitality using standard Likert scales. Health states measured by SF-6D item scores were transformed into standardized health utility values using a weighted algorithm described by Brazier et al.[19] and used with permission from the Department of Health Economics and Decision Science at the University of Sheffield, Sheffield, UK. This algorithm determines a normalized value that an individual patient places on their particular health state described using the SF-6D questionnaire. Health utility values range from 0.3 to 1.0 where lower values represent lower/worse valuations of health state and 1.0 representing perfect health. A minimal clinically important difference over time of at least 0.03 for SF-6D values has been previously defined.[20]

Missed productivity

During each study evaluation time point, participants in both treatment arms were also asked to recall the number of days (out of the previous 90 days) that were missed or impacted due to CRS-related symptoms (eg, missed work days, school days, or volunteer time).

Data management and statistical analyses

Study data was stripped of all patient health information and manually entered into a relational database (Microsoft Access; Microsoft Corp., Redmond, WA). Statistical analyses were completed using SPSS v.22 statistical software (IBM Corp., Armonk, NY) and SF-6D values were estimated using SPSS syntax provided by the University of Sheffield. Baseline study population characteristics, clinical measures of disease severity, disease-specific QOL scores, and SF-6D values were evaluated descriptively and data normality was verified for all continuous measures using graphical analysis. Mean follow-up (months) for the medical management and treatment crossover subgroups was determined from the original enrollment date whereas follow-up from the surgical group was calculated from the date of sinus surgery. All statistical comparisons utilized complete case analysis.

Simple analysis of variance (ANOVA) and Kruskal-Wallis omnibus tests were used to evaluate between treatment group comparisons for all continuous variables with adjustments for pairwise multiple comparisons when significant. Chi-square (χ^2) and Fisher's exact testing was used to evaluate differences in the prevalence of comorbid conditions and patient characteristics between treatment groups. Two-tailed matched pairs *t* tests or Wilcoxon signed rank tests were used to evaluate changes in SF-6D values between study time points. Two-tailed Spearman's rank correlation coefficients (R_s) were utilized to evaluate correlation between SF-6D values and measures of diseases severity and productivity. Repeated measures ANOVA, with Greenhouse-Geisser corrections to evaluate level III within-subject differences over time, were used to evaluate significant improvement over time across each distinct treatment modality. All statistical comparisons assumed a 0.050 error probability.

Results

Final study cohort and baseline comparisons

The final study cohort was comprised of 212 study participants who met inclusion criteria and were enrolled between March 2011 and November 2013. Baseline characteristics and medical comorbidities are described in Table 1 for the medical management (n = 40; 19%), surgical intervention (n = 152; 72%), and treatment crossover (n = 20; 9%) subgroups. Total follow-up times for 6-month and 12-month interval evaluations were (mean ± standard deviation) 5.7 ± 1.2 and 11.8 ± 1.4 months, respectively. Medical management and surgical intervention subgroups were followed for similar average times at the 6-month (5.8 ± 0.9 vs 5.7 ± 1.1; $p = 0.490$) and 12-month (12.1 ± 1.3 vs 11.8 ± 1.4; $p = 0.213$) evaluations. Treatment crossover participants

TABLE 1. Comparison of baseline characteristics and medical comorbidity for CRS patients electing medical management, surgical intervention, or treatment crossover

	Medical management (n = 40)		Surgical intervention (n = 152)		Treatment crossover (n = 20)		
Baseline characteristics	Mean ± SD	n (%)	Mean ± SD	n (%)	Mean ± SD	n (%)	*p*
Age (years)	54.1 ± 13.0		53.3 ± 14.6		57.0 ± 15.0		0.563
Male		21 (53)		76 (50)		12 (60)	–
Female		19 (48)		76 (50)		8 (40)	0.694
Previous sinus surgery		20 (50)		78 (51)		17 (85)	0.015
Nasal polyposis		17 (43)		56 (37)		10 (50)	0.468
Deviated septum		11 (28)		67 (44)		4 (20)	0.031
Turbinate hypertrophy		3 (8)		24 (16)		1 (5)	0.202
Asthma		12 (30)		47 (31)		7 (35)	0.920
Aspirin sensitivity		5 (13)		10 (7)		2 (10)	0.444
Allergies (history)		8 (20)		24 (16)		6 (30)	0.277
Allergies (mRAST confirmed)		13 (33)		56 (37)		8 (40)	0.824
Depression		4 (10)		27 (18)		2 (10)	0.373
Current smoker		0 (0)		3 (2)		0 (0)	0.546
Alcohol consumption		23 (58)		78 (51)		8 (40)	0.441

CRS = chronic rhinosinusitis; mRAST = modified radioallergosorbent testing; SD = standard deviation.

were followed for approximately 12 months during which 11 patients (55%) elected ESS within the first 6 months of follow-up and 9 patients (45%) elected ESS between 6 and 12 months of follow-up. Participants electing treatment crossover to ESS were found to have a significantly higher prevalence of previous sinus surgery compared to both the medical management ($\chi^2 = 6.91$; $p = 0.009$) and the surgical intervention ($\chi^2 = 8.11$; $p = 0.004$) subgroups after adjusting for pairwise multiple comparisons. Similarly, treatment crossover participants were found to have a significantly smaller prevalence of deviated septum compared to the surgical intervention group ($\chi^2 = 4.23$; $p = 0.040$).

Mean differences in clinical measure of disease severity, health utility values, and missed days of productivity between subgroups electing medical management, surgical intervention, and treatment crossover are compared in Table 2. Participants initially electing surgical intervention reported significantly worse average utility values ($p = 0.023$) and greater average productivity days lost ($p = 0.009$) due to symptoms of CRS compared to the medical management group after adjusting for pairwise multiple comparisons. Treatment crossover participants also reported significantly greater average productivity days lost compared to the medical management group ($p = 0.011$). Mean baseline SF-6D values were compared across baseline characteristics and comorbid conditions between treatment modality (Table 3).

Mean baseline SF-6D utility values were significantly worse in the surgical intervention subgroup for patients without a history of previous sinus surgery ($p = 0.011$), without nasal polyposis ($p = 0.011$), and with aspirin sensitivity ($p = 0.008$) compared to medical management after adjusting for multiple comparisons. No significant differences in mean baseline SF-6D utility values for the treatment crossover subgroup across any patient characteristic. Baseline utility values were not found to significantly correlate with either baseline CT or endoscopy scores but were found to significantly correlate with past missed days of productivity in all treatment groups (Table 4).

Longitudinal changes in SF-6D values per treatment modality

Both statistical and clinically meaningful significant improvement in SF-6D health utility values over time was reported by all participants electing ESS (n = 152; $F_{(2)} = 37.69$; $p < 0.001$), but not by all participants electing continued medical management for symptoms of CRS (n = 40; $F_{(2)} = 0.03$; $p = 0.967$) or participants selecting treatment crossover (n = 20; $F_{(2)} = 2.36$; $p = 0.115$; Fig. 1) during the study duration. No significant difference in SF-6D values was found between baseline and 6-month evaluations in the medical management group ($p = 0.746$); however, significant improvement was reported for the group electing ESS ($p < 0.001$). Mean improvement in SF-6D values was

TABLE 2. Comparison of baseline clinical measure of disease severity, health state utility values, missed days of productivity for across treatment modality for chronic rhinosinusitis*

	Medical management (n = 40)	Surgical intervention (n = 152)	Treatment crossover (n = 20)	*p*
Clinical measures of disease severity				
CT score	13.3 ± 6.7	13.1 ± 5.9	13.0 ± 7.1	0.985
Endoscopy score	6.6 ± 3.9	6.5 ± 3.7	8.4 ± 5.1	0.293
Health state utility				
SF-6D value	0.76 ± 0.12	0.70 ± 0.15	0.69 ± 0.14	0.069
Productivity				
Missed days (out of past 90)	4.2 ± 13.7	9.6 ± 20.5	8.3 ± 12.9	0.017

*Values are mean ± SD.
CT = computed tomography; SD = standard deviation; SF-6D = Medical Outcomes Study Short Form-6D.

reported by the treatment crossover group between baseline and 6 months, but not to a significant level ($p = 0.055$). No significant differences in mean SF-6D values were found between 6-month and 12-month for any treatment group ($p \geq 0.786$).

Average baseline SF-6D values were similar between the surgical intervention and treatment crossover groups ($p = 0.826$); however, due to sample size limitations only the surgical intervention group reported significantly worse average baseline utility values compared to the medical management group ($p = 0.023$). Average SF-6D values were statistically similar between all treatment groups at 6-month follow-up ($p \geq 0.183$) and 12-month follow-up ($p \geq 0.269$).

Bivariate correlations

Bivariate correlations between SF-6D values and measures of disease severity were also evaluated at both 6-month (Table 5) and 12-month (Table 6) follow-up. Health utility values were not found to significantly correlate with endoscopy scores for any treatment modality subgroup at either follow-up time point but were found to be significantly correlated again with past missed days of productivity at both follow-up time points for the medical management and surgical intervention treatment groups.

Discussion

Health utility values quantify an individual's preference for his or her current state of health. These values are unique when compared to traditional CRS-specific measures of QOL (22-item Sino-Nasal Outcome Test [SNOT-22], Rhinosinusitis Disability Index [RSDI], Chronic Sinusitis Survey [CSS]) because they allow for comparison across disease states and form the basis for which quality adjusted life years (QALYs) are derived. QALYs are the preferred metric used in cost effectiveness analysis, which can provide valuable information for healthcare resource allocation. Prior studies have projected that ESS is more cost effective than medical therapy to treat refractory CRS with an estimated cost effectiveness ratio of $5,901.90 per QALY for ESS vs medical therapy.[21]

A change in health utility of 0.03 has been validated among many different chronic disease states to represent clinically significant change that alters patient's subjective well-being by 1 point on a 5-point global rating of change scale (5 = "much better health"; 4 = "somewhat better health"; 3 = "no change in health"; 2 = "somewhat worse health"; and 1 = "much worse health").[20] Baseline health utility values for all CRS patients in this study were significantly less than reported U.S. norms (0.81) and similar to other chronic disease states (Fig. 2) in which utility values have been reported.[22]

Participants electing ESS achieved significant improvement in mean utility from 0.70 ± 0.15 at baseline to 0.79 ± 0.14 at 6 months, with stabilization through 12 months (0.78 ± 0.15, $p = 0.800$). Similarly, the literature supports ESS in improving health utility values for recalcitrant CRS. In 2011, Soler et al.[5] reported clinically significant improvements in baseline disease specific QOL scores as well as utility values (0.087) following ESS. In 2013, Rudmik et al.[23] reported additional long-term improvement in utility values after ESS at 5-year follow-up of a prospective cohort. Most importantly, long-term health utility values reached an average of 0.80, which is comparable to the U.S. norm of 0.81.[6,9,23]

Patients who elected continued medical management reported a significantly better baseline utility as compared to those who elected surgery (0.76 ± 0.12 vs 0.70 ± 0.15, $p \leq 0.001$). Interestingly, there were no significant differences in objective measures such as baseline CT or endoscopy scores between the medical and surgical groups, highlighting the difficulty in stratifying CRS patients and prognosticating outcomes based on imaging and physical exam. However, worse baseline utility values were significantly correlated to increased missed days of productivity, which supports

TABLE 3. Comparison of mean baseline SF-6D health state utility values between treatment modality across patient characteristics*

Baseline characteristics	Medical management (n = 40)	Surgical intervention (n = 152)	Treatment crossover (n = 20)	*p*
Age (years)				
18–40 (n = 38)	0.76 ± 0.14	0.69 ± 0.14	0.77 ± 0.04	0.318
41–60 (n = 95)	0.73 ± 0.13	0.69 ± 0.14	0.63 ± 0.13	0.146
61–86 (n = 59)	0.80 ± 0.07	0.73 ± 0.15	0.73 ± 0.14	0.316
Gender				
Male	0.76 ± 0.12	0.73 ± 0.15	0.73 ± 0.14	0.666
Female	0.75 ± 0.13	0.67 ± 0.14	0.65 ± 0.13	0.067
Previous sinus surgery				
Present	0.72 ± 0.12	0.69 ± 0.16	0.72 ± 0.14	0.749
Absent	0.80 ± 0.11	0.71 ± 0.13	0.69 ± 0.14	0.042
Nasal polyposis				
Present	0.75 ± 0.14	0.72 ± 0.15	0.68 ± 0.15	0.563
Absent	0.77 ± 0.10	0.69 ± 0.14	0.71 ± 0.12	0.036
Deviated septum				
Present	0.72 ± 0.11	0.69 ± 0.14	0.69 ± 0.14	0.680
Absent	0.77 ± 0.12	0.71 ± 0.15	0.70 ± 0.14	0.122
Turbinate hypertrophy				
Present	0.63 ± 0.05	0.66 ± 0.14	0.8 ± –	0.573
Absent	0.77 ± 0.12	0.71 ± 0.14	0.69 ± 0.14	0.054
Asthma				
Present	0.73 ± 0.16	0.69 ± 0.16	0.68 ± 0.15	0.614
Absent	0.77 ± 0.10	0.71 ± 0.14	0.71 ± 0.13	0.078
Aspirin sensitivity				
Present	0.85 ± 0.09	0.63 ± 0.11	0.76 ± 0.05	0.021
Absent	0.75 ± 0.12	0.71 ± 0.15	0.69 ± 0.14	0.268
Allergies (history)				
Present	0.81 ± 0.14	0.70 ± 0.14	0.72 ± 0.13	0.192
Absent	0.74 ± 0.11	0.70 ± 0.15	0.69 ± 0.14	0.221
Allergies (mRAST confirmed)				
Present	0.79 ± 0.11	0.72 ± 0.15	0.64 ± 0.16	0.061
Absent	0.74 ± 0.12	0.69 ± 0.15	0.73 ± 0.11	0.271
Depression				
Present	0.68 ± 0.14	0.60 ± 0.09	0.57 ± 0.07	0.283
Absent	0.77 ± 0.12	0.72 ± 0.15	0.71 ± 0.13	0.263
Current smoker				
Present	0.0 ± 0.0	0.68 ± 0.10	–	–
Absent	0.76 ± 0.12	0.70 ± 0.15	0.70 ± 0.14	0.079
Alcohol consumption				
Present	0.77 ± 0.11	0.74 ± 0.14	0.70 ± 0.12	0.413
Absent	0.74 ± 0.14	0.66 ± 0.14	0.70 ± 0.15	0.081

*Values are mean ± SD.
mRAST = modified radioallergosorbent testing; SD = standard deviation; SF-6D = Medical Outcomes Study Short Form-6D.

TABLE 4. Bivariate correlation coefficients between baseline SF-6D health state utility values, clinical measures of disease severity, and missed days of productivity

	Medical management (n = 40)		Surgical intervention (n = 152)		Treatment crossover (n = 20)	
	R_s	*p*	R_s	*p*	R_s	*p*
Clinical measures of disease severity						
CT score	0.173	0.336	0.069	0.400	−0.055	0.824
Endoscopy score	0.093	0.574	−0.021	0.797	−0.096	0.689
Productivity						
Missed days (out of past 90)	−0.470	0.003	−0.510	<0.001	−0.510	0.022

CT = computed tomography; R_s = Spearman's rank correlation coefficient; SF-6D = Medical Outcomes Study Short Form-6D.

TABLE 5. Bivariate correlation coefficients between 6-month SF-6D health state utility values, clinical measures of disease severity, and missed days of productivity

	Medical management (n = 40)		Surgical intervention (n = 152)		Treatment crossover (n = 20)	
	R_s	*p*	R_s	*p*	R_s	*p*
Clinical measures of disease severity						
Endoscopy score	−0.241	0.352	−0.039	0.706	−0.212	0.447
Productivity						
Missed days (out of past 90)	−0.336	0.039	−0.421	<0.001	−0.504	0.028

R_s = Spearman's rank correlation coefficient; SF-6D = Medical Outcomes Study Short Form-6D.

TABLE 6. Bivariate correlation coefficients between 12-month SF-6D health state utility values, clinical measures of disease severity, and missed days of productivity

	Medical management (n = 40)		Surgical intervention (n = 152)		Treatment crossover (n = 20)	
	R_s	*p*	R_s	*p*	R_s	*p*
Clinical measures of disease severity						
Endoscopy score	0.015	0.960	0.056	0.637	−0.290	0.416
Productivity						
Missed days (out of past 90)	−0.412	0.010	−0.546	<0.001	0.115	0.651

R_s = Spearman's rank correlation coefficient; SF-6D = Medical Outcomes Study Short Form-6D.

the use of health utility values to determine economic impact of this disease process. The estimated productivity cost associated with refractory CRS is about $10,000 per patient.[24]

In this study, patients who elected continued medical management reported stable mean utility values up to 12 months. Despite lack of improvement of mean utility from baseline in the medical management group, their overall mean health utility was comparable to the surgical group at 6-month ($p = 0.257$) and 12-month follow-up ($p = 0.269$). These findings support prior studies that show a tendency for patients to self-select appropriate therapy based on their QOL.[25] Patients with a mild reduction in QOL measures chose medical therapy, whereas those with moderate to severe QOL impairment chose ESS.[6,9,26,27] Further research is needed to further clarify the specific QOL factors that drive patients to choose medical management.

Recent studies have also attempted to clarify the role of medical management for refractory CRS. Smith and Rudmik[28] showed severe reductions in baseline QOL, significant worsening of endoscopy scores, and increased missed days of work in refractory CRS patients treated with medical therapy while waiting to undergo ESS. These patients report worse baseline QOL than the patients in this study who elected medical management and achieved stable QOL. This variation in outcome highlights the importance of accurate assessment of the impact of the chronic disease process in shared patient-provider decision-making.

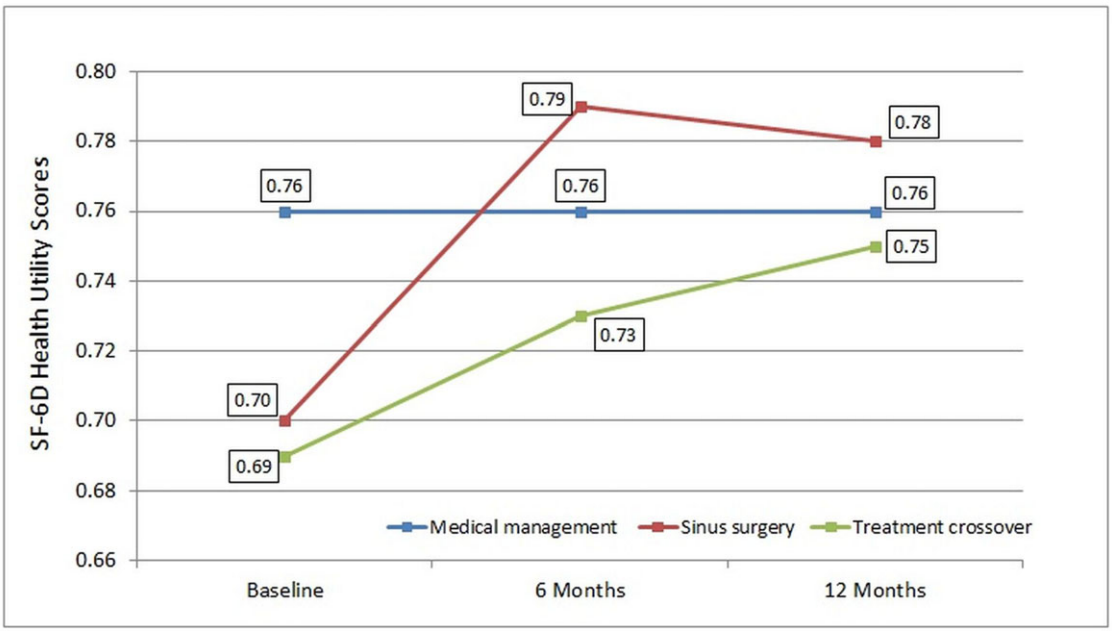

FIGURE 1. Average longitudinal health utility SF-6D health utility values for study participants in the medical management group (n = 40), surgical intervention group (n = 152), and treatment crossover group (n = 20). SF-6D = Medical Outcomes Study Short Form-6D.

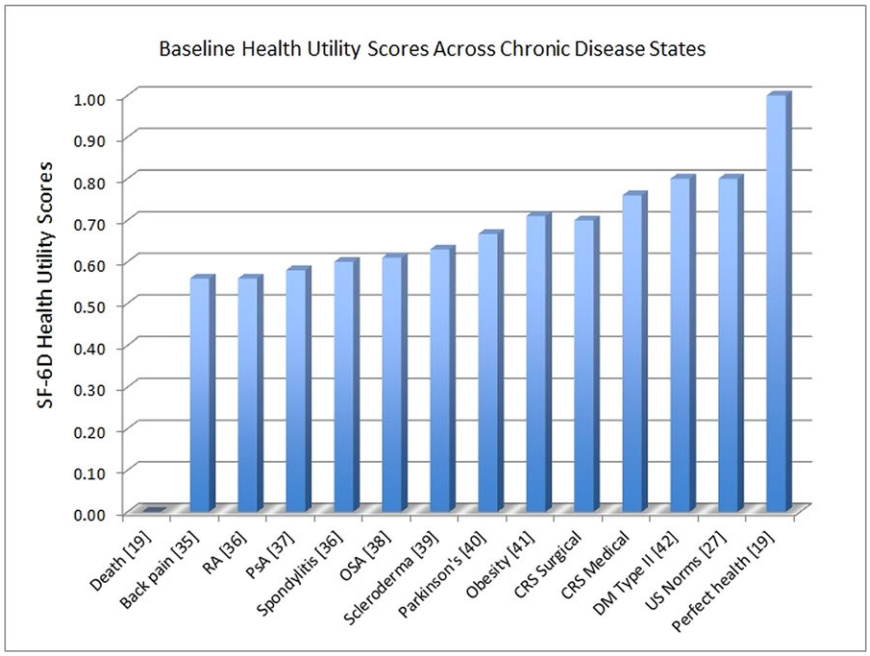

FIGURE 2. Baseline health utility values for a variety of chronic disease processes. CRS = chronic rhinosinusitis; DM = diabetes mellitus; PsA = psoriatic arthritis; OSA = obstructive sleep apnea; RA = rheumatoid arthritis; SF-6D = Medical Outcomes Study Short Form-6D; US = United States.[19,27,35–42]

Maintenance of health utility values over time with continued medical management in the current cohort may be interpreted in several ways. First, no improvement in health utility may be interpreted as festering disease burden. In this setting, patients continue to experience detriment to health-related QOL despite medical therapy. On the other hand, lack of improvement may also be interpreted as therapeutic control of the chronic disease process at an acceptable health utility state for this patient group. The stabilization of utility with medical management in CRS patients is comparable to medical management of other chronic disease processes such as type 2 diabetes (Fig. 3).

Average baseline SF-6D values reported in the treatment crossover group (0.69 ± 0.14) were similar to the surgical group (0.70 ± 0.15; $p = 0.826$), but lower than the medical group (0.76 ± 0.12), though this was not statistically significant. In addition, 85% of the crossover group had prior history of ESS. In the setting of prior ESS, lower

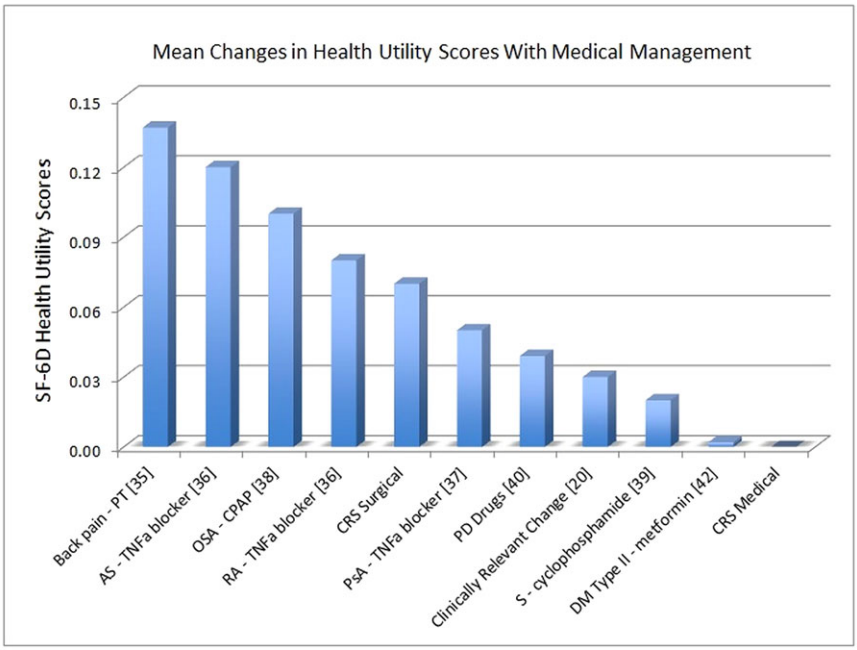

FIGURE 3. Mean changes in health utility values after medical management. AS = ankylosing spondylitis; CPAP = continuous positive airway pressure; CRS = chronic rhinosinusitis; DM = diabetes mellitus; OSA = obstructive sleep apnea; PD = Parkinson's disease; PsA = psoriatic arthritis; PT = physical therapy; RA = rheumatoid arthritis; S = scleroderma; SF-6D = Medical Outcomes Study Short Form-6D; TNFa = tumor necrosis factor-alpha.[20,35–40,42]

average baseline utility values suggest that additional continued medical therapy is unlikely to further improve QOL or health utility. Delayed ESS, in appropriate CRS candidates, has been associated with increased healthcare utilization.[29] The finding that medical management stabilizes health utility may only be applicable to a self-selected group of recalcitrant CRS patients with a relatively high baseline health utility.

There are several caveats to consider when interpreting the results from this study. A small subset of patients (n = 20) elected to cross over from the medical management to the surgical intervention cohort, and these patients were analyzed separately. Evaluating this patient subgroup using an intention-to-treat analysis is not wholly appropriate given that the initial treatment assignment was not randomized. Because of the small sample size of this group and the variations in crossover points, it is difficult to draw definitive conclusions when comparing this crossover group to the medical and surgical groups.

Results from this study may lack generalizability because patients were recruited from academic, tertiary rhinology centers and may represent a specific group of patients with greater burden of disease as compared to average patients with CRS. In addition, to be eligible for this study, many patients failed a course of maximal medical therapy with oral steroids. Prior definitions of maximal medical therapy only included topical nasal spray and antibiotics.[30] Once patients fail oral steroids, continued medical management may be less palatable. As previously reported by Smith et al.,[25] lack of improvement or worsening of QOL may be a factor driving patient decision-making to elect ESS. These factors may explain the unbalanced sample size, with 40 individuals choosing medical management as opposed to 152 individuals electing ESS, and reflect the overall patient populations in these enrollment centers. The prevalence of patients who elected treatment crossover to ESS also reduced the size of the medical management cohort. However, this medical cohort with refractory CRS is comparable in size, baseline characteristics, and clinical measures of disease severity to other medical cohorts in the literature and represents recruitment at 4 large rhinology centers.[13,30,31] Although medical management was not standardized in the current study, the multiinstitutional nature of the study reflects current clinical practice and represents real world prescribing practices and outcomes.

Interpretation of published utility values can be challenging because a single best health-related QOL construct has not been established for CRS.[32] Rather, there are several different QOL instruments from which health utility values can be derived, including EuroQOL 5-Dimension (EQ-5D) survey, Health Utilities Index Mark 2, Health Utilities Index Mark 3, SF-6D, Assessment of Quality of Life, and the Quality of Well- Being Index.[33] The SF-6D and EQ-5D are the 2 most commonly employed constructs within the CRS literature.[3,5,6,9,34] Health utility values are derived from different QOL instruments are not interchangeable because of differing conceptualization, content, size, and methods for computing health utility.[33] The mean baseline health utility value resulting from SF-6D for participants electing ESS in this study was 0.70 ± 0.15. In contrast, the

mean baseline utility value resulting from EQ-5D was 0.81 as reported by Remenschneider et al.[6] Both instruments show comparable gains in utility (SF-6D: 0.08; EQ-5D: 0.08) after ESS, which supports the use of each instrument in cost-analyses. The health utility values reported herein provide insight into patients' view of their global health-related QOL and will inform future cost-analysis and economic evaluations for medically managed CRS patients. Future studies should confirm our initial results and ideally would include long-term follow-up for more accurate evaluations of economic impact.

Conclusion

Patients with recalcitrant CRS electing continued medical management report better baseline health utility compared to patients electing ESS, and their utility values remained stable during up to 12 months of follow-up. Patients electing ESS had lower baseline utility values and showed significant improvement in utility over 12 months after surgery. Outcomes from this study may be used to improve the accuracy of future cost-utility analyses for management of CRS with either medical therapy or ESS. Multiinstitutional long-term studies are required to confirm these findings.

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ORIGINAL ARTICLE

Investigation of bacterial repopulation after sinus surgery and perioperative antibiotics

Leah J. Hauser, MD[1], Diana Ir, BS[2], Todd T. Kingdom, MD[1], Charles E. Robertson, PhD[3,4,5], Daniel N. Frank, PhD[2,3] and Vijay R. Ramakrishnan, MD[1]

Background: **Endoscopic sinus surgery (ESS) enjoys high success rates, but repopulation with pathogenic bacteria is 1 of the hallmarks of poorer outcomes. There are many hypothesized sources of repopulating bacteria; however, this process remains largely unexplored. This study examined changes in the sinus microbiome after ESS and medical therapies to identify potential sources for postsurgical microbial repopulation.**

Methods: **Samples from the anterior nares, ethmoid sinus, and nasopharynx were taken at the time of surgery from 13 subjects undergoing ESS for chronic rhinosinusitis (CRS). Patients were treated postoperatively with 2 weeks of oral antibiotics and saline rinses. The ethmoid sinus was sampled at 2 and 6 weeks postoperatively; microbiota were characterized using quantitative polymerase chain reaction (qPCR) and 16S ribosomal RNA (rRNA) gene sequencing. The Morisita-Horn beta-diversity index (M-H) was used to compare similarity between samples.**

Results: **The bacterial burden of the ethmoid was higher 2 weeks postoperatively than 6 weeks postoperatively ($p = 0.01$). The 6-week samples most closely represented the anterior nares and ethmoid at surgery (M-H = 0.58 and 0.59, respectively), and were least similar to the nasopharynx (M-H = 0.28). Principal coordinates analysis (PCoA) plots illustrate that the ethmoid microbiota temporarily shifted after surgery and antibiotics but returned toward baseline in many subjects.**

Conclusion: **Bacterial communities colonizing the ethmoid 6 weeks postoperatively were most similar to anterior nasal cavity and pretreatment sinus microbial profiles, indicating a high degree of resilience in the sinonasal microbiome of most subjects. Interestingly, surgery and postoperative antibiotic therapy does not appear to reduce bacterial burden, but rather, shifts the microbial consortia.** © 2015 ARS-AAOA, LLC.

Key Words:
sinusitis; chronic rhinosinusitis; bacteria; microbiome; pyrosequencing; bacterial repopulation

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Chronic rhinosinusitis (CRS) is a chronic inflammatory disorder of the paranasal sinuses, in which bacteria may play some role.[1] Surgical therapy and medical treatment in the early postoperative period are directed at improving sinus ventilation, eradicating pathogenic bacteria, and perhaps restoring microbiome disturbances to a healthy state. Although 72% to 90% of patients have good postoperative outcomes,[2–5] a subset of patients have continued disease requiring further medical and surgical therapy.

Repopulation with pathogenic bacteria is 1 of the hallmarks of a poor outcome after endoscopic sinus surgery (ESS).[6,7] Many theories have been proposed for the source of bacterial repopulation, including persistence of bacterial

[1]*Department of Otolaryngology–Head and Neck Surgery, University of Colorado, Boulder, CO;* [2]*Division of Infectious Diseases, University of Colorado, Boulder, CO;* [3]*The Microbiome Research Consortium, University of Colorado, Aurora, CO;* [4]*Department of Biostatistics and Informatics, University of Colorado, Boulder, CO;* [5]*Department of Molecular, Cellular, and Developmental Biology, University of Colorado, Boulder, CO*

Correspondence to: Vijay R. Ramakrishnan, MD, Department of Otolaryngology–Head and Neck Surgery, University of Colorado, 12631 E. 17th Ave, B-205, Boulder, CO 80045; e-mail: vijay.ramakrishnan@ucdenver.edu

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reservoirs within paranasal sinus biofilms, in intramucosal sites, or within the nasopharynx.[8–10] Up to 75% of post-ESS infections may be from bacterial isolates not present at the time of surgery, suggesting that opportunistic de novo bacteria are responsible for recalcitrant CRS, implicating patient-specific alterations in immunity.[11] However, it has also been hypothesized that bacterial repopulation may arise from an extranasal source, including introduction from the skin or direct inoculation from water irrigation bottles.[9,12] The goals of this study were to examine changes in the sinus microbiome following ESS and initial postoperative medical therapies in order to identify potential sources for postsurgical microbial repopulation.

Patients and methods

Study design and population

This cross-sectional study was approved by the Institutional Review Board of the University of Colorado (COMIRB protocol number 11–1442). The diagnosis of CRS was made according to the 2007 Adult Sinusitis Guidelines, and accordingly, CRS patients were initially managed medically with a minimum trial of saline rinses, oral antibiotics, and topical intranasal steroids.[13] Those with continued evidence of disease who elected to undergo functional endoscopic sinus surgery (FESS)[14] were enrolled in the study. The extent of surgery was determined by extent of disease and ranged from maxillary antrostomy with anterior ethmoidectomy to complete bilateral surgery addressing all paranasal sinuses. Meticulous mucosal-sparing surgical technique was used. Patients less than 18 years of age, with antibiotic use within 1 month of surgery (systemic or topical), or with cystic fibrosis, immunodeficiency, or autoimmune diseases were excluded from the study. Postoperatively, patients were routinely placed on sinus irrigations and a 2-week course of oral antibiotics (amoxicillin-clavulanate, or clarithromycin if penicillin-allergic). Bacterial load was hypothesized to be the lowest after treatment (FESS with irrigation at completion of surgery,[15] followed by 2 weeks of postoperative antibiotics and saline rinses), and then bacterial repopulation was expected to subsequently occur in the following weeks. As such, we compared microbiota present at the time of surgery, 2 weeks postoperatively, and 6 weeks postoperatively.

Sample collection

Subjects were recruited between November 2013 and May 2014. All swabs were collected using CultureSwabs (BD, Franklin Lakes, NJ), rotating at least 5 full turns until fully saturated. Samples were collected at surgery or in clinic during the 2-week and 6-week postoperative appointments. At surgery, swabs were endoscopically guided to the anterior nares and nasopharynx and, once open, into the ethmoid sinus, with care taken to avoid contamination by neighboring sites. At postoperative visits, swabs were endoscopically guided to the ethmoid cavity and sampled in an identical fashion. CultureSwabs for DNA extraction were placed on ice upon collection and frozen at −80°C until DNA extraction.

16S amplicon library construction

DNA was extracted from all samples using the UltraClean™ DNA Isolation Kit (Mo Bio, Carlsbad, CA). Bacterial profiles were determined by broad-range amplification and sequence analysis of 16S rRNA genes following previously described methods.[16,17] In brief, amplicons were generated using primers that target approximately 340 base pairs (bp) of the V1V2 variable region of the 16S rRNA gene (primers 27FYM [Frank et al.[18]] and 338R,[19] modified by adding dual indexes and Illumina adapter sequences; Illumina, San Diego, CA, USA). Illumina paired-end sequencing was performed on the MiSeq platform with version v2.3.0.8 of the MiSeq Control Software and version v2.3.32 of MiSeq Reporter, using a 600-cycle version 3 reagent kit (all from Illumina).

As described,[17] Illumina MiSeq paired-end sequences were sorted by sample via barcodes in the paired reads with a Python script (Python Software Foundation; https://www.python.org). The sorted paired reads were merged using the phrap assembly software.[20,21] Potential chimeras identified with Uchime (usearch6.0.203_i86linux32)[22] using the Schloss and Westcott[23] Silva reference sequences were removed from subsequent analyses. This process generated 11,989,194 high-quality sequences for 69 samples (2 anterior nares failed to amplify with 16S primers), with a median of 105,889 sequences/sample (IQR, 45,883 to 259,155). Assembled sequences were aligned and classified with SINA (1.2.11)[24] using the 418,497 bacterial sequences in Silva 115NR99 (Quast et al.[25]) as reference configured to yield the Silva taxonomy. Operational taxonomic units (OTUs) were produced by clustering sequences with identical taxonomic assignments. Relative abundances of OTUs were calculated for each subject by dividing the sequence counts observed for each OTU by the total number of high-quality bacterial 16S rRNA sequences generated for the subject. All sequence libraries had Good's coverage scores ≥99% at the rarefaction point of 15,000 sequences, indicating that sequence coverage was excellent.

Statistical analysis

Similarity between the microbiomes of pairs of patient samples (ie, beta-diversity) was measured using the abundance-based Morisita-Horn index (using the "vegdist" R command). Similarity/dissimilarity in community composition (ie, beta-diversity) was assessed using a permutation-based multiple analysis of variance (PERMANOVA) test, implemented by the adonis function of the vegan R package.[26] Values of p were generated using 5000 label permutations, with beta-diversity measured using the Morisita-Horn index. The R (v3.0.3, http://cran.r-project.org)[27] and Explicet (v2.9.4, http://www.explicet.org)[28] software packages were used for data display, analysis, and figure generation.

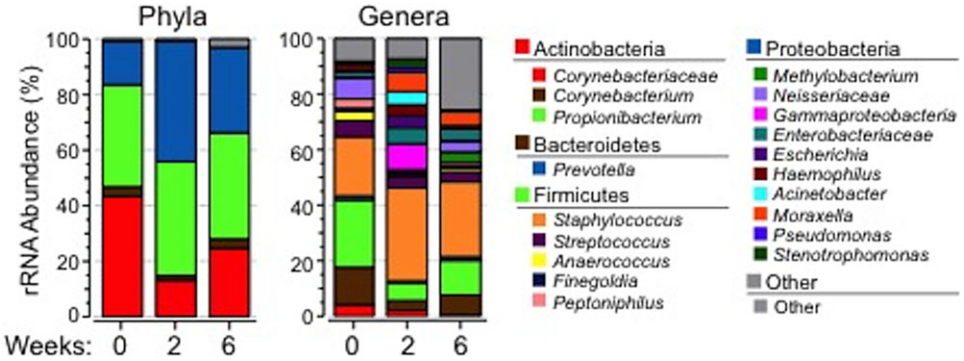

FIGURE 1. Phyla and genera of ethmoid bacterial communities over time. Bars represent the average relative abundances of the phyla and genera present in the ethmoid samples at 0, 2, and 6 weeks postoperatively. rRNA = ribosomal RNA.

Results

Thirteen subjects met the criteria for inclusion in the study and 12 subjects had adequate sampling for analysis of each subsite and time point. The mean age of our subjects was 56.6 years (range, 28–77 years). Sixty-one percent (61%) had polyps and asthma and 46% were undergoing revision surgery. Subjects had moderate disease severity based average Lund-Mackay computed tomography (CT) and Lund-Kennedy endoscopy scores of 10.7 ± 4.6 and 5.7 ± 2.2, respectively. The average relative abundances of the phyla and genera present in the ethmoid samples at 0, 2, and 6 weeks postoperatively is depicted in Figure 1.

Overall bacterial burden was estimated using total qPCR 16S bacterial gene copy numbers. The mean $\log_{10}$ of the gene copy number of the ethmoid samples at the time of surgery, 2 weeks, and 6 weeks postoperatively were 3.53, 4.30, and 3.47, respectively (Fig. 2). The bacterial burden of the ethmoid swab was significantly higher at the 2-week time point (immediately after completion of antibiotics) than at 6 weeks postoperatively ($p = 0.03$, by 2-tailed paired t test).

The Morisita-Horn beta-diversity index (M-H) was used to compare the similarities of microbiomes between pairs of samples (a value of 0 indicates no similarity, whereas a value of 1 indicates identical microbial community composition). All samples (anterior nares, ethmoid, and nasopharynx at the time of surgery, and ethmoid 2 weeks postoperatively) were compared to the 6-week postoperative population (Fig. 3). Additionally, the 2-week ethmoid postoperative sample was compared to the ethmoid sample at the time of surgery. The 6-week postoperative sample was most closely matched to the anterior nares and ethmoid samples taken at the time of surgery (mean M-H = 0.58 and 0.59, respectively), suggesting that these sites may have the most impact on bacterial repopulation postoperatively. The nasopharynx was the least similar to the bacterial makeup of the ethmoid specimens 6 weeks postoperatively (M-H = 0.29 and 0.18, respectively), suggesting that it likely to does not contribute to postoperative bacterial recolonization. The 6-week ethmoid samples were less similar to the 2-week samples (M-H = 0.40) than to the baseline ethmoid samples (M-H = 0.59).

Principal coordinates analysis (PCoA) plots illustrate that the ethmoid microbiota shifted after surgery and antibiotic administration but returned toward the original baseline in many of the patients (Fig. 4). The results of a PERMANOVA test indicated that variability in microbiomes was driven more by intersubject variation ($p = 0.0004$) than by time-point of sampling ($p = 0.5$) when both variables were entered into the regression as predictor variables. None of the clinical variables that we assessed (allergies, asthma, polyposis, purulence) were significant predictors of microbiome structure after adjusting for subject and sampling time-point.

Among the ethmoid samples, no significant differences in OTU richness (ie, the number of OTUs per subject) were noted between baseline, 2-week, or 6-week samples. However, the complexity of 2-week ethmoid samples trended toward being significantly lower than the 6-week samples (mean Shannon diversity index of 1.9 ± 1.2 vs 2.9 ± 1.1, respectively; $p = 0.09$); baseline samples were of an intermediate complexity (2.4 ± 0.8), but did not differ significantly from either the 2-week or 6-week samples.

To evaluate for potential contamination during sampling, average Morisita-Horn similarities were calculated comparing the anterior nares, the ethmoid, and the nasopharynx samples at the time of surgery. The anterior nares and ethmoid samples were the most similar (M-H 0.81); however, this is not surprising given these were both subsequently found to be potential sources for repopulation of the ethmoid cavity. The bacterial population of the nasopharynx was not similar to either the ethmoid cavity or the anterior nares (M-H 0.46, 0.43), indicating there was likely little contamination of the nasopharynx swab when passing through the proximal sinonasal cavity.

Discussion

Recent work has begun to elucidate the composition and biodiversity of the sinus microbiome in both health and

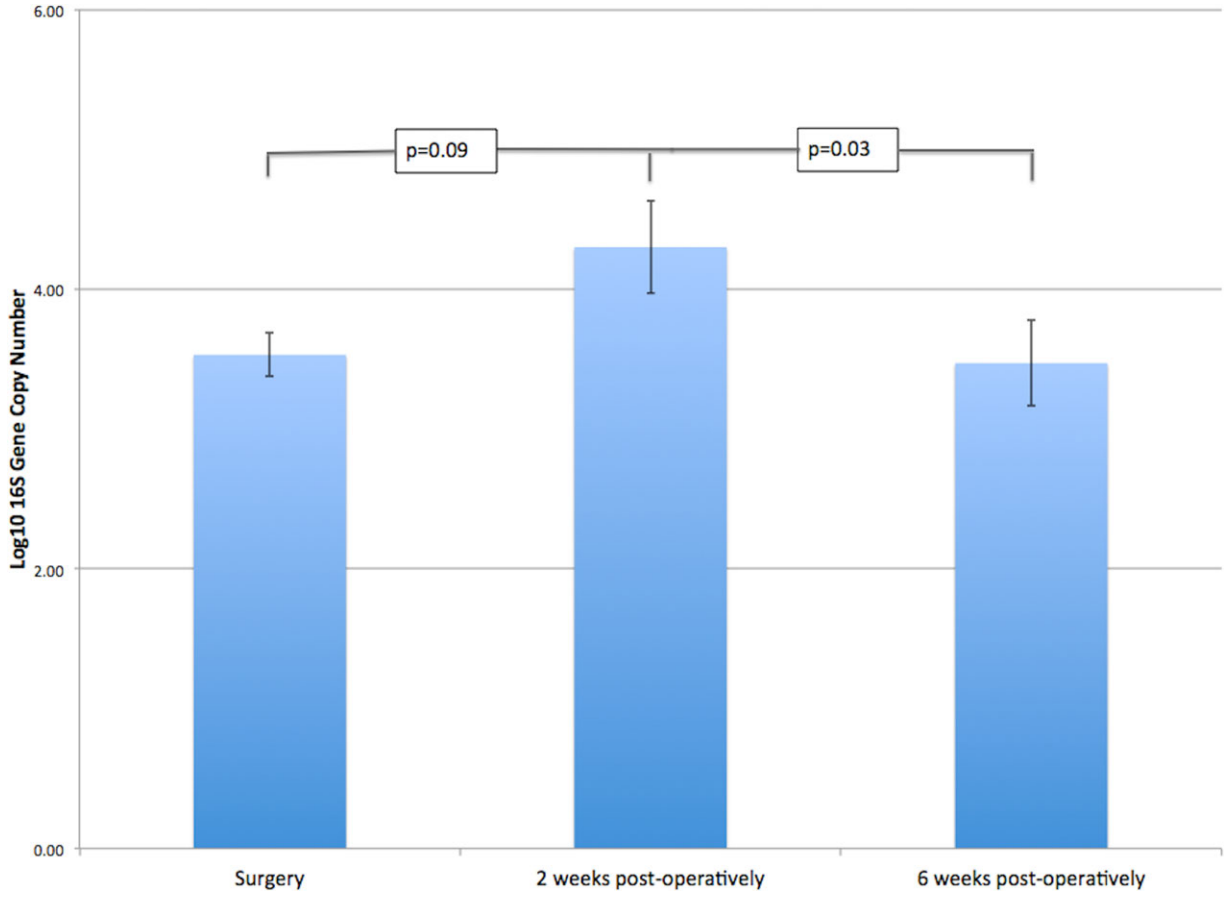

FIGURE 2. Bacterial loads in sinus specimens. Bars show the mean qPCR 16S gene copy number of the ethmoid sample at the time of surgery, 2 weeks, and 6 weeks postoperatively. Bacterial load showed a trend toward increase in total bacteria at 2 weeks compared to the time of surgery ($p = 0.09$), and significantly more total bacteria at 2 weeks compared to 6 weeks ($p = 0.03$). Error bars indicate standard error of the mean. qPCR = quantitative polymerase chain reaction.

disease. Microbial cultivation studies have shown that pathogen recolonization is a hallmark of poor outcomes after ESS. The source of these bacteria has been debated and little is known about how the sinus microbiome is established or transformed in the postoperative period after surgery, rinses, and antibiotics. Surprisingly, we found that the bacterial burden of the ethmoid swab was higher in the early postoperative period than at 6 weeks and the time of surgery. This may be a result of broad disruption of mucociliary and immune function from surgical intervention, despite meticulous mucosal preservation FESS technique and irrigation at the end of surgery. Our findings strongly indicate that antibiotic therapy after surgery is not eliminating local flora during the wound healing process. Additionally, the bacterial makeup at measured time points was quite different. Bacterial communities colonizing the ethmoid at 6 weeks postoperatively were most similar to anterior nasal cavity and pretreatment sinus microbial profiles, suggesting these sites may be likely sources for bacterial repopulation, or alternatively, that all sites may naturally return to their baseline states.

The microbiome is a diverse, complex community of microbiota that exists in a delicate symbiotic relationship within a human microenvironment.[29–31] Initial investigations into this complex human-microbial relationship in the sinuses have shown that treatment interventions such as intranasal corticosteroid use may alter the sinonasal microbiota and that medical management of acute exacerbations of CRS may decrease diversity,[32,33] but more research is needed to understand the effects of these and other therapies. We expected to find that the paranasal sinuses would have relatively low bacterial loads after sinus surgery, irrigation, and postoperative antibiotics; however, our data showed that bacterial load actually increased. Although the sinuses are not sterile in either healthy or diseased states, the effects of such therapeutic interventions on the sinus microbiome and the implications for patient outcomes remain largely unknown.[34,35] Studies from the gut microbiome suggest that antibiotic administration results in a decrease in the diversity of the gut microbiota, which can sometimes be prolonged.[36,37] For instance, a murine model found that following an antibiotic-induced disturbance, the microbial composition would often return to baseline within a number of weeks, although some communities exhibit persistently depleted diversity despite returning to pretreatment microbial densities.[36] Antibiotic-treated mice

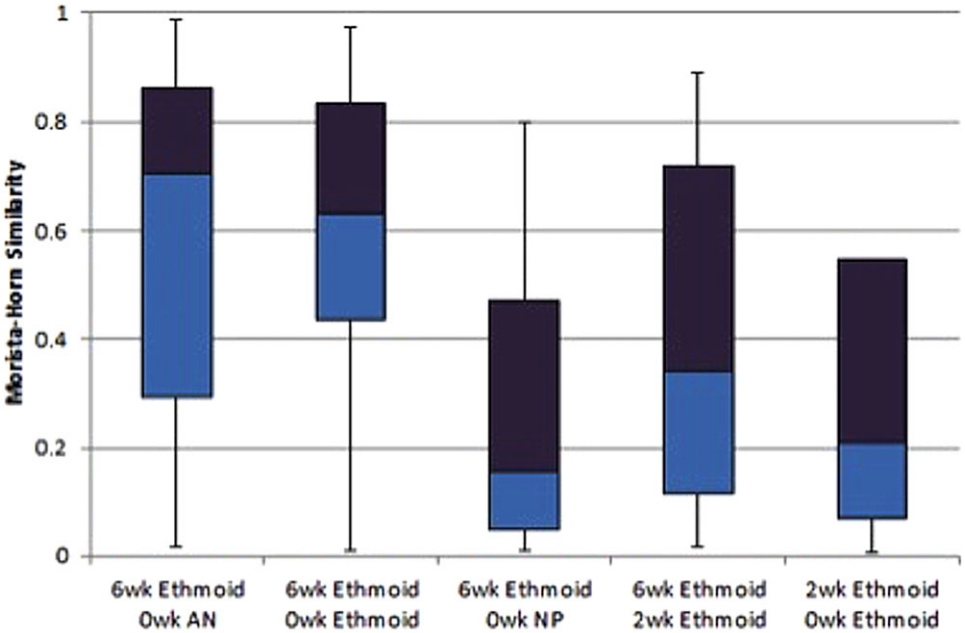

FIGURE 3. Similarity of bacterial communities between time points and sampling sites. The Morisita-Horn similarity index was used to quantify differences in microbiota in order to compare the 6-week ethmoid sample to the anterior nares, ethmoid, and nasopharynx at the time of surgery, the ethmoid at 2 weeks postoperatively, and between the ethmoid at 2 weeks postoperatively and the ethmoid at the time of surgery. The 6-week ethmoid sample was most similar to the anterior nares and ethmoid samples at the time of surgery, suggesting these may be potential sources for repopulation of bacteria postoperatively. *A value of 1 indicates identical bacterial community, and 0 is complete dissimilarity. AN = anterior nasal cavity, AN = anterior nares; NP = nasopharynx.

exhibit altered immune responses and are more susceptible to other bacterial infections.[36,38] A study investigating the effects of antibiotics and steroids on the sinonasal microbiome in acute exacerbations of CRS changes in the sinonasal microbiome similarly found a decrease in diversity at the completion of courses of antibiotics and steroids. Though this suggests that antibiotics may contribute to a decrease in diversity, resolution of the acute exacerbation may also have contributed to the changes seen, as there was no baseline steady-state sample collected.[33] There is evidence in humans to support that a more diverse microbiome is associated with improved health outcomes and less disease burden.[35,39,40] We noted a trend toward a less complex bacterial community after surgery and antibiotics, which became more diverse again at the 6-week time point ($p = 0.09$). More significant temporal differences in microbial diversity may have been more evident in a larger cohort. These results suggest that treatment interventions (surgery and antibiotics) can increase bacterial diversity; whether these changes will contribute to improved clinical outcomes is currently under investigation. Our data illustrate an initial perturbation in the microbiome due to therapeutic intervention, from which many subjects may recover their preoperative bacterial community and some may continue to shift toward a new and different community makeup, a model that has been previously proposed for microbiome effects on disease states.[37] In humans, resilience is variable by subsite and subject, but the nasal cavity appears to be 1 of the most stable,[41] as supported by our findings.

Possible sources for the bacteria that recolonize the sinuses after sinus surgery include reservoirs within paranasal biofilms, colonized intramucosal sites refractory to antibiotic therapy, within the nasopharynx, or even de novo bacteria from extranasal sources.[8–11] We found that 6-week postoperative microbiota most closely represented the anterior nares and ethmoid samples from the time of surgery, and were least similar to the nasopharynx, suggesting that the former sites may be critical reservoirs for sinus microbiota.

New research suggests that in multiple mucosal surfaces individuals do in fact have signature bacterial species and even strains.[42] We have previously showed that the anterior nares microbiome is stable over time in the absence of mitigating factors such as antibiotics[43] and also that a more diverse sinus microbial ecology is associated with healthy sinuses.[44] In this study, our preoperative and postoperative ethmoid samples were largely similar (mean M-H 0.59), indicating that this "fingerprint" may persist in the sinuses, but can be subject to milder changes. Although it is possible that we may have seen more resiliency in our samples, or more recovery of baseline microbiota, if we had sampled the ethmoids at a later time point, it was thought that 6 weeks was enough time to reach a new postoperative steady state because microbiota in the gut have been noted to return to baseline within 2 to 4 weeks after cessation of antibiotics.[7,9,11,29,36,45] It is also possible that microbial disruptions caused by surgical and medical interventions leave a patient susceptible to recolonization by opportunistic pathogens. Further study will hopefully elucidate the

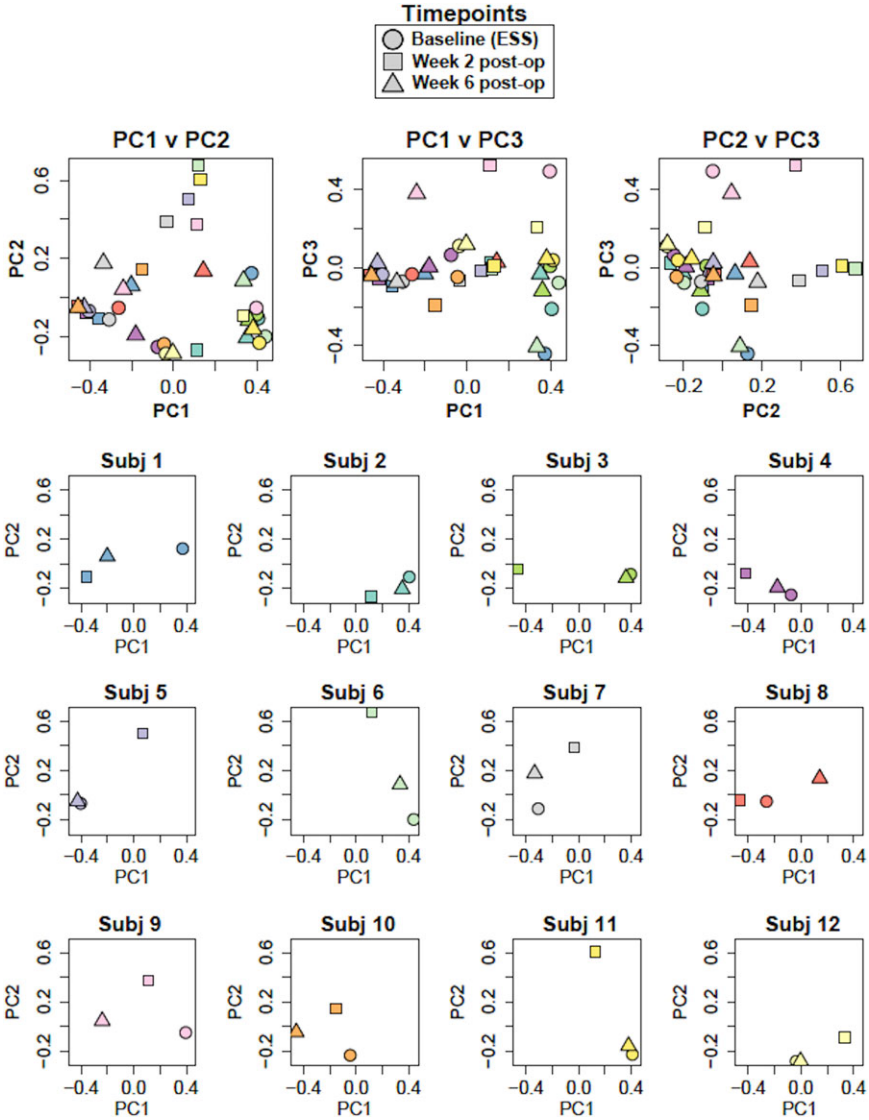

FIGURE 4. PCoA of microbial communities. PCoA was performed on genus-level microbiome data using Morisita-Horn similarity scores calculated on each pair of samples. The top 3 plots show the distribution of samples along PC1-PC2, PC1-PC3, and PC2-PC3. Baseline, 2-week, and 6-week samples are designated by circles, squares, and triangles, respectively. Each subject is designated by a unique color. The bottom 12 plots display the PC1-PC2 plots for individual subjects. ESS = endoscopic sinus surgery; PCoA = principal coordinates analysis.

complex interplay between the microbiome and therapeutic interventions.

Conclusion

Bacterial communities colonizing the ethmoid at 6 weeks postoperatively were most similar to anterior nasal cavity and pretreatment sinus microbial profiles, indicating the resilience of these sites and suggesting they may be potential sources for repopulation of bacteria postoperatively. Bacterial communities appear to largely return to their normal preoperative state, with some degree of interpersonal variation, identifying another variable that could affect therapeutic outcomes. Interestingly, postoperative antibiotic therapy did not reduce the bacterial burden, but rather shifted the microbial consortia.

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Squeeze bottle versus saline spray after endoscopic sinus surgery for chronic rhinosinusitis: A pilot multicentre trial

K. I. Macdonald, M.D., F.R.C.S.C.,[1] E. D. Wright, M.D.C.M., M.Ed.,[2] L. J. Sowerby, M.D., F.R.C.S.C.,[3] B. W. Rotenberg, M.D., F.R.C.S.C.,[3] C. J. Chin, M.D.,[3] L. Rudmik, M.D., M.Sc., F.R.C.S.C.,[4] D. D. Sommer, M.D., F.R.C.S.C.,[5] S. Nayan, M.D.,[5] M. DesRosiers, M.D., F.R.C.S.C.,[6] M. A. Tewfik, M.D.C.M., M.Sc., F.R.C.S.C.,[6] C. J. Valdes, M.D.,[6] E. Massoud, M.B., M.Sc., F.R.C.S.C.,[7] D. Thomas, M.D., M.Sc.,[7] S. J. Kilty, M.D., F.R.C.S.C.,[1] A. Vescan, M.D., F.R.C.S.C.,[8] B. Mechor, M.D., M.Sc., F.R.C.S.C.,[4] F. Lavigne, M.D., F.R.C.S.C.,[9] M. Fandino, M.D., M.Sc.,[8] A. R. Javer, M.D., F.R.C.S.C.,[10] and I. J. Witterick, M.D., M.Sc., F.R.C.S.C.[8]

ABSTRACT

Background: *There is a need for controlled trials to guide the perioperative management of patients undergoing endoscopic sinus surgery (ESS). The authors performed a pilot multicenter trial to compare two types of saline delivery devices in this population.*

Methods: *Patients were randomized to high volume saline irrigation with a squeeze bottle and low volume saline spray after ESS in patients with chronic rhinosinusitis (CRS). Surgeons were blinded to treatment, and one-month postoperative scores for sinonasal outcomes [Sinonasal Outcome Test-22 (SNOT-22)] scale, nasal and sinus symptom score (NSS), and perioperative sinus endoscopy (POSE) scale were compared with preoperative scores.*

Results: *Nine centers provided data for 86 patients. All three outcomes measures improved significantly for both groups. Saline spray: SNOT-22 48.8 versus. 23.7, treatment effect 25.1 (95% confidence interval [CI], 17.9–32.2), POSE 21.1 versus. 8.4, treatment effect 12.7 (95% CI, 9.2–16.1), and NSS 8.2 versus 5.0, treatment effect 3.1 (95% CI, 1.4–4.9) pre- and postoperatively, respectively (all $p < 0.0001$). Squeeze bottle: SNOT-22 49.5 versus 23.6, treatment effect 25.9 (95% CI, 20.3–31.6), POSE 18.6 versus 9.2, treatment effect 9.3, (95% CI 6.7–12.0), and NSS 9.0 versus 5.7, treatment effect 3.3 (95% CI, 2.3–4.3) pre- and postoperatively, respectively (all $p < 0.0001$). Analysis of variance did not identify a difference between the two treatment groups. Subgroup analysis based on preoperative disease severity did not change the nonassociation of saline bottle with outcome measures. Post hoc sample size calculation determined that 176 patients is required to detect an 8.9-point difference in SNOT-22 scores.*

Conclusion: *In this pilot multicenter trial examining patients with chronic rhinosinusitis undergoing ESS, both squeeze bottle and saline spray showed significant improvement in SNOT-22, POSE, and NSS scores at one-month postoperatively. Because the study was nonpowered, we cannot rule out a potential difference between the two treatment groups.*

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Chronic rhinosinusitis (CRS) is a common inflammatory condition of the upper respiratory tract lasting more than 12 weeks. CRS has an estimated prevalence of 5% in the Canadian population,[1] and up to 16% in some adult populations in the United States.[2] Sinusitis is associated with a major societal health care burden, costing billions of dollars a year in North America.[3,4]

The medical treatment of CRS includes topical saline and corticosteroid sprays, systemic steroids, and antimicrobials. Specifically, saline nasal irrigation (SNI) is a safe, nonpharmacologic treatment and is an important and effective treatment option in CRS management.[5,6] SNI can vary by concentration (*e.g.*, hypertonic, isotonic, and hypotonic) and device (*e.g.*, bulb syringe, nasal mist, and squeeze bottle).

[1]Department of Otolaryngology, Head and Neck Surgery, University of Ottawa, Ottawa ON, [2]Division of Otolaryngology, Head and Neck Surgery, FRCSC, University of Alberta, Edmonton AB, [3]Department of Otolaryngology, Head and Neck Surgery, Western University, London, ON, [4]Division of Otolaryngology, Head and Neck Surgery, University of Calgary, Calgary AB, [5]Division of Otolaryngology, Head and Neck Surgery, McMaster University, Hamilton ON, [6]Department of Otolaryngology, Head and Neck Surgery, McGill University, Montreal QC, [7]Division of Otolaryngology, Head and Neck Surgery, Dalhousie University, Halifax NS, [8]Department of Otolaryngology, Head and Neck Surgery, University of Toronto, Toronto ON, [9]Department of Otolaryngology, Head and Neck Surgery, Universite de Montreal, Montreal QC, and [10]Division of Otolaryngology, Head and Neck Surgery, University of British Columbia, Vancouver BC

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Address correspondence to Kristian Macdonald, M.D., F.R.C.S.C., 1081 Carling Avenue, G-3, Ottawa ON, Canada K1Y 4G2

E-mail address: kristian.macdonald@gmail.com

Despite a lack of controlled trials, there is an overall consensus agreement for the use for SNI in the CRS population.[7] Three studies, all more than 15 years old, examined saline formulations that are currently unavailable in North America.[8–10] Harvey *et al.* explored how irrigation is delivered and retained in the sinuses, using more common devices.[11,12] In a cadaveric model, they compared squeeze bottle with saline spray devices and found a greater sinus cavity delivery ($p < 0.02$) in the former. More recently, an Australian prospective trial randomized 74 postsurgical CRS patients to various saline formulations. They found that irrigation with Ringer's solution resulted in improved quality of life measures and endoscopic mucosal appearances, compared with normal and hypertonic saline.[13]

Examples of popular high-volume low-pressure and low-volume formulations include squeeze bottle (NeilMed Pharmaceuticals, Inc., Santa Rosa, CA) and saline spray (Salinex, Sandoz, QC, Canada), respectively. These are positive pressure treatments[11] that are used globally, despite insufficient evidence demonstrating safety or efficacy. This is likely in part because topical saline sprays are considered safe, they do not require a prescription, and they are heavily marketed. To date, there are no studies comparing high-volume, low-pressure devices with low-volume devices in the postoperative CRS patient.

The authors hypothesized that there is an advantage of squeeze bottle over saline spray. The mechanical effect of high volume (240 mL) irrigation debrides and cleans a larger surface area of sinonasal mucosa. A saline spray bottle contains 30 mL, a small portion of which is expelled with each actuation and therefore may not have the same cleansing effect.

There is growing interest to establish a collaborative Canadian Rhinology group to perform multicenter clinical trials. In addition to

Table 1. **Study inclusion/exclusion criteria**

Inclusion Criteria	Exclusion Criteria
Documented diagnosis of unilateral or bilateral CRS	Pregnant
Documented failed medical treatment of CRS	Cystic fibrosis
18–85 years of age	Diagnosed immotile cilia syndrome
Planned ESS for the treatment of CRS	Diagnosed immunodeficiency syndrome
Able to read and understand English	Diagnosed fungal sinusitis
	Sinonasal tumors or obstructive lesions

CRS = chronic rhinosinusitis.

addressing the above clinical question, this pilot study was performed to determine the feasibility of performing such trials.

METHODS

The authors conducted a prospective, multicenter, single blind, randomized trial evaluating symptom and endoscopic outcomes of squeeze bottle versus saline spray in patients who had endoscopic sinus surgery (ESS) for CRS. One-month postoperative scores were compared with preoperative scores.

Initial contact for center study participation was made to 19 practicing Canadian otolaryngologists who had an interest in rhinology. The standard initial information package explained the purpose and protocol of the study. Surgeons who agreed to participate were then guided for study initiation at their center. Each surgeon could enlist the aid of one resident or research assistant.

Because this was a pilot study to determine the feasibility of performing collaborative multicenter trials, effort was made to design a short, feasible trial with a reasonable number of patients. As such, no sample size calculation was performed, and each center was asked to enroll 10 patients who were offered ESS for CRS. The inclusion and exclusion criteria are listed in Table 1.

The primary outcome was successful study completion, with at least 10 participating surgeons each contributing final data on 80% of enrolled patients (total of 80 patients). Secondary outcomes included symptom-based and endoscopic questionnaires: the Sinonasal Outcome Test-22 (SNOT-22), the perioperative sinus endoscopy (POSE) scale, and the nasal and sinus symptoms score (NSS). Preoperative computed tomography (CT) scans were graded using the Lund-Mackay (LM) score.[14]

The SNOT-22 survey is a rhinology-specific quality of life instrument, based on 22 items. It is reliable, valid, responsive, and easy to use.[15] The POSE scoring system has been used to endoscopically assess the sinonasal cavities in ESS patients and compares well with the Lund-Kennedy endoscopy staging system.[16] Each sinonasal cavity site is graded from 0 to 2, based on the degree of inflammation and/or purulence observed, with a total possible score of 20. For our purposes, an adjusted scale with a denominator of 40 was generated for comparison of the two treatment groups. This calculation has been previously described and allows for comparison between patients with varying extent of sinus surgery.[16]

The NSS was developed at McGill University by DesRosiers and colleagues. It is a five-item scale for patients to rate the perceived disability from 0 (no symptoms) to 3 (as bad as it can be). The items include congestion, pain, headache, need to blow nose, and postnasal drip.

Treatment Allocation

Randomization was performed independently for each center with a computer software program, with patients allocated to either "A" or "B." Equally weighted boxes were prepared by NeilMed Pharmaceuticals, and five boxes of bottle A and five boxes of bottle B were sent by mail to each participating surgeon. Only the designated representative at NeilMed Pharmaceuticals and the administrative assistant for the senior author (I.J. Witterick) were aware of treatment allocation. In this way, surgeons were blinded to bottle allocation.

On the day of the surgery, patients were provided with their allocated box and instructed to use the device "two sprays in each nostril twice daily for one month." The directions were the same for both devices. No other specific instructions were given to participating surgeons, and they were free to treat the patient with other medications as per their usual perioperative protocol.

The trial was registered through ClinicalTrials.gov, Unique Identifier NCT01575223. Because NeilMed Sinus Rinse is considered a natural product (NPN 800271420), and not a medication, Health Canada approved the usage of this product for our study, without a formal Clinical Trial Application. The trial qualified as a phase IV trial. (See Health Canada website for more information.)

Statistical Analysis

Primary analysis was performed according to an intention-to-treat analysis. To encourage surgeon participation, there was no attempt to determine a potential center-by-treatment interaction, and instead, data were grouped together.

Preoperative and one-month postoperative SNOT-22, POSE, and NSS scores for the two treatment groups were compared. Patients were stratified according to disease severity using the LM score to determine whether this influenced the association of bottle on outcome measures.

Demographic variables for each bottle type were compared using χ^2 analysis for categorical variables, and paired Student's *t*-test for continuous variables. Analysis of variance was performed to compare the difference in outcome measures between the two treatment groups. Finally, logistic regression models were formulated with the baseline variables included. This was to determine whether controlling for any baseline variables changed the association of bottle type and outcome measure.

95% confidence intervals were calculated, and a *p*-value of 0.05 was set. Results from each center were weighted according to the number of subjects recruited from that center. Based on the variances of the two treatment groups, a sample size calculation was performed for future studies. Analyses were performed with SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

Nineteen surgeons were initially approached for study participation. From March 2012 to November 2013, 11 surgeons from nine centers provided data for 86 patients. Each participating surgeon achieved local institutional ethics board approval. Nine surgeons provided data for at least eight patients. Of the eight surgeons who did not participate, three did not respond to the initial request to participate, three agreed to participate but did not proceed with ethics board submission, and two initiated but did not complete ethics approval.

The two treatment groups were similar in age, gender, primary versus revision surgery, and preoperative SNOT-22, POSE, NSS, and LM scores (Table 2), Patients allocated to the saline spray group were significantly more likely to have CRS with polyps (CRSwP) than CRS without polyps: 31 (72%) versus 12 (28%), respectively, compared with those in the squeeze bottle group: CRSwP, 24 (56%) versus CRS without polyps, 19 (44%), $p = .03$, respectively.

There was significant improvement in the three outcome measures for both treatment groups (Fig. 1). All differences were very highly significant. Comparing the two treatment groups, there was no difference in the pre- and postoperative treatment effects (Fig. 2).

Although no individual center results were displayed, each participating site showed the same magnitude of treatment effect (*i.e.*, all

Table 2. **Baseline characteristics by treatment group**

	Saline Spray (n = 43)	Squeeze Bottle (n = 43)	p-value
Age, years	48.1 (43.8–52.3)	44.5 (40.4–48.7)	0.91
Gender, n (%)			
Male	30 (69.8)	25 (58.1)	
Female	13 (30.2)	18 (41.9)	0.12
Surgery, n (%)			
Primary	21 (48.8)	27 (62.8)	
Revision	22 (51.2)	16 (37.2)	0.07
Polyps, n (%)			
CRSsP	12 (27.9)	19 (44.2)	
CRSwP	31 (72.1)	24 (55.8)	0.03
Preop scales			
SNOT-22 (score/110, CI)	48.8 (42.2–55.4)	49.5 (43.2–55.8)	0.89
POSE (score/40, CI)	21.1 (18.2–24.0)	18.6 (15.5–21.7)	0.88
NSS (score/15, CI)	8.2 (7.0–9.3)	9.0 (8.1–9.8)	0.04
LM (score/24, CI)	17 (15.4–18.6)	15.1 (13.3–16.9)	0.79
Missing, n (%)	3 (6.7)	6 (12.2)	

Categorical variables were compared with χ^2 analysis. Continuous variables were compared with t-test. Preoperative scale scores were weighted to the number of patients from each center. CI = confidence interval; CRSsP = chronic rhinosinusitis without polyposis; CRSwP = chronic rhinosinusitis with polyposis; NSS = nasal and sinus symptom scale; LM = Lund-Mackay scale; Preop = preoperative; POSE = perioperative sinus endoscopy scoring system; SNOT-22 = sinonasal outcomes test-22 scale.

outcomes showed improvement postoperatively, with little difference between saline spray and squeeze bottle).

Subgroup Analysis by Preoperative CT, LM Score

The median value for the LM preoperative CT score was 17.0. Those with more severe preoperative disease (LM > 17.0) were compared with those with less severe disease (LM < 17.0). There were 44 patients in the severe group, and 42 in the less severe group. The main outcome effects were the same as in the whole group, with the severe disease group showing no difference between saline spray or squeeze bottle: mean difference in preoperative and postoperative SNOT-22 scores 27.7 (95% CI, 20.0–35.5) versus 33.2 (95% CI, 24.3–42.0), p = .36, in POSE scores 17.5 (95% CI, 13.5–21.6) versus 11.9 (95% CI, 7.4–16.5), p = .07, and in NSS scores 3.2 (95% CI, 1.3–5.2) versus 4.1 (95% CI, 1.9–6.3), p = .54, respectively. Similarly, those with less severe preoperative disease showed no difference between saline spray or squeeze bottle: mean difference in preoperative and postoperative SNOT-22 scores 21.5 (95% CI, 11.1–31.9) versus 20.0 (95% CI, 10.8–29.2), p = .83, in POSE scores 6.0 (95% CI, 2.1–9.9) versus 7.2 (95% CI, 3.8–10.6), p = .64, and in NSS scores 3.0 (95% CI, 0.8–5.1) versus 2.6 (95% CI, 0.7–4.5), p = .81.

Multivariate Analysis Controlling for Presence of Polyps

As shown in Table 1, patients in the saline spray group were significantly more likely to have CRSwP than those in the squeeze bottle group. To determine the effect that the presence of polyps may have on the outcomes for saline spray and squeeze bottle, logistic regression analysis was performed, controlling for the presence of polyps. Three analyses were run, with difference in pre- and postoperative SNOT-22, POSE, and NSS scores as outcomes. For all three outcome measures, the presence of polyps was not found to be a significant predictor. Similarly, whether the presence of polyps variable was in the model, there was still no significant association between bottle type and outcome measure (all p > 0.05, all 95% confidence intervals overlapping 0) (data not shown).

Sample Size Calculation

To help guide future studies, variances from the differences in preoperative and postoperative SNOT-22 scores were used to perform a sample size calculation. The authors agreed on a minimally clinically important difference in SNOT-22 of 8.9.[17] A total of 176 (88 in each arm) patients would be required to detect this difference, with a significance level (α) of 0.05 and 80% power, using a two-sided two-sample t-test.

DISCUSSION

This group of Canadian rhinologists was successful in carrying out a multicenter trial. A similar United States trial with three centers enrolled 302 CRS patients who had ESS.[18] With an average follow-up of 17.4 months, most patients improved across multiple quality of life outcomes. Another United States collaborative trial enrolled 31 otolaryngologists and 117 patients having either medical or surgical therapy for CRS, with 12-month follow-up.[19] Again, quality of life measures improved significantly postoperatively. The authors here concluded, "This study demonstrated the feasibility of multicenter outcome studies in chronic rhinosinusitis and generated testable hypotheses for future investigation."

Despite the limitations of a pilot study, our patient numbers and results compare well with the two multicenter trials above. We achieved impressive recruitment of surgeons and patients, with nine surgeons recruiting at least 80% of the required number of patients. Interestingly, our sample size calculation determined that doubling the enrollment would have sufficiently powered the data.

Similar to previous studies on ESS for CRS, patients in both groups improved significantly postoperatively.[18–22] Because our sample was not powered to detect a difference, we cannot make conclusions on the nonassociation between bottle type and outcome improvement, without risk of a type II error (not detecting a difference when there really is one).

We gained knowledge for the successful conduct of future multicenter trials. A longer follow-up period would help determine a clinically meaningful difference between the two treatment arms. To minimize residual confounding and increase generalizability, we could include more covariates, such as the extent of surgery, middle meatal stenting, prescribed medications such as oral steroids and antibiotics, postoperative infections,[23] frequency of postoperative debridement, and measures of patient compliance.

In general, surgeons who worked with a research assistant or resident were more likely to complete the study. Although at times burdensome and time consuming, all local institutional ethics board applications were

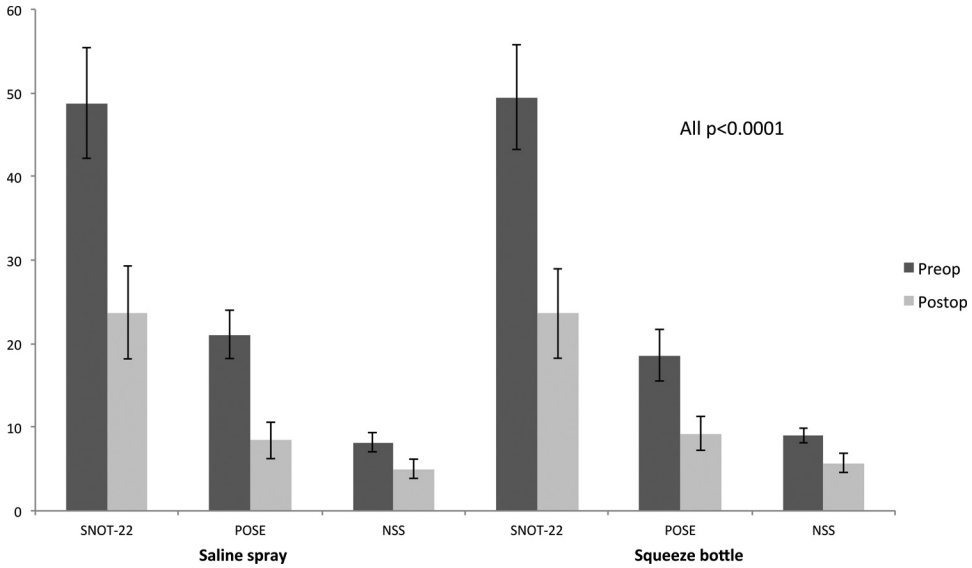

Figure 1. Preoperative versus postoperative scale scores by saline bottle. Preop = preoperative; Postop = postoperative. Error bars represent 95% confidence intervals; p-values were very highly significant for all preoperative versus postoperative scale scores, using a t-test comparing means. Scale scores were weighted to the number of patients from each center.

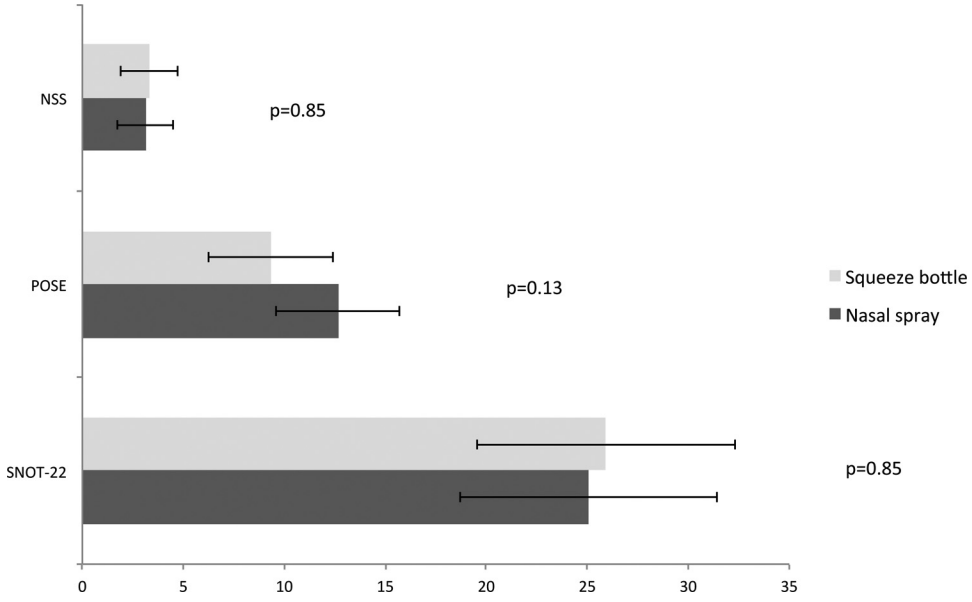

Figure 2. *Postoperative improvement in scale scores. Mean changes in postoperative versus preoperative scores were compared between saline spray and squeeze bottle using analysis of variance (ANOVA). Scale scores were weighted to the number of patients from each center. Error bars represent 95% confidence intervals. The study was not powered to detect a difference between the two-treatment arms.*

successful. A national and uniform ethics board approval for all participating centers would immensely improve efficiency.

A potential disadvantage of our results is selection bias, for both the surgeon and the patient. Surgeons were instructed to recruit consecutive patients to help minimize this bias. Patients who agreed to participate in the trial may have had more or less severe disease than patients who usually have ESS for CRS, which could bias the results toward or away from the null hypothesis. Another potential disadvantage is that patients were not blinded to treatment allocation, which may have influenced their responses on the subjective forms. However, postoperative changes in SNOT-22 and NSS scores were similar to changes in POSE scores, which were rated by blinded surgeons. In addition, these potential disadvantages, selection bias, and lack of blinding are common obstacles to performing randomized surgical trials.[24,25]

The authors of this study are ideally situated for multicenter trials. These are for the most part surgeons at academic centers, who are fellowship trained with a special interest in rhinology, experienced in clinical trials, and have access to CRS patients in all the major Canadian cities. This pilot study demonstrates our capacity to effectively collaborate, and the lessons learned will help ensure success in future trials.

CONCLUSION

This study demonstrated the feasibility of multicenter trials with this group of Canadian rhinologists. Both treatment groups of squeeze bottle and saline spray, in patients having ESS for CRS, showed significant improvement in SNOT-22, POSE, and NSS scores at one-month postoperatively. Because this was a nonpowered pilot study, we could not rule out a difference between in outcomes between the two treatment groups.

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The Laryngoscope

Complication Rates After Functional Endoscopic Sinus Surgery: Analysis of 50,734 Japanese Patients

Sayaka Suzuki, MD; Hideo Yasunaga, MD, PhD; Hiroki Matsui, MPH; Kiyohide Fushimi, MD, PhD; Kenji Kondo, MD, PhD; Tatsuya Yamasoba, MD, PhD

Objective: The complication rates associated with different types of functional endoscopic sinus surgery (FESS) remain to be fully examined.

Study Design: Retrospective cohort study.

Methods: We extracted data from the Japanese Diagnosis Procedure Combination database on 50,734 patients (aged $\geq$ 16 years) who underwent FESS for chronic rhinosinusitis between 2007 and 2013. We focused on specific types of surgery and stratified the patients into three groups: group 1 (single sinus surgery), group 2 (multiple sinus surgery), and group 3 (whole sinus surgery). Patient characteristics and early postoperative complications including cerebrospinal fluid (CSF) leakage, orbital injury, severe hemorrhage, and toxic shock syndrome (TSS) that occurred during 1 to 2 weeks of each hospitalization were compared. Multivariable logistic regression analysis was performed to assess the association between overall complication rate and background characteristics, with adjustment for within-hospital clustering.

Results: The overall complication rate was 0.50%; the rates of CSF leakage, orbital injury, hemorrhage requiring surgery, blood transfusion, and TSS were 0.09%, 0.09%, 0.10%, 0.18%, and 0.02%, respectively. Ethmoidectomy combined with sphenoidotomy was associated with higher overall complication rates (1.40%). The rate of orbital injury was highest in group 2, whereas that of other complications did not differ significantly among the groups. Extent of FESS showed no significant association with overall complication rate.

Conclusion: More extensive FESS was not associated with increased rates of postoperative CSF leakage, hemorrhage, or TSS. Multiple sinus surgery was associated with a higher rate of orbital injury. The extent of surgery did not significantly affect the overall complication rate.

Key Words: Chronic rhinosinusitis, functional endoscopic sinus surgery, intraoperative complication, postoperative complication, nationwide study, types of surgery.

Level of Evidence: 2b.

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INTRODUCTION

Functional endoscopic sinus surgery (FESS) for chronic rhinosinusitis (CRS) was introduced in the 1980s and is now one of the most commonly performed otorhinolaryngological procedures.[1,2] The term describes many different procedures, such as maxillary antrostomy, ethmoidectomy, and a combination of two or more surgeries, but classification of FESS procedures according to the extent of surgery has not been well standardized.

Functional endoscopic sinus surgery is generally a safe procedure, but serious complications may occur. Reported complication rates vary widely because of differences in study populations and study periods, with cerebrospinal fluid (CSF) leakage reported in 0.004% to 0.55% of cases, orbital hematoma or injury reported in 0.02% to 6.6% of cases, severe hemorrhage reported in 0.19% to 3.9% of cases,[3–14] and toxic shock syndrome (TSS) reported in 0.017% of cases.[15] Because complications are rare, a large sample size is needed to determine complication rates. The sample sizes of most previous studies were too small to accurately assess postoperative morbidity after FESS, which limits the usefulness of the conclusions.[16] To our knowledge, the largest study reporting complications after FESS was conducted in the United States (n = 62,823),[4] but that study did not evaluate outcomes according to the specific type of surgery performed.

The aim of this retrospective observational study was to investigate the rates of early postoperative complications (CSF leakage, meningitis, orbital injury, orbital hematoma, binocular movement disorder, hemorrhage requiring surgery or blood transfusion, and TSS) recorded during each hospitalization (hereafter referred to as *complication rates*) using a nationwide inpatient

From the Department of Clinical Epidemiology and Health Economics, School of Public Health (S.S., H.Y., H.M.); the Department of Otolaryngology and Head and Neck Surgery, Faculty of Medicine (S.S., K.K.,T.Y.), The University of Tokyo; and the Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School of Medicine (K.F.), Tokyo, Japan

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Send correspondence to Sayaka Suzuki, MD, Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 1130033, Japan. E-mail: sayasuzuki-tky@umin.ac.jp

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database in Japan. First, we described the complication rates according to the specific types of surgery, including maxillary antrostomy, ethmoidectomy, sphenoidotomy, and surgeries for two or more sinuses. Next, we compared the complication rates according to the type of FESS performed (single, multiple, or whole sinus surgery). Finally, we analyzed the association between overall complication rate and background characteristics.

MATERIALS AND METHODS

Data Source

Data were obtained from the Diagnosis Procedure Combination (DPC) database, which is a national inpatient database in Japan that includes administrative claims data and discharge abstract data. This study was approved by the institutional review board of The University of Tokyo, Japan. Because of the anonymous nature of the data, informed consent was not required.

For each patient, the database includes: 1) the main diagnoses, comorbidities at admission, and complications after admission, coded by International Statistical Classification of Diseases (ICD)−10 codes; 2) surgical interventions, coded by original Japanese codes; 3) age, sex, and patient characteristics; 4) procedure costs; and 5) type of hospital (academic or nonacademic). The database includes the dates of all surgical procedures and blood transfusions. Codes for procedures, medication, blood transfusion, surgery, and anesthesia are almost complete because they are compulsory for health care cost reimbursement. To maximize accuracy of the data, the physicians in charge are required to record the information about diagnoses, comorbidities, and therapies from patients' medical charts. In the DPC database, the diagnoses of comorbidities after admission can be clearly distinguished from those of comorbidities at admission. The duration of data collection in the database was 6 months (July 1 to December 31) each year from 2007 to 2010, and it was extended to the entire year from 2011. All 82 academic hospitals across Japan are obliged to participate in the DPC database, whereas the participation of community hospitals is voluntary. The number of patients included in 2012 was 6.8 million, which represents more than 50% of all inpatient admissions to acute care hospitals in Japan.[17] A more detailed description has previously been published.[18]

Patient Selection

Data were extracted for patients who underwent sinus surgery from July 2007 to March 2013 (51 months in total). Patients were included if they had a diagnosis of chronic sinusitis (ICD-10 code: J32x) or nasal polyps (J33x) at the time of admission and underwent sinus surgery during the admission. The exclusion criteria were: 1) meningitis (G00x to G03x), meningoencephalitis (G04x, G05x), abscess of orbit (H050), abscess of face (i.e., frontal abscess in patients with frontal sinusitis, and buccal abscess in those with maxillary sinusitis; L020), or intra-/extracranial abscess (G060, G062) at the time of admission; 2) malignant neoplasm (Cxx); 3) papilloma or other benign neoplasm of the paranasal or nasal cavities (D14.0); 4) benign neoplasm of the meninges (D32x); 5) benign neoplasm of the brain or another part of the central nervous system (D33x); 6) neoplasm of uncertain or unknown behavior of the brain or another part of the central nervous system (D43x); 7) neoplasm of the pituitary gland (D44.3); 8) age $\leq$ 15 years; and 9) Caldwell-Luc operation, Killian operation, or surgery for organic hematoma.

We focused on the following surgeries: maxillary antrostomy; ethmoidectomy; sphenoidotomy; frontal sinusotomy combined with/without ethmoidectomy (FE); ethmoidectomy and sphenoidotomy (ES); ethmoidectomy and maxillary antrostomy (EM); ethmoidectomy and maxillary antrostomy with frontal sinusotomy (EMF); ethmoidectomy and maxillary antrostomy with sphenoidotomy (EMS); and surgery for all the sinuses on one side (EMFS). Patients were divided into three groups according to the extent of surgery performed: group 1, single sinus surgery (maxillary antrostomy, ethmoidectomy, sphenoidotomy); group 2, multiple sinus surgery (procedure for two or more sinuses, including FE, ES, EM, EMF, and EMS); and group 3, whole sinus surgery (EMFS). Because frontal sinusotomy is usually combined with ethmoidectomy, we classified it as group 2. The number of patients who underwent turbinectomy was counted. We excluded patients who received two or more types of sinus surgery during a single hospitalization and included patients who underwent only one type of the abovementioned surgery in each hospitalization.

Patient Background Characteristics and Outcomes

The patient background characteristics assessed were age, sex, Charlson Comorbidity Index (CCI),[19,20] smoking status (nonsmoker/current or ex-smoker), allergic rhinitis, asthma, aspirin-induced asthma (AIA), and image-guided surgery (IGS) (yes/no).

Cerebrospinal fluid leakage was identified by the ICD-10 code for CSF leakage (G960) or by surgery to repair CSF leakage. Postoperative meningitis and meningoencephalitis were identified by the ICD-10 codes G00x to G05x. Total cranial complications included CSF leakage with/without surgery and postoperative meningitis/meningoencephalitis. Orbital injury was identified by the ICD-10 codes for orbital hematoma (H052), disorder of binocular movement (H519), fracture of the orbital floor (S023), other orbital parts (S028), or by surgery to repair orbital fractures. Total orbital injury included orbital injury with/without surgery, orbital hematoma, and disorders of binocular movement. Severe bleeding was identified by the use of blood transfusion or surgery for hemostasis after sinus surgery. Toxic shock syndrome was identified by the ICD-10 codes for streptococcal sepsis (A40x) or other sepsis (A41x) after admission and by the Japanese text data for "toxic shock."

Statistical Analysis

Patient characteristics and complications were compared among the three groups of patients using the t test or χ^2 test, as appropriate. Multivariable logistic regression analysis was performed to analyze the association between each type of complication and patient background characteristics, including age, sex, smoking status, CCI, allergic rhinitis, asthma, IGS, extent of surgery, and type of hospital (academic or nonacademic), with adjustment for within-hospital clustering using a generalized estimating equation.[21] To assess the multicollinearity between the independent variables, we checked variance inflation factors for each independent variable. A variance inflation factor of more than 10 was considered to show multicollinearity. A P value < 0.05 was considered statistically significant. All analyses were performed using the Statistical Package for Social Sciences 20.0 (IBM SPSS Corp., Armonk, NY).

RESULTS

Among 80,152 patients who underwent sinus surgery during the study period, 64,466 had a diagnosis of chronic sinusitis or nasal polyps at the time of

TABLE I.
Patient Characteristics According to the Extent of Surgery.

	All (n = 50,734)	Group 1 (n = 3,616)	Group 2 (n = 29,034)	Group 3 (n = 18,084)	*P* Value
Age (years), mean ± SD	54.0 ± 15.4	56.1 ± 16.5	54.0 ± 15.7	53.5 ± 14.7	< 0.001
Sex (male), n (%)	33,191 (65.4)	2,186 (60.4)	18,452 (63.6)	12,553 (69.4)	< 0.001
CCI, n (%)					
0	49,181 (96.9)	3,504 (96.9)	28,171 (97.0)	17,506 (96.8)	0.387
≥ 1	1,553 (3.1)	112 (3.1)	863 (3.0)	578 (3.2)	
Smoking, n (%)					
current or ex-smoker	12,642 (24.9)	756 (20.9)	7,070 (24.4)	4,816 (26.6)	< 0.001
nonsmoker	26,088 (51.4)	1,974 (54.6)	15,182 (52.3)	8,932 (49.4)	
unspecified	12,004 (23.7)	886 (24.5)	6,782 (23.4)	4,336 (24.0)	
Allergic rhinitis, n (%)	1,865 (3.7)	113 (3.2)	1,069 (3.7)	683 (3.8)	0.163
Asthma, n (%)	3,861 (7.6)	163 (4.5)	1,559 (5.4)	2,139 (11.8)	< 0.001
AIA, n (%)	293 (0.6)	15 (0.4)	111 (0.4)	167 (0.9)	< 0.001
Image-guided surgery, n (%)	3,867 (7.6)	193 (5.3)	1,897 (6.5)	1,777 (9.8)	< 0.001
Academic hospitals, n (%)	16,119 (31.8)	1,110 (30.7)	7,707 (26.5)	7,302 (40.4)	< 0.001

Group 1, single sinus surgery; group 2, multiple sinus surgery; group 3, whole sinus surgery.
AIA = aspirin-induced asthma; CCI = Charlson Comorbidity Index; SD = standard deviation.

admission. Of these, 2,550 patients were excluded for the following reasons: meningitis or meningoencephalitis (n = 52); orbital abscess (n = 58), facial abscess (n = 4) or intra-/extracranial abscess (n = 4) at the time of admission; malignant neoplasm (n = 366); papilloma or other benign neoplasm of the paranasal or nasal cavities (n = 2,105); benign neoplasm of the meninges (n = 32); benign neoplasm of the brain or another part of the central nervous system (n = 12); neoplasm of uncertain or unknown behavior of the brain or another part of the central nervous system (n = 55); neoplasms of the pituitary gland (n = 40); or age ≤ 15 years (n = 1,377). A total of 57,588 patients who underwent endoscopic sinus surgery were identified. Of those, 2,226 were excluded because they underwent the Caldwell-Luc operation, Killian operation, or surgery for organic hematoma. We also excluded 4,628 patients who received two or more types of sinus surgery during hospitalization. The remaining 50,734 eligible patients from 706 hospitals were divided into three groups: group 1 (single sinus surgery), group 2 (multiple sinus surgery), and group 3 (whole sinus surgery).

Table I shows the patient characteristics in each group. Patients in group 1 were older (mean age 56.1 years) than those in group 2 (mean age 54.0 years) and group 3 (mean age 53.5 years). The proportions of patients with CCI and allergic rhinitis were similar among the three groups. Of the 3,861 asthma patients, 293 patients had AIA. The proportions of current/ex-smokers and patients with asthma were greater in groups 2 and 3 than in group 1, and those with AIA were greater in group 3 than in group 1 or 2, suggesting that current/ex-smokers and patients with asthma or AIA received more extensive sinus surgery. There was a linear relationship between the frequency of IGS and the extent of sinus surgery. The proportion of patients treated at academic hospitals was lower in group 2 (26.5%) than in group 3 (40.4%) and group 1 (30.7%).

Table II details the overall complication rates in each type of surgery. More than one-third of patients had EM (n = 17,291) or EMFS (n = 18,084), followed by EMF (n = 7,358) and EMS (n = 2,818). The overall complication rate was highest in ES (1.40%), whereas those in other surgeries were all < 1%. The rate of CSF leakage was highest in FE (0.23%), followed by EMF (0.20%). The rate of orbital injury was highest in EM (0.15%), followed by FE (0.12%). The rates of postoperative hemorrhage requiring surgery, blood transfusion, and TSS were highest in ES and were 0.28%, 0.70%, and 0.28%, respectively. No patient had a postoperative brain abscess.

Table III shows the overall complication rates in all of the groups and complication rates according to the extent of FESS. The overall complication rate was 0.50% (254/50,734). The rate of CSF leakage with or without surgery was not significantly different among groups 1, 2, and 3 (χ^2 test). However, the rate of total orbital injury was significantly higher in group 2 than in the other groups (0.03%, 0.15%, and 0.13% in groups 1, 2, and 3, respectively; $P = 0.016$). The rate of postoperative hemorrhage requiring surgery or blood transfusion was not significantly different among the three groups. A wider extent of sinus surgery was associated with a longer duration of anesthesia ($P < 0.001$), longer length of postoperative hospital stay ($P < 0.001$), and higher total cost ($P < 0.001$). Among all patients, the mean duration of anaesthesia was significantly longer in patients with any complication than in patients with no complication (226 ± 113 minutes vs. 162 ± 65 minutes; $P < 0.001$). Postoperative length of stay (days, mean ± standard deviation [SD]) for patients with any complication (n = 254) was significantly longer than for patients with no complication (n = 50,480) (15.3 ± 19.2 days vs. 7.2 ± 2.9 days, $P < 0.001$).

TABLE II.
Complication Rates According to Specific Type of Surgery.

n (%)	Group 1			Group 2					Group 3
	Maxillary Antrostomy	Ethmoidectomy	Sphenoidotomy	FE	ES	EM	EMF	EMS	EMFS
Total	1,501	1,695	420	853	714	17,291	7,358	2,818	18,084
Overall complications	6	4	1	6	10	75	41	15	96
	(0.40%)	(0.25%)	(0.24%)	(0.70%)	(1.40%)	(0.43%)	(0.56%)	(0.53%)	(0.53%)
Total cranial complications*	0	2	0	2	2	11	15	2	18
		(0.12%)		(0.23%)	(0.28%)	(0.06%)	(0.20%)	(0.07%)	(0.10%)
CSF leakage in total	0	1	0	2	1	11	15	2	14
		(0.06%)		(0.23%)	(0.14%)	(0.06%)	(0.20%)	(0.07%)	(0.08%)
CSF leakage requiring surgery	0	0	0	0	0	1	3	1	1
						(0.01%)	(0.04%)	(0.04%)	(0.01%)
Meningitis	0	1	0	0	1	0	0	0	4
		(0.06%)			(0.14%)				(0.02%)
Total orbital injury†	0	1	0	2	0	29	11	1	13
		(0.06%)		(0.23%)		(0.17%)	(0.15%)	(0.04%)	(0.07%)
orbital injury requiring surgery	0	0	0	0	0	2	0	0	0
						(0.01%)			
Hemorrhage requiring surgery	2	0	0	1	2	13	4	5	25
	(0.13%)			(0.12%)	(0.28%)	(0.08%)	(0.05%)	(0.18%)	(0.14%)
Blood transfusion	3	1	1	1	5	21	12	8	39
	(0.20%)	(0.06%)	(0.24%)	(0.12%)	(0.70%)	(0.12%)	(0.16%)	(0.28%)	(0.22%)
Toxic shock syndrome	1	0	0	0	2	2	2	0	3
	(0.07%)				(0.28%)	(0.01%)	(0.03%)		(0.02%)

*Included CSF leakage with/without surgery and postoperative meningitis.
†Included orbital injury with/without surgery, orbital hematoma, and binocular movement disorders.
Group 1, single sinus surgery; group 2, multiple sinus surgery; group 3, whole sinus surgery
CSF = cerebrospinal fluid; ES = ethmoidectomy and sphenoidotomy; EM = ethmoidectomy and maxillary antrostomy; EMF = ethmoidectomy and maxillary antrostomy with frontal sinusotomy; EMS = ethmoidectomy and maxillary antrostomy with sphenoidotomy; EMFS = surgery for all the sinuses on one side; FE = frontal sinusotomy combined with/without ethmoidectomy.

The overall complication rate was not significantly different between patients with asthma (0.34%, 13/3,861) and patients without asthma (0.48%, 226/46,873) ($P = 0.216$), between patients with AIA (0.68%, 2/293) and patients without AIA (0.47%, 237/50,441) ($P = 0.595$), or between current/ex-smokers (0.45%, 57/12,642) and nonsmokers (0.44%, 116/26,088) ($P = 0.352$). The overall complication rates in patients with and without IGS were 0.7% (26/3,867) and 0.5% (228/46,867), respectively ($P = 0.073$). The postoperative length of stay (days, mean $\pm$ SD) was 7.8 ± 4.4 and 7.1 ± 3.1 ($P < 0.001$), respectively; and total costs (USD) were $\$7,853 \pm \$2,621$ and $\$6,423 \pm \$2,262$ ($P < 0.001$), respectively, in the groups with or without IGS.

Table IV details the results of multivariable regression analysis. Variance inflation factors were all less than 1.5, indicating no multicollinearity. Charlson Comorbidity Index ≥ 1 was associated with a higher overall complication rate, and comorbid asthma with a smaller rate. No significant association with overall complication rate was seen for age, sex, smoking status, allergic rhinitis, extent of surgery, IGS, or type of hospital.

Turbinectomy was performed in 2,193 patients. Among these, only three patients received surgery for hemostasis, and none required blood transfusion. Of the three patients, two underwent turbinectomy combined with EMFS, and one underwent turbinectomy combined with EM.

DISCUSSION

The results of this study show that the overall complication rate after FESS in Japan is low at 0.50% (254/50,734). This figure is comparable to those reported in previously studies (0.23% to 11.7%).[3–14] Higher proportions of complications were found in specific types of surgery, including ES, FE, and EMF. Each complication rate was not associated with the extent of sinus surgery, except for total orbital injuries. Charlson Comorbidity Index ≥ 1 was independently associated with the overall occurrence of complication, whereas other factors including extent of surgery, IGS, and type of hospital were not.

Functional endoscopic sinus surgery is widely accepted as a safe and standard treatment in Japan and other countries for CRS that is refractory to nonsurgical treatment. Although rare, major complications such as CSF leakage, orbital injury, and severe hemorrhage requiring surgical intervention may occur even in experienced hands because of the anatomical proximity of the sinuses to the orbit and the anterior skull base. CSF leakage and orbital injury may have a negative impact on the patient's life. Toxic shock syndrome is a rare acute

TABLE III.
Complication Rates According to Surgical Type.

	All (n = 50,734)	Group 1 (n = 3,616)	Group 2 (n = 29,034)	Group 3 (n = 18,084)	*P* Value
Overall complications, n (%)	254 (0.50)	11 (0.30)	147 (0.51)	96 (0.53)	0.207
Total cranial complications*, n (%)	50 (0.10)	2 (0.06)	32 (0.11)	18 (0.10)	0.685
CSF leak in total, n (%)	46 (0.09)	1 (0.03)	31 (0.11)	14 (0.08)	0.251
CSF leak requiring surgery, n (%)	6 (0.01)	0	5 (0.02)	1 (0.01)	0.417
Meningitis, n (%)	6 (0.01)	1 (0.03)	1 (0.00)	4 (0.02)	0.128
Total orbital injury †, n (%)	57 (0.09)	1 (0.03)	43 (0.15)	13 (0.13)	0.016
Orbital injury requiring surgery, n (%)	2 (0.00)	0	2 (0.00)	0	0.474
Hemorrhage requiring surgery, n (%)	52 (0.10)	2 (0.06)	25 (0.09)	25 (0.14)	0.149
Blood transfusion, n (%)	91 (0.18)	5 (0.14)	47 (0.16)	39 (0.22)	0.338
Toxic shock syndrome, n (%)	10 (0.02)	1 (0.03)	6 (0.02)	3 (0.02)	0.896
Duration of anesthesia (minute, mean ± SD)	161 ± 66	124 ± 59	149 ± 60	185 ± 67	< 0.001
Postoperative length of stay (day, mean ± SD)	7.2 ± 3.2	6.9 ± 4.0	7.2 ± 3.0	7.3 ± 3.4	< 0.001
Total cost (USD, mean ± SD)	6535 ± 2324	4271 ± 1940	5931 ± 1851	7958±2293	< 0.001

Group 1, single sinus surgery; group 2, multiple sinus surgery; group 3, whole sinus surgery.
*Included CSF leakage with/without surgery and postoperative meningitis.
†Included orbital injury with/without surgery, orbital hematoma, and binocular movement disorders.
CSF = cerebrospinal fluid; SD = standard deviation; USD = United States dollar.

multisystem disorder, caused by toxins produced by Staphylococcus aureus or group A streptococcus. Early diagnosis and immediate therapy including removal of nasal packing, drainage of pus, and antibiotics are essential for the treatment of TSS.[22–25] Physicians should provide patients with adequate information regarding these potential complications prior to FESS.[26–29] Knowledge of the risks associated with the different types of surgery is useful for providing information to patients undergoing FESS.

Only a few previous studies reported on associations between the extent of surgery and surgical outcomes.[6,9,13] One study found that complication rates were higher in patients who underwent more extensive sinus surgery.[9] Intra- and postoperative hemorrhage (1.3%), CSF leakage (1.1%), and orbital hematoma (0.6%) were the most common complications in 3,402 patients who underwent FESS by a single surgeon, and extensive disease status was associated with a higher risk of complications. A prospective study in the United Kingdom (n = 3,128) [13] found that the complication rate was associated with the extent of disease measured in terms of symptom severity and health-related quality of life but not with surgical characteristics including the extent of surgery (simple polypectomy/antral washout vs. inferior meatus/middle meatus/anterior ethmoid surgery vs. distal sinus surgery). A recent retrospective study (n = 2,596) also did not find an association between complications and the extent of surgery.[6] It should be noted, however, that these studies were limited by small sample sizes.

In the current large-scale nationwide study, FESS procedures were categorized into three groups according to the extent of surgery. The results show that a wider extent of surgery was not necessarily associated with a higher rate of each complication. The extent of surgery itself was not significantly associated with the overall complication rate after adjustment for other background factors. More extensive sinusitis and polyps could have resulted in absence of surgical landmarks because of the long duration of mucosal inflammation or increased pressure on the surrounding structures, and absence of surgical landmarks could have made the procedures more difficult and impacted negatively on surgical outcomes. Another view exists, however, that the occurrence of any intraoperative complication may have impeded

TABLE IV.
Multivariable Logistic Regression Analysis.

Factors	Odds Ratio	95% Confidence Interval	*P* Value
Age, by 10-year increase	0.98	0.88–1.08	0.639
Sex (female)	0.73	0.52–1.02	0.065
Smoking category (vs. nonsmoker)			
Current/ex-smoker	0.91	0.63–1.34	0.644
Unspecified	1.12	0.80–1.56	0.506
CCI (≥ 1 vs. 0)	4.56	3.01–6.91	<0.001
Asthma	0.50	0.25–0.99	0.046
Allergic rhinitis	1.01	0.54–1.89	0.985
Extent of surgery (vs. group 1)			
Group 2	1.68	0.88–3.22	0.117
Group 3	1.69	0.90–3.20	0.105
Image-guided surgery	1.31	0.84–2.04	0.232
Academic hospital	1.40	0.92–2.13	0.119

Group 1, single sinus surgery; group 2, multiple sinus surgery; group 3, whole sinus surgery.
CCI = Charlson Comorbidity Index.

continuation of the planned surgery, resulting in a lower rate of complications in more extensive sinus surgery.

In this study, none of the rates of CSF leakage, meningitis, orbital hematoma, binocular movement disorder, postoperative hemorrhage requiring surgery/blood transfusion, or TSS was associated with the extent of sinus surgery. However, the rate of total orbital injury was associated with the extent of sinus surgery and was highest in group 2. Most cases of orbital injury were treated conservatively. Complete removal of the diseased mucosa, reopening of the sinus, and drainage of effusion could have contributed to the safety of procedures in group 3.

Regarding specific types of surgery, ES had the highest overall complication rate (1.40%), followed by FE and EMF. The association between surgery for ethmoid sinus and a higher rate of complications would be inevitable due to the anatomical location of the ethmoid sinus adjacent to the orbit and anterior skull base and because it contains the anterior ethmoidal artery. Additional frontal sinusotomy or sphenoidotomy for EM showed only a slight increase in the overall complication rate. Taking into consideration the higher complication rate in ES than in EMS, additional maxillary antrostomy could have allowed a better understanding of the anatomical landmarks. However, because of the difference in the sample sizes between ES and EMS, the results should be interpreted cautiously.

Considering that the development of paranasal sinuses is almost complete by the age of 15 years,[30,31] the insignificant association between age and overall complication rate is plausible.

Previous studies suggested that IGS in FESS for CRS accurately confirmed the paranasal anatomy, especially in patients with poor surgical landmarks because of CRS itself, individual anatomical distortion, or previous surgery, and possibly contributed to favorable surgical outcomes.[32,33] However, a reduction in clinical complications with IGS has not been statistically confirmed. The current study also showed no significant association between IGS and overall complication rate. However, no definitive conclusions could be drawn because the data on revision surgery or paranasal anatomy was not available in the current study. Selection bias by physicians for IGS cannot be eliminated because of the retrospective nature of this study; that is, patients with more complex paranasal anatomy may have been more likely to have received IGS.

The reduced risk of overall complications in patients with asthma was shown in the multivariable regression analysis in our study, in contrast to the results of a previous study from Japan.[14] The possible explanation for this may be that asthma patients were more likely to receive early surgery because FESS in asthma patients may improve clinical outcomes of asthma.[34]

The proportion of sinus surgeries performed in academic hospitals in Japan may be higher than that in Western countries. This may be related to differences in clinical practices and health care systems between countries. Postoperative intranasal packing is routinely performed in most Japanese hospitals. In Japan, patients usually stay in hospital for several days after sinus surgery for follow-up medical care and in case of severe bleeding after the removal of nasal packing. Furthermore, FESS is widely performed both by trainees or ear, nose, and throat specialists (in Japan, qualified as board-certified otorhinolaryngologists), and in academic hospitals and nonacademic hospitals.

Several limitations of this study should be acknowledged. First, this was a retrospective observational study, without random treatment assignment. Unrecorded confounding factors such as preoperative Lund-Mackay CT score, revision surgery, each surgeon's experience, synechia formation, and individual anatomical distortions may have affected complication rates and the duration of anesthesia. Second, comorbidities are generally recorded less accurately in an administrative claims database than in planned prospective studies. The relatively low complication rate in our study could be explained by differences in the definition of each complication between studies. Symptoms and signs are generally less likely to be reported in administrative databases, and recorded complications are considered to be underestimated. Additionally, delayed complications, which were reported in a previous study,[4] were not identified in the current study and would likely lead to an underestimation of the complication rates.

CONCLUSION

This study used a nationwide Japanese inpatient database to evaluate the current complication rates after FESS for CRS, according to the specific types of surgery and the extent of surgery (single sinus surgery, multiple sinus surgery, or whole sinus surgery). The overall complication rate was low (0.50%). ES was associated with the highest overall complication rate (1.40%). Whole sinus surgery was not associated with higher rates of CSF leakage, orbital injury requiring surgery, or postoperative hemorrhage requiring surgery or blood transfusion than less extensive sinus surgery. The extent of surgery was not independently associated with the overall occurrence of complications.

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Oral corticosteroids in the management of chronic rhinosinusitis with and without nasal polyps: Risks and benefits

David M. Poetker, M.D., M.A.

ABSTRACT

Background: *Oral steroids are synthetic mimics of adrenal cortex hormones and are considered a staple in the management of chronic rhinosinusitis due to their anti-inflammatory effects. Despite their common use, many providers are not familiar with the potential risks of the drugs.*

Methods: *Literature review.*

Results: *An overview of the existing data on the risks of oral steroids is presented as well as a review of the malpractice lawsuits with regard to oral steroid use and a discussion of the data that support the use of oral steroids in patients with chronic rhinosinusitis with and those without nasal polyps.*

Conclusion: *It is essential for providers to be aware of the potential complications of a medication, the medical jurisprudence of the drugs, and the data that support their use.*

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Oral steroids are a mainstay of treatment in the management of sinonasal inflammatory disease, are commonly used, and are considered by many rhinologists to constitute a key component of "maximal" medical therapy.[1] Their anti-inflammatory effects to treat the inflammation associated with chronic rhinosinusitis (CRS) as well as their antifibroblast effects to reduce postoperative scar formation are the most common reasons for their widespread use.[2] Despite their common use, many providers are not familiar with the potential risks of the drugs.

The objectives of this review were to present an overview of the existing data on the risks of oral steroids. This was not intended to be an exhaustive review because other articles exist that specifically outline those risks.[3] We plan to discuss what is known about specific risks, review the lawsuits regarding oral steroid use, and finally, discuss the data that support the use of oral steroids in patients with CRS, with and without nasal polyps.

COMPLICATIONS OF STEROID USE

Morphologic Changes

Redistribution of adipose tissue, a common effect associated with prolonged oral steroids, is known as "corticosteroid-induced lipodystrophy" or "cushingoid" changes, and includes truncal obesity, facial adipose tissue (moon facies), and dorsocervical adipose tissue (buffalo hump).[4] The rate and incidence is variable but has been reported to occur in 15% of patients in <3 months, with daily doses equivalent to 10–30 mg of prednisone.[4] Higher doses and longer durations of corticosteroids seem to increase the frequency of adipose tissue redistribution.[5] The risk is reportedly higher in women, patients <50 years of age, and patients with either a high initial body mass index or a high calorie intake.[5]

From the Division of Otolaryngology, Department of Surgery, Zablocki VA Medical Center, Milwaukee, Wisconsin

D. Poetker is a speaker for Intersect ENT and a consultant for GlaxoSmithKline

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Address correspondence to David M. Poetker, M.D., Division of Rhinology and Sinus Surgery, Department of Otolaryngology and Communication Sciences, Medical College of Wisconsin, 9200 W Wisconsin Avenue, Milwaukee, WI 53226

E-mail address: dpoetker@mcw.edu

Hyperglycemia

Steroids increase blood sugars by stimulating proteolysis, promoting gluconeogenesis, and inhibiting glucose uptake.[6] In addition, steroids cause an insulin resistance by decreasing the ability of adipocytes and hepatocytes to bind insulin. This effect can occur within hours of beginning therapy but seems to decrease with prolonged use.[6] Synthetic steroids are many times more potent than natural steroids at decreasing carbohydrate tolerance.[6] Upon cessation of the steroids, the inhibition of glucose uptake and metabolism usually returns to normal.[6] Despite their common use, the degree of hyperglycemia caused by steroids has not been clearly established.

Infection

Although steroids increase circulating neutrophils by enhanced release from bone marrow and reduced migration from blood vessels, the number of lymphocytes, monocytes, basophils, and eosinophils decrease due to a migration from the vascular bed to lymphoid tissue.[7] Steroids can impair neutrophil function by reducing their adherence to vascular endothelium and their bactericidal activity; inhibit antigen-presenting cells by limiting chemotaxis, phagocytosis, and the release of cytokines; decrease the expression of inflammatory mediators; and may inhibit B-cell production of immunoglobulins.[7,8] Interestingly, steroid administration on an alternate day schedule has been shown to reduce their negative impact on leukocyte function.[8]

Two large meta-analyses found that the rate of infections were significantly higher in patients treated with steroids.[9,10] Further review found that patients who received a daily dose of <10 mg per day or a cumulative dose of <700 mg of prednisone did not have an increased rate of infectious complications.[10] Although the disease processes for which the patients are being treated may themselves be independent risk factors for infection, close review of the included studies identified few patients with diseases known to increase risk for infection.[9,10] Additional studies demonstrated that patients treated with glucocorticoids are at increased risk for developing invasive fungal infections, pneumocystosis, and viral infections, especially in patients who have undergone bone marrow transplantation.[4,11–15]

Wound Healing

Steroids inhibit the natural wound healing process by decreasing the influx of macrophages, which may decrease phagocytosis as well as growth factor and/or cytokine production.[16–19] Steroids can also delay reepithelialization, decrease the fibroblast response, slow capillary proliferation, and inhibit collagen synthesis and wound maturation.[16,18,20]

Bone Metabolism

The role of steroids in bone loss is well described and may occur through several different mechanisms. First, steroids reduce intestinal calcium absorption; increase urinary calcium excretion, which stimulates parathyroid hormone production; and increase osteoclast activity and release calcium into the blood stream. In addition, steroids inhibit osteoblast activity, which negatively impacts trabecular bone formation.[21,22] Corticosteroids also suppress the production of adrenal androgens, which decreases their beneficial effect on bone formation.[22] Lastly, glucocorticoids have been found to cause apoptosis of osteoblasts and osteocytes,[23] which has been shown to occur within several weeks of use but slows after 6 months.[23]

There are conflicting data as to whether a daily dose or a cumulative dose has a more significant clinical effect on bone density. Fracture risks have also been shown to increase based on dose, duration, age, sex, and body weight.[4] Studies have demonstrated that supplemental calcium and vitamin D as well as bisphosphonates can help reduce the corticosteroid-induced loss of bone mineral density.[4] Analysis of data indicates that these effects are reversible with cessation of the steroids.[24]

Avascular Necrosis

Corticosteroid use has also been associated with avascular necrosis (AVN) or osteonecrosis. This complication has been correlated with cumulative dose and has been seen primarily in the head of the femur, although other bones can be affected.[21] The etiology is not understood but is thought to be due to decreased blood flow or impaired perfusion of the bone.[21,25,26]

Two retrospective reviews of patients with AVN of the femoral head outlined the steroid courses in those patients.[27,28] The first review had a mean cumulative dose of 850 mg of prednisone (range, 290–3300 mg), and the mean duration of therapy was 20.5 days (range, 6–39 days). The second review reported an AVN risk of 0.3%. The mean cumulative dose was equivalent to 673 mg of prednisone (range, 389–990 mg of prednisone equivalents), and the mean duration was 20 days (range, 15–27 days).[28]

Ophthalmic

The most commonly encountered ophthalmologic adverse effects include posterior-subcapsular cataract formation and increased intraocular pressure or glaucoma.[29] The incidence seems to be dependent on dose and duration of steroid use, with most doses of ≥10 mg daily for at least 1 year before the onset of cataract formation.[29] How steroids lead to cataracts is unclear. Theories include binding of lysine residues that lead to opacities in the lens and coagulation of lens proteins due to steroid impairment of the sodium-potassium pumps of the lens.[29]

Increased intraocular pressure can lead to visual field loss, optic disc cupping, and optic nerve atrophy. Steroids can cause significant increases in intraocular pressure in ~5% of the patients within the first few weeks of therapy, with up to 36% of patients developing at least a moderate (5 mm Hg or higher) increase in pressure with prolonged use.[22] The route of administration seems to play an important role, with topical ophthalmic and systemic administration having very high correlations with the incidence of glaucoma. The exact mechanism by which corticosteroids cause glaucoma is unknown.[21,22]

Gastrointestinal

Large meta-analyses of randomized, placebo-controlled trials failed to show an association between steroid use and peptic ulcer disease.[9,30] Interestingly, these studies did find that patients who used prednisone had peptic ulcer–type symptoms more frequently than did the control patients. The researchers hypothesized that this may be due to the lower sensitivity of barium studies that detect ulcers in the preendoscopic era.[9]

Adrenal Suppression

In the normal, nonstressed adult, the adrenal gland secretes the equivalent of 5–7 mg of prednisone per day.[7,31] Exogenous steroids increase the circulating corticosteroid levels, which can lead to a negative feedback on the hypothalamic-pituitary-adrenal axis.[32] There is a lack of consistency in the dose of exogenous steroids required for adrenal suppression due to individual variability as well as the specific synthetic corticosteroid administered.[4,33] Postmortem studies showed atrophy of adrenal glands after as few as 5 days of corticosteroid therapy.[4] Retrospective studies identified no definitive cases of adrenal suppression with prednisone doses <5 mg per day, even if that dose is taken for many months; however, when the doses were increased to 10 mg daily for only 4 days, there was a significant decrease in plasma cortisol.[34,35] The incidence of clinically evident adrenal insufficiency is unknown, yet it is believed to be much lower than the incidence based on objective measures.[4]

Psychiatric

The most common psychiatric manifestations of steroids include agitation, anxiety, distractibility, fear, hypomania, indifference, insomnia, irritability, lethargy, mood lability, pressured speech, restlessness, and tearfulness. Severe reactions include mania, depression, or a mixed state.[36]

There is a dramatic variability in the reported incidence of steroid-induced psychiatric adverse effects, reflective of the unpredictability of these reactions. A meta-analysis reported an incidence of 27.6% (range, 13–62%) of individuals experienced mild-to-moderate psychiatric complications from corticosteroid use, whereas only 5.7% (range, 1.6–50%) reported severe complications.[37]

Steroid dose has been found to be the most significant risk factor, with a reported 1.3% incidence in patients who received a daily prednisone dose of ≤40 mg. That risk increased to 18.4% in those who received >80 mg daily.[38] The reduction of the dose resulted in resolution of symptoms. Interestingly, a past reaction is not predictive of a future reaction, nor is past tolerance predictive of future tolerance.[36] Additional studies have not been able to correlate a history of psychiatric illness with a psychiatric reaction to prednisone.[39]

LITIGATION

Several studies reviewed specific litigation that involved steroid use. The National Association of Insurance Commissioners, the state officials who oversee the insurance industry, reported their malpractice claims in 1976. In their review, adrenal steroids accounted for 5.9% of claims.[40] In 1977, the California Medical Association and the California Hospital Association reviewed >20,000 patient charts to look for both claims filed and events that had the potential for compensation but claims were not filed. They found that adrenocorticoids were responsible for 7.6% of events.[40] A review performed by the Physician Insurers Association of America studied lawsuit data provided by the liability insurance companies within their association.[41] The association reviewed 117,000 claims and found that medication errors were the second most frequent reason for claims against physicians and that steroids were the second most common drug class implicated in the lawsuits, which involved 12% of the claims. The Risk Management Foundation of the Harvard Medical Institution analyzed the malpractice claims between 1990 and 1999.[42] Three percent of the medication-related claims involved corticosteroids.

A review of the WESTLAW computerized legal database (Thomson Reuters, New York, NY) searched for all jury verdict reports that involved steroid use from 1996 to 2008.[43] Eighty-three cases that involved steroid use were analyzed. The most common allegation was AVN, which resulted from steroid use and accounted for 39% of the cases. Changes in mood, including anxiety, depression, and psychosis, were the second most common allegation, in 16%. Infection and vision change each accounted for 12% of the allegations from

steroid use. Thirty-four of the cases were either decided for the plaintiff or settled with an average indemnity payment of $1.15 million. A more complete discussion of litigation associated with steroid use can be found in the review by Poetker and Smith.[44]

USE OF STEROIDS IN CRS

Recently, an iterative review was performed that evaluated the data that support the use of steroids in patients with CRS.[45] The researchers initially evaluated the data that supported steroids in patients with CRS and without nasal polyps by identifying four level-4 studies. Despite the common use of oral steroids for CRS without nasal polyps, there is no study that evaluated its efficacy as a single agent for CRS. In fact, there are no high-level studies that support steroid use even as a component of a multidrug regimen. High-quality studies are needed to validate efficacy and proper dosing. Given the potential risks of oral steroids, the expert panel thought that the use of oral steroid in CRS without polyposis is optional. They indicated that patients with more severe disease may have a more favorable benefit-to-harm ratio than patients with mild disease.

When evaluating the use of oral steroids in patients with CRS and with nasal polyps, 16 articles were identified,[50–65] 5 of which had level-2 evidence.[61–65] All the studies showed positive changes in the majority of the parameters evaluated. Analysis of the data supports the use of oral steroids in patients with CRS and with nasal polyps in the immediate and short-term period. All the studies showed benefit with very few adverse effects, and no severe adverse events were reported. The researchers made a strong recommendation for the use of oral steroids in the management of patients with CRS and with nasal polyps, provided the use was short term. They further recommended the perioperative use of oral steroids in these patients, based on two level-2 studies[66,67] and one level-3 study,[68] which showed improved visualization during surgery and improved postoperative courses.

Multiple treatment options exist for CRS, with each option carrying varying degrees of success in the management of the disease.[69] One must keep in mind that all treatment options carry risks. These include the risks of surgery as well as the risks of antibiotics.[70,71] The relative risks must be considered, weighed, and discussed. Ultimately, it is the patient who must accept these risks, and it is the provider's responsibility to educate the patient by ensuring that an informed decision is made.

CONCLUSION

In this review, I attempted to provide an overview of the existing data of the risks of oral steroid use, the lawsuits associated with their use, and the data that support the use of steroids in the CRS patient population. No medication or intervention is without risk. Providers need to be aware of the potential complications and the data that support the use to provide the best care possible.

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ORIGINAL ARTICLE

Efficacy of long-term low-dose macrolide therapy in preventing early recurrence of nasal polyps after endoscopic sinus surgery

Anastasia Varvyanskaya, MD and Andrey Lopatin, MD, Dr Med Sci

Background: **This study assessed efficacy of clarithromycin "long-term" macrolide therapy as an adjunct to maintenance therapy with nasal corticosteroids to prevent recurrence of nasal polyps (NP) after functional endoscopic sinus surgery (FESS).**

Methods: **A total of 66 patients with chronic rhinosinusitis and bilateral NP were randomized into 3 study arms, 22 patients in each arm. After FESS, patients in the first and second groups were treated with clarithromycin 250 mg/day for 12 and 24 weeks, respectively, whereas patients in the third group did not receive any clarithromycin. Patients in all 3 groups received maintenance therapy with mometasone furoate 400 μg/day. Patient assessment was conducted before the surgery and 6, 12, and 24 weeks after surgery, using a visual analogue scale (VAS), 20-item SinoNasal Outcome Test (SNOT-20), acoustic rhinometry, rhinomanometry, saccharin transit time, nasal endoscopy, computed tomography (CT) of paranasal sinuses, and measurement of the level of eosinophil cationic protein (ECP) in their nasal secretions.**

Results: **The study confirmed efficacy of "long-term" macrolide therapy, resulting in significant improvement of all parameters except acoustic rhinometry and VAS in both clarithromycin groups as compared to the control. Concentration of ECP in the nasal secretions increased dramatically after surgery, then returned to baseline levels after 12 and 24 weeks of treatment with clarithromycin. In the control group, ECP level continued to increase and was significantly higher at the endpoint. Both groups with clarithromycin showed significantly better endoscopic and CT scores than the control group at the end point.**

Conclusion: **"Long-term" low-dose clarithromycin 250 mg/day is able to control eosinophilic inflammation and prevent early relapse of NP after FESS.** © 2014 ARS-AAOA, LLC.

Key Words:
chronic rhinosinusitis; endoscopic sinus surgery; medical therapy of chronic rhinosinusitis; computed tomography; SNOT-20

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Chronic rhinosinusitis (CRS) often occurs in association with nasal polyps (NP). In 1 study CRS with NP (CRSwNP) was diagnosed in 4% of an entire population[1] and is associated with bronchial asthma (BA) in 7% to 13% of cases.[2] In addition, aspirin-exacerbated respiratory disease (AERD) and NP are present in a large number of patients (ranging, 36-96%).[3] In CRSwNP the predominate inflammatory cell is the eosinophil, which is found in both the tissue and in the airway mucus in almost all patients with CRSwNP. Although the role of infection (neutrophilic inflammation) has been investigated it does not seem to be a primary factor in the development of CRSwNP although CRSwNP is associated with BA. Allergy seems to be a comorbid condition and not a primary factor in the development of CRSwNP.[4] At present, neither medical nor surgical treatment can ensure permanent control or enduring cure. Currently the only proven treatment for effective control of CRSwNP is topical nasal steroid sprays with or without systemic glucocorticosteroids (GCS). Recurrent CRSwNP is not always prevented even with systemic GCS and the side effects can be serious, including cataracts and vertebral collapse.[5] Because disease control can be difficult even with systemic GCS we decided to study treatment with "long-term" therapy (3-6 months and more) using low dose macrolide antibiotics. Apparently

Ear, Nose, and Throat (ENT) Clinic, Sechenov First Moscow State Medical University, Moscow, Russia

Correspondence to: Andrey S. Lopatin, MD, Dr Med Sci., Partizanskayast. 33, bld 1, 55, 121351, Moscow, Russia; e-mail: lopatin.andrey@inbox.ru

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TABLE 1. Baseline characteristics of the 3 treatment arms

Parameters	Group 1 (antibiotics 24 weeks)	Group 2 (antibiotics 12 weeks)	Group 3 (control no antibiotic)	All study patients
Mean age (years)	42.3	49.7	54.9	48.7
Gender distribution (male/female)	14/8	9/13	13/9	36/30
Atopy confirmed by skin prick tests (patients)	6	7	6	19 (28.7%)
Concomitant asthma (patients)	13	12	10	35 (53%)
Revision surgery (patients)	17	18	17	52 (79%)
Mean number of previous sinus surgeries	3.0 ± 1.4	3.7 ± 1.8	2.8 ± 1.6	3.2
Mean interval between last surgery and enrollment into the study (months)	19.2 ± 8.7	17.0 ± 8.2	21.8 ± 6.2	19.4
SNOT-20 (points)	2.20 ± 0.54	2.64 ± 0.49	2.44 ± 0.18	2.42
VAS (points)	8.2 ± 0.71	8.7 ± 0.87	7.7 ± 0.91	8.1
Sniffing Sticks test (points)	2.4 ± 0.92	0.9 ± 0.80	2.2 ± 1.28	1.86
Saccharin transit time (minutes)	15.6 ± 4.1	20.4 ± 6.4	22.8 ± 3.7	17.9
EAS (points)	12.09 ± 0.96	12.78 ± 0.92	11.42 ± 1.09	12.12
Total nasal resistance (Pa/cm^3/second)	4.22 ± 2.1	2.09 ± 1.2	2.25 ± 1.0	2.85
Total nasal cavity volume (cm^3)	8.53 ± 1.20	9.00 ± 1.69	9.97 ± 2.33	9.17
Lund-Mackay CT score (points)	21.68 ± 1.2	21.84 ± 1.66	21.2 ± 1.57	21.60
ECP level in nasal secretion (ng/mL)	412.2 ± 123.1	279.4 ± 85.9	330.8 ± 104.5	340.8

CT = computed tomography; EAS = endoscopic appearances score; ECP = eosinophil cationic protein; SNOT-20 = 20-item SinoNasal Outcome Test; VAS = visual analogue scale.

it is the non-antimicrobial properties of the macrolides (erythromycin, roxithromycin, clarithromycin) that contribute to their anti-inflammatory effects, which includes inhibition of both neutrophilic and eosinophilic inflammation. The macrolides are capable of modulating the immune response, inhibiting polyp growth, destroying biofilms, and enhancing the protective properties of the respiratory tract mucosa.[6–9]

Macrolide effectiveness in patients with CRS without NP has been confirmed; however, their efficacy in CRSwNP patients has not been thoroughly investigated.[4] Therefore, our prospective randomized controlled study was designed to evaluate the efficacy and safety of a long-term course (3 and 6 months) of low-dose clarithromycin therapy in patients with CRSwNP after functional endoscopic sinus surgery (FESS).

Patients and methods

A total of 66 patients (36 men and 30 women) aged from 18 to 77 (average, 48.7) years with bilateral CRSwNP confirmed by endoscopy were recruited. The study period was from January 2008 to March 2011. All 66 patients were randomly assigned (sealed envelope system) to 1 of 3 study groups (22 patients per group) as follows: group 1 (antibiotics for 24 weeks); group 2 (antibiotics for 12 weeks); and group 3 (control, no antibiotics).

All 3 groups received topical nasal steroid spray (mometasone furoate), 400 μg/day for 24 weeks after FESS. The macrolide antibiotic used in both groups 1 and 2 was clarithromycin 250 mg/day (Klacid; Abbott Laboratories, Abbott Park, Illinois, USA). The majority of patients (79%) had at least 1 previous sinus surgery without long-term success; the mean number of previous surgeries in all 66 patients was 3.2 (Table 1).

Exclusion criteria included the following: unilateral CRSwNP, macrolide intolerance, use of systemic steroids, pregnancy, lactation, and severe somatic diseases. We excluded all patients who were on systemic steroids because in Russia, systemic steroid therapy is reserved only for severe BA patients. It would be unethical to discontinue systemic steroids in these BA patients; in addition, systemic steroids could have a negative impact on reliability of our study results. The Ethics Committee of the Sechenov First Moscow State Medical University, required that all patients in all 3 groups maintain use of topical nasal steroids after FESS otherwise NP can rapidly reoccur.[10]

After recruitment, all 66 patients underwent bilateral FESS performed by the same surgeon (senior author Lopatin A.). Patients in group 1 (antibiotics for 24 weeks) and group 2 (antibiotics for 12 weeks) began long-term therapy with clarithromycin 250 mg/day on the first postoperative day and over 24 weeks (6 months) or 12 weeks

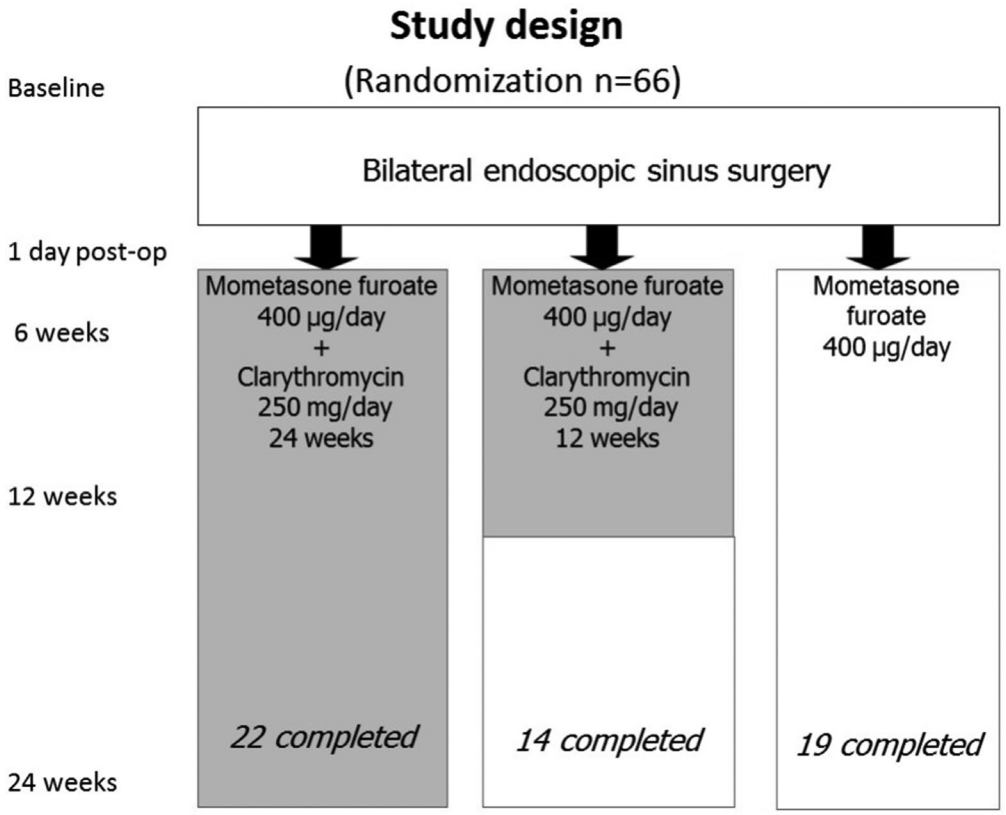

FIGURE 1. Study flowchart.

(3 months), respectively. On the 7th day after surgery, all patients began maintenance therapy with mometasone furoate nasal spray (Nasonex, MSD, Merck & Co., Inc., NJ, USA) 400 μg/day for a full 6 months, including group 3 (control no antibiotics) patients. The Ethics Committee approved the final study protocol with all enrolled 66 patients signing consent forms.

Patients were carefully followed and seen at 6 weeks, 12 weeks, and 24 weeks after FESS (Fig. 1). Results of treatment were based on evaluation of the following tests.

20-item SinoNasal Outcome Test (SNOT-20)

The 20-item SinoNasal Outcome Test (SNOT-20) is a questionnaire for evaluating the quality of life (QoL) in rhinosinusitis patients.[11]

Visual analogue scale

The disease severity was assessed by the patients' subjective evaluation on the 10-cm visual analogue scale (VAS); 1 cm on the scale reflected 1 point of the patient's assessment; 0 to 3 points corresponded to mild disease, 3 to 7 points corresponded to moderate disease, and 7 to 10 points corresponded to severe disease.

Olfactory test

The "Sniffin Sticks test," extended version (Burghart Messtechnik GmbH, Wedel, Germany) was used for each patient.[12] Odor identification was assessed by means of 16 test tubes with different odors. The number of correct answers was related to the degree of olfactory disturbance, with 16 being the maximum score possible. A score from 0 to 6 reflects anosmia, a score from 7 to 12 is termed hyposmia, whereas a score ranging from 13 to 16 is normal.

Saccharin transit time test

This test measures the transit time for a saccharin particle to pass from the anterior head of the inferior nasal turbinate to the pharynx when the patient first experiences the sensation of a sweet taste.

Nasal endoscopy

Endoscopy was performed with a rigid 2.7-mm endoscope (Karl Storz, Tutlingen, Germany) without decongestion. Semiquantitative scores were recorded for polyps, edema, discharge, crusting, and scarring at baseline, 6 weeks, 12 weeks, and at the final assessment 24 weeks after FESS. These results were evaluated using an endoscopic appearance score (EAS).[4,13] Polyps were graded by size from 0 to 3 points; an absence of polyps was scored as 0, polyps appearing only in middle meatus were scored as 1; polyps extending beyond the middle meatus but not obstructing the nose were scored a 2; and polyps completely obstructing the nose were scored a 3. Discharge was scored as follows: 0 = no discharge; 1 = clear, thin discharge; and

2 = thick, purulent discharge. The mucosal edema was scored as follows: 0 = absent; 1 = mild; 2 = severe. Crusting and scarring in the postoperative cavity was scored as follows: 0 = absent; 1 = mild; and 2 = severe; these findings were evaluated for the right and left nasal cavity separately.

Active anterior rhinomanometry and acoustic rhinometry

The active anterior rhinomanometry (AAR) and acoustic rhinometry (AR) studies were carried out with the SRE 2000® device (Rhinometrics, Lynge, Denmark), which allowed performing both tests: AAR objectively assessed both nasal resistance and nasal airflow whereas AR reflected the geometry and the volume of the entire nasal cavity.

Multislice computed tomography

Multislice computed tomography (CT) of the nose and paranasal sinuses was performed prior to and 6 months after FESS on all patients. One-half-centimeter (5 mm) slices in both the axial and coronal planes were obtained. The degree of opacification of a particular sinus (0-2) and the ostiomeatal complex (0 = intact, 2 = occluded) were calculated using the Lund-Mackay scoring system.[4,13]

Eosinophil cationic protein

Eosinophil cationic protein (ECP) contents in the nasal discharge was measured using a collection kit with data generated by the automatic chemiluminescent analyzer IMMULITE® 1000 (Siemens Healthcare Diagnostics Inc, NY, USA). To collect the mucus, a piece of sterile foam-rubber sponge measuring 20 × 20 × 5 mm was introduced into the middle meatus for 20 minutes. After removal, the sponge was placed in a 10-mL test tube and centrifuged for 3 minutes at a velocity of 4000 rpm allowing for collection of 0.2 to 1.0 mL of mucus for further analysis. The test sensitivity was 0.2 ng/mL.

Microbiological testing

Nasal swab for microbiological testing was collected from the middle nasal meatus prior to FESS and at all postoperative visits. Culture and sensitivity (resistance) testing was performed using bacteriological analyzer Walk Away-40 (Dade Behring, Marburg, Germany) and the disk diffusion method (Becton Dickinson discs with clarithromycin, USA). Results were estimated according to the CLSI (clinical and laboratory standards institute) recommendations.

Skin prick tests

Skin prick tests for indoor and outdoor allergens were performed in all patients using standard methods.

Final assessment of treatment results

Final assessment of treatment results was carried out using the changes of EAS and Lund-Mackay CT scores at 24 weeks after FESS.

Statistical analysis

After consulting a medical statistician, the results obtained were entered into a computerized database and processed using the statistical software package SPSS version 17.0 for Windows. Wilcoxon signed rank tests were performed to evaluate treatment effects at various time points. Values were presented as means ± standard deviations. Changes within and between groups were considered statistically significant when p values were <0.05.

Results

Eleven patients were dropped from the study for various reasons: 8 patients in group 2 (antibiotics for 12 weeks) were withdrawn. One patient developed abdominal pain after starting clarithromycin therapy; a second patient was withdrawn because of nightmares beginning 3 days after starting clarithromycin treatment. One female in the same group developed an exacerbation of erosive duodenitis 2 months after enrollment and was withdrawn whereas 5 others were withdrawn because of noncompliance. One female patient in group 3 (control no antibiotics) was excluded because of pregnancy and 2 others in this group were withdrawn because of noncompliance. Therefore, 55 patients completed the study and at the last visit all 22 patients in group 1 (antibiotics for 24 weeks) completed the study, 14 patients remained in group 2 (antibiotics for 12 weeks), and 19 patients remained in group 3 (control no antibiotics).

Thirty-five patients had BA, and 27 of these 35 patients presented with AERD. Atopy was confirmed by skin prick tests in 19 of the 66 initial patients. There were no significant differences between the 3 groups regarding age, sex, presence of atopy, severity of the disease, and number of previous surgeries, as well as all the other initial parameters that we examined. Baseline characteristics of each of the 3 treatment arms: group 1 (antibiotics for 24 weeks), group 2 (antibiotics for 12 weeks), and group 3 (control no antibiotics) are presented in Table 1.

Treatment results were better for patients completing the course of long-term clarithromycin treatment in group 1 (antibiotics for 24 weeks) and group 2 (antibiotics for 12 weeks) compared to patients in group 3 (control no antibiotics).

Statistically significant differences ($p < 0.05$) were obtained for all parameters (but not at every visit) between the study medication groups 1 and 2 and group 3 (control no antibiotics) with the only exception being for VAS and AR where statistically significant evidence was not achieved.

SNOT-20

The initial SNOT-20 scores were 2.20 ± 0.54 in group 1 (antibiotics for 24 weeks), 2.64 ± 0.49 in group 2 (antibiotics for 12 weeks), and 2.44 ± 0.18 in group 3 (control no antibiotics). After the FESS, QoL improved and the severity of the rhinosinusitis symptoms was relieved in all study

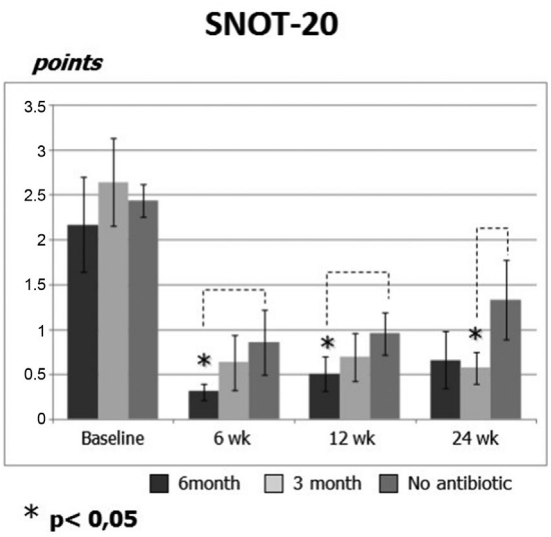

FIGURE 2. Evaluation of SNOT-20 values, mean questionnaire scores (*$p < 0.05$). SNOT-2 = 20-item SinoNasal Outcomes Test.

TABLE 2. SNOT-20 evaluation (points)

Visits	Group 1 (antibiotics 24 weeks)	Group 2 (antibiotics 12 weeks)	Group 3 (control no antibiotic)
Baseline	2.20 ± 0.54	2.64 ± 0.49	2.44 ± 0.18
6 weeks	0.31 ± 0.09*	0.63 ± 0.31	0.85 ± 0.35
12 weeks	0.52 ± 0.19*	0.69 ± 0.26	0.95 ± 0.24
24 weeks	0.68 ± 0.32	0.57 ± 0.17*	1.33 ± 0.44

*Significant differences between study and control groups ($p < 0.05$).
SNOT-20 = 20-item SinoNasal Outcome Test.

subjects. However, SNOT-20 scores of patients in group 1 (antibiotics for 24 weeks) at visits 6 weeks and 12 weeks after FESS (0.31 ± 0.09 and 0.52 ± 0.19, respectively) as well as SNOT-20 scores of patients in group 2 (antibiotics for 12 weeks) at the final visit (0.57 ± 0.17) were significantly better than the patients in group 3 (control no antibiotics) at the same visits; 0.85 ± 0.35, 0.95 ± 0.24, and 1.33 ± 0.44, respectively ($p < 0.05$), (Fig. 2, Table 2).

VAS scores

Differences in changes of VAS scores between the study (groups 1 and 2) and the control group (group 3 no antibiotics) did not reach statistical significance (Table 3).

Olfactory test

Severe olfactory dysfunction was detected in all study subjects prior to FESS. Complete or almost complete loss of the ability to identify odors (anosmia) was noted when the nose was totally obstructed (blocked) by diffuse nasal polyps. None of these 66 patients received systemic steroids prior to FESS. At the second and third visits, olfaction significantly improved in all 3 patient groups, although no patients reached normal values. Statistically significant difference in the mean number of correct answers ($p < 0.05$) was revealed only between group 1 (antibiotics for 24 weeks) (9.5 ± 1.3) and group 3 (control no antibiotics) (4.4 ± 0.5) at the second visit 6 weeks after surgery (Table 4).

TABLE 3. VAS evolution (points)

Visits	Group 1 (antibiotics 24 weeks)	Group 2 (antibiotics 12 weeks)	Group 3 (control no antibiotic)
Baseline	8.1 ± 0.7	8.7 ± 0.9	7.7 ± 0.9
6 weeks	1.4 ± 0.5	2.0 ± 0.9	1.8 ± 0.5
12 weeks	1.4 ± 0.5	2.1 ± 0.9	2.2 ± 0.6
24 weeks	1.6 ± 0.5	2.2 ± 0.5	3.0 ± 1.1

VAS = visual analogue scale.

TABLE 4. Sniffin' Sticks test (points)

Visits	Group 1 (antibiotics 24 weeks)	Group 2 (antibiotics 12 weeks)	Group 3 (control no antibiotic)
Baseline	2.4 ± 0.9	0.9 ± 0.8	2.2 ± 1.3
6 weeks	9.5 ± 1.3*	6.4 ± 2.1	4.4 ± 0.5
12 weeks	9.0 ± 1.7	9.1 ± 2.4	5.6 ± 2.2
24 weeks	8.8 ± 1.6	8.6 ± 2.7	6.7 ± 2.1

*Significant differences between study and control groups ($p < 0.05$).

TABLE 5. Saccharin transit time (minutes)

Visits	Group 1 (antibiotics 24 weeks)	Group 2 (antibiotics 12 weeks)	Group 3 (control no antibiotic)
Baseline	15.6 ± 4.1	20.4 ± 6.4	22.8 ± 3.7
6 weeks	13.8 ± 3.2	14.6 ± 4.9	19.7 ± 3.6
12 weeks	13.6 ± 3.0*	18.6 ± 3.7	21.0 ± 4.1
24 weeks	11.9 ± 2.7	17.4 ± 3.0	15.8 ± 1.5

*Significant differences between study and control groups ($p < 0.05$).

Saccharin transit time

Similarly, 12 weeks after surgery significant reduction (improvement) of the saccharin transit time was observed in group 1 (antibiotics for 24 weeks) (13.6 ± 3.0 minutes) as compared with group 3 (control no antibiotics) (21.0 ± 4.1 minutes) (Table 5).

AR and AAR

There was no significant difference in the acoustic rhinometry parameters (nasal cavity volume, minimal cross-sectional area) between all groups. However, nasal resistance measured by anterior rhinomanometry in group 1

TABLE 6. Nasal resistance (Pa/cm^3/second) as measured by anterior rhinomanometry

Visits	Group 1 (antibiotics 24 weeks)	Group 2 (antibiotics 12 weeks)	Group 3 (control no antibiotic)
Baseline	4.22 ± 2.11	2.09 ± 1.2	2.25 ± 1.00
6 weeks	0.23 ± 0.03	0.23 ± 0.03	0.26 ± 0.06
12 weeks	0.19 ± 0.01	0.19 ± 0.02	0.22 ± 0.03
24 weeks	0.23 ± 0.02*	0.19 ± 0.02*	1.94 ± 1.50

*Significant differences between study and control groups ($p < 0.05$).

TABLE 7. Total nasal cavity volume (cm^3) as measured by acoustic rhinometry

Visits	Group 1 (antibiotics 24 weeks)	Group 2 (antibiotics 12 weeks)	Group 3 (control no antibiotic)
Baseline	8.53 ± 1.20	9.00 ± 1.69	9.97 ± 2.33
6 weeks	17.35 ± 2.74	15.58 ± 1.77	14.29 ± 1.55
12 weeks	17.62 ± 2.79	15.27 ± 2.27	16.33 ± 3.73
24 weeks	16.74 ± 1.96	14.68 ± 2.06	13.59 ± 2.82

(antibiotics for 24 weeks) and group 2 (antibiotics for 12 weeks) was significantly lower (better breathing) (0.23 ± 0.02 and 0.19 ± 0.02 Pa/cm^3/second, respectively) than in group 3 (control no antibiotics) (1.94 ± 1.50 Pa/cm^3/second) at endpoint (Tables 6 and 7).

CT scans

Before initiation of treatment, mean values for the Lund-Mackay score in the first, second, and third patient groups did not differ significantly, being 21.68 ± 1.20, 21.84 ± 1.66, and 21.2 ± 1.57, respectively. The mean score of paranasal sinus opacification on CT scans dramatically decreased (improved) in all 3 groups 6 months after FESS. However, a significant difference was observed only between group 1 (antibiotics for 24 weeks) with a mean score of 9.71 ± 2.21, and group 3 (control no antibiotics) with a mean score of 16.66 ± 2.32 ($p < 0.05$). In group 2 (antibiotics for 12 weeks) the mean score was 12.62 ± 4.15, but this difference did not reach statistical significance (Fig. 3, Table 8).

Nasal endoscopy

Patients on clarithromycin therapy in group 1 (antibiotics for 24 weeks) and group 2 (antibiotics for 12 weeks) showed better EAS at each visit when compared to patients in group 3 who did not take antibiotics (Fig. 4, Table 9). Twenty-four weeks after surgery mean EAS were: 1.52 ± 0.87 in group 1 (antibiotics for 24 weeks) and 2.42 ± 1.61 in group 2 (antibiotics for 12 weeks), and these results were

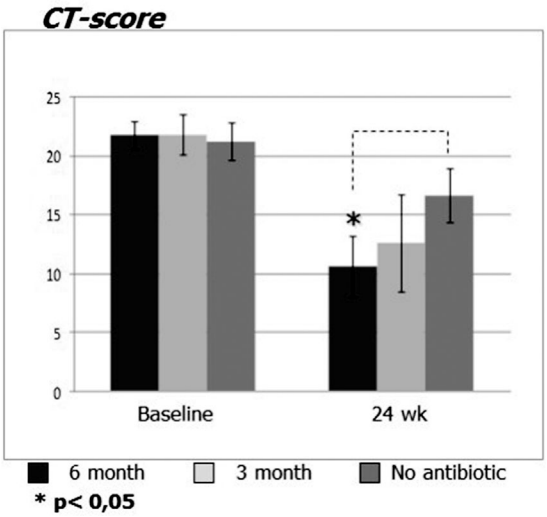

FIGURE 3. Evaluation of CT scores, mean scores according to Lund-Mackay scale (*$p < 0.05$). CT = computed tomography.

TABLE 8. Lund-Mackay CT score evaluation (points)

Visits	Group 1 (antibiotics 24 weeks)	Group 2 (antibiotics 12 weeks)	Group 3 (control no antibiotic)
Baseline	21.68 ± 1.19	21.84 ± 1.66	21.20 ± 1.57
24 weeks	9.71 ± 2.21*	12.62 ± 4.15	16.66 ± 2.32

*Significant differences between study and control groups ($p < 0.05$).
CT = computed tomography.

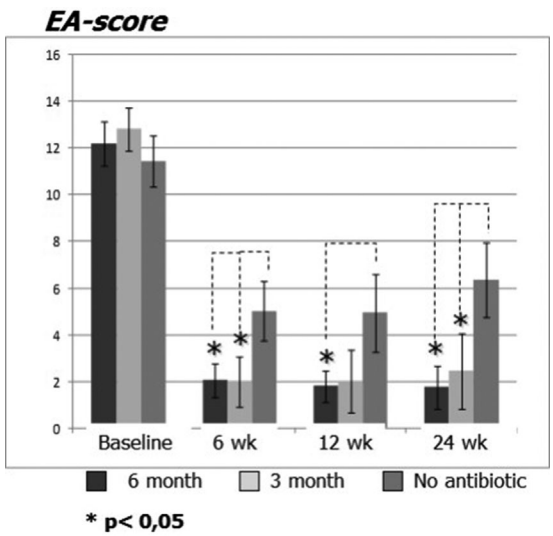

FIGURE 4. Evaluation of endoscopic findings in the nasal cavity calculated according to Endoscopic Appearance Score (*$p < 0.05$).

significantly better than group 3 (control no antibiotics) 6.35 ± 1.58 ($p < 0.05$) (Fig. 4, Table 9).

One of the most impressive cases demonstrating efficacy of postoperative long-term macrolide therapy is presented in Figure 5.

TABLE 9. EAS (points)

Visits	Group 1 (antibiotics 24 weeks)	Group 2 (antibiotics 12 weeks)	Group 3 (control no antibiotic)
Baseline	12.09 ± 0.96	12.78 ± 0.92	11.42 ± 1.09
6 weeks	2.05 ± 0.73*	2.00 ± 1.06*	5.00 ± 1.27
12 weeks	1.61 ± 0.62*	2.00 ± 1.34	4.92 ± 1.66
24 weeks	1.52 ± 0.87*	2.42 ± 1.61*	6.35 ± 1.58

*Significant differences between study and control groups ($p < 0.05$).
EAS = endoscopic appearances score.

The most remarkable results occurred in the evaluation of ECP concentration postoperatively. Before the surgery, median values of ECP concentrations in all 3 patients groups did not differ significantly, being 412.2 ± 123.1, 279.4 ± 85.9, and 330.8 ± 104.5, respectively. Six weeks after surgery, the ECP level in the nasal discharge increased in all study patients, being 553.2 ± 115.5, 604.0 ± 173.2, and 660.0 ± 171.6 ng/mL in groups 1, 2, and 3, respectively. Twelve weeks after FESS, a significant decrease of the ECP level in the nasal discharge was clearly observed in group 1 (antibiotics for 24 weeks): 153.6 ± 98.8 ng/mL ($p = 0.028$), and in group 2 (antibiotics for 12 weeks): 290.4 ± 77.2 ng/mL ($p = 0.036$). ECP level in the nasal discharge in group 3 (control no antibiotics) patients did not change significantly and was recorded as 654.0 ± 184.9 ng/mL ($p = 0.25$). Only in group 1 (antibiotics for 24 weeks) did the ECP concentration remain at the same low level (154.8 ± 89.8 ng/mL) at 24 weeks. In group 2 (antibiotics for 12 weeks) there was a slight increase of the ECP levels up to 338.1 ± 83.1 ng/mL ($p = 0.084$) when these patients were studied at 24 weeks (3 months after stopping the antibiotics); however, with a p value of 0.084, the difference was not statistically significant. The mean ECP level in the nasal discharge in group 3 (control no antibiotics) rose significantly to 1000.0 ± 222.7 ng/mL ($p = 0.041$) (Fig. 6, Table 10). It is important to note that the ECP level in patients treated with the macrolides over a full 6 months (group 1) was significantly lower than in those patients in group 2, who stopped the antibiotic therapy after 3 months of treatment.

Side effects were uncommon with discontinuation of antibiotic therapy required in only 3 patients. Liver enzymes levels (alanine transaminase [ALT], aspartate

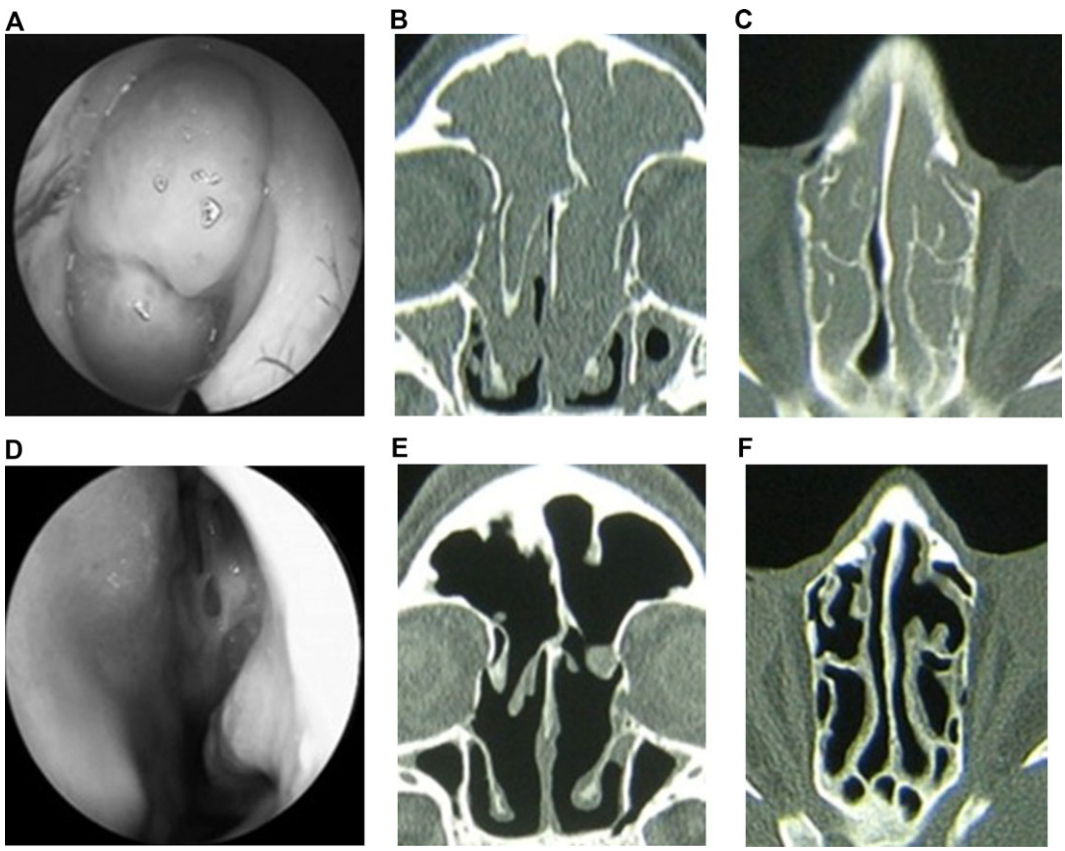

FIGURE 5. Endoscopic appearance and CT scans of 26-year-old male patient (CRSwNP, bronchial asthma, 5 previous sinus surgeries) before and after FESS followed by 6-month course of low-dose clarithromycin therapy. Before FESS: (A) large polyps completely block left nasal cavity; (B, C) total opacification of paranasal sinuses and signs of osteitis on axial and coronal CT scans. Six months after FESS: (D) no visible polyps, multiple synechiae in the left ethmoid cavity; (E, F) sinuses are pneumatized, slight thickening of the ethmoid mucosa. CRSwNP = chronic rhinosinusitis with nasal polyposis; CT = computed tomography; FESS = functional endoscopic sinus surgery.

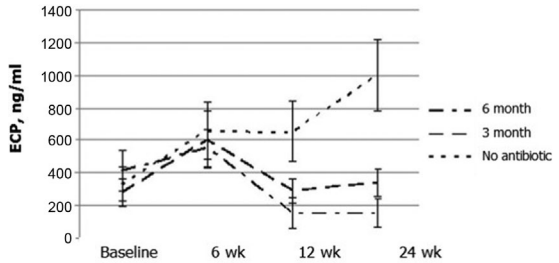

FIGURE 6. Evaluation of ECP concentration in the nasal discharge, in ng/mL. ECP = eosinophil cationic protein.

aminotransferase [AST], and alkaline phosphatase [ALP]) remained normal in all patients.

Microbiological study of the swabs from the middle meatus revealed a wide spectrum of bacteria. The most common organism was *Staphylococcus aureus* (30% of patients), followed by *Staphylococcus epidermidis* (25%), *Streptococcus haemolyticus* (11%), *Escherichia coli* (9%), *Pseudomonas aeruginosa* (6%), and *Enterobacter aerogenes* (6%). Bacterial spectrum changed significantly after the surgery, but the proportion between clarithromycin-resistant strains (13%) and clarithromycin-sensitive strains (87%) remained the same. At the study conclusion, some macrolide-sensitive bacterial strains did acquired resistance to clarithromycin. Interestingly, an opposite phenomenon occurred as well; initially some bacterial strains resistant to macrolides were replaced by some bacterial strains sensitive to macrolides. In general, the number of clarithromycin-resistant strains (13%) remained constant throughout the course of long-term clarithromycin treatment.

Discussion

The current evidence supports the idea that long-term low-dose treatment with macrolides is effective when reserved for recalcitrant nonatopic CRS patients in whom topical nasal steroids and saline irrigations have failed to control symptoms.[14,15] In atopic CRSwNP patients, BA and AERD macrolide therapy has not been useful.[16,17]

In the more recent literature long-term low-dose macrolide therapy has been reported to be effective in CRS, including those patients with elevated immunoglobulin E (IgE) levels and BA. A recent prospective study demonstrated that an 8-week course of clarithromycin therapy was equally effective in both atopic and nonatopic patients with nasal polyposis.[18] In a retrospective study, CRS patients with atopy responded well to long-term macrolide treatment, whereas patients who smoked had the poorest treatment outcome.[19]

The results of our study demonstrated that long-term low-dose macrolide therapy prevents early recurrence of nasal polyps after FESS, including patients with atopy and BA. There was a clear correlation between atopy and the severity of disease because our atopic patients had higher VAS scores (Spearman's rank correlation coefficient 0.332; $p = 0.01$). The presence of atopy correlated with higher

TABLE 10. ECP level in nasal secretion (ng/mL)

Visits	Group 1 (antibiotics 24 weeks)	Group 2 (antibiotics 12 weeks)	Group 3 (control no antibiotic)
Baseline	412.2 ± 123.1	279.4 ± 85.9	330.8 ± 104.5
6 weeks	553.2 ± 115.5	604.0 ± 173.2	660.0 ± 171.6
12 weeks	153.6 ± 98.8*	290.4 ± 77.2*	654.0 ± 184.9
24 weeks	154.8 ± 89.8**	338.1 ± 83.1*	1000.0 ± 222.7

*Significant differences between study and control groups ($p < 0.05$).
**Significant difference between the group 1 and both control group 3 and group 2 ($p < 0.05$).
ECP = eosinophil cationic protein.

ECP levels in the nasal discharge (0.834; $p = 0.01$). These findings suggest that symptom severity is directly related to the intensity of the eosinophilic inflammation. Unfortunately, we did not investigate total IgE levels in a majority of patients; therefore, subgroup analysis of those patients with low IgE levels was not possible.

A most remarkable study finding was the changing ECP levels in the nasal secretions after FESS and during the postoperative period with macrolide therapy. In group 3 (control no antibiotics) we noted an almost 3-fold increase of the mean ECP level 6 weeks after surgery. This finding of an elevated ECP level after FESS in these group 3 patients reflects an exacerbation of the eosinophilic inflammation caused by the surgery that could not be adequately controlled with intranasal topical steroids alone. On the other hand, in treatment groups 1 (antibiotics for 24 weeks) and 2 (antibiotics for 12 weeks) there was a gradual decrease of the ECP levels with long-term low-dose clarithromycin treatment, reflecting control and reduction of the eosinophilic inflammation.

One goal of this work was to study the efficacy of a longer (6 months) treatment course when compared to the relatively short (3 months) course of low-dose macrolide therapy. The data suggested some benefit from a longer antibiotic course but the difference between group 1 (antibiotic 24 weeks) and group 2 (antibiotic for 12 weeks) failed to reach statistical significance in the majority of patients. Nonetheless, there is some evidence that a longer duration of treatment group 1 (antibiotics 24 weeks) appears to be more effective than a shorter course seen in group 2 (antibiotics for 12 weeks).

The CT scores for group 1 (antibiotics 24 weeks) patients was 9.71 ± 2.21, which was significantly lower than in group 3 (control no antibiotics), with readings of 16.66 ± 2.32 at endpoint. The difference between group 2 (antibiotics for 12 weeks) and group 3 (control no antibiotics) did not reach statistical significance (Table 8). There were significant differences in the mean ECP levels in groups 1 and 2 at the endpoint, indirectly confirming that a 6-month antibiotic course reduces the eosinophilic inflammation, thereby preventing early recurrence of nasal polyps. Obviously, oral steroid use would certainly be considered

the standard of care in the United Sates and some other Western countries, especially in the setting of postoperative eosinophilic inflammation flare-up. However, in countries such as Russia where systemic corticosteroid therapy in CRSwNP is extremely uncommon, long-term macrolides therapy might be an alternative option because it carries less risk of systemic side effects.

We did not find an increase in macrolide resistant bacterial cultures from the middle meatus after a long-term, low-dose course 250 mg/day of clarithromycin therapy, agreeing with previous studies that also failed to find resistant microorganisms after long-term treatment with azithromycin and erythromycin.[17,20] Of course, the risk of developing antibiotic-resistant strains of bacteria induced by the long-term macrolide therapy is always possible.

Although a placebo arm was not designed into our protocol and patients were not blinded when receiving additional therapy, we evaluated 6 different objective methods in all 3 study groups. All investigators were blinded when evaluating and grading the results of nasal endoscopy, CT scans, and all other tests. A future randomized double-blind placebo-controlled study, with a large sample size, would be required to determine the efficacy of long-term macrolide therapy, particularly in preventing the recurrence of nasal polyps after FESS. In addition, such a study could hopefully predict which CRSwNP patients would benefit from long-term antibiotic treatment and if this treatment increases the risk of inducing significant bacterial resistance.

Conclusion

Results of this study demonstrated the efficacy and relative safety of long-term (6 months) low-dose (250 mg/day) macrolide (clarithromycin) therapy for preventing early recurrence of nasal polyps in patients with CRSwNP after FESS. Despite limited clinical data, our evidence suggests that patients with recurrent CRSwNP (surgical failures) deserve a trial of low-dose clarithromycin treatment (250 mg daily for 3-6 months), which may be initiated immediately after FESS along with maintenance therapy using topical nasal steroids.

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ORIGINAL ARTICLE

Safety of long-term high-volume sinonasal budesonide irrigations for chronic rhinosinusitis

Kristine A. Smith, MD[1], Gabrielle French, BSc[2], Bradford Mechor, MD[1] and Luke Rudmik, MD, MSc[1]

Background: **Off-label high-volume sinonasal budesonide irrigations are commonly used during the management of chronic rhinosinusitis (CRS). Although short-term use (4 to 8 weeks) has been demonstrated to be safe, the long-term effects on the hypothalamic-pituitary-adrenal (HPA) axis remain unclear. The objective of this study is to determine whether CRS patients using long-term (minimum greater than 12 months) budesonide sinonasal irrigations have evidence of HPA axis suppression.**

Methods: **Patients with CRS being managed with high-volume sinonasal budesonide irrigations were recruited from 2 tertiary level rhinology clinics between March 2014 and July 2015. Inclusion criteria were as follows: (1) adult (age greater than 18 years); (2) guideline-based diagnosis of CRS; (3) previous endoscopic sinus surgery; (4) minimum of twice daily high-volume sinonasal budesonide irrigation (concentration of 1 mg per irrigation; total daily dose of 2 mg); and (5) a minimum of 12-month duration. Exclusion criteria included systemic corticosteroid use within 3 months of HPA axis testing. The primary outcomes were morning (AM) serum cortisol levels and, when indicated, cosyntropin stimulation levels.**

Results: **A total of 35 patients fulfilled eligibility criteria and underwent HPA axis testing. Mean duration of budesonide sinonasal irrigation therapy use was 38.2 months (2.9 years). The mean ± standard deviation (SD) AM serum cortisol was 431.2 ± 146.9 nmol/L (normal, 200 to 650 nmol/L). Subsequent cosyntropin stimulation tests, in indicated patients (n = 19), demonstrated no evidence of HPA axis suppression.**

Conclusion: **Outcomes from this study suggest that daily high-volume sinonasal budesonide irrigations fail to produce evidence of HPA axis suppression with prolonged courses lasting longer than 2 years.** © 2016 ARS-AAOA, LLC.

Key Words:
chronic rhinosinusitis; sinusitis; medical therapy; safety; budesonide; topical therapy; corticosteroid; irrigations

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Chronic rhinosinusitis (CRS) is a common inflammatory disease of the paranasal sinuses that affects approximately 5% to 11% of the general population.[1,2] Maintenance medical therapy is essential for successful long-term disease control in the majority of CRS patients.[3,4] Common medical strategies generally include high-volume isotonic irrigations and topical intranasal corticosteroids, as well as systemic corticosteroids, antibiotics, leukotriene pathway modulators, and allergy control.[3] Adequate delivery of topical intranasal corticosteroids continues to be one of the greatest barriers to decreasing sinonasal mucosal inflammation.[5] High-volume irrigation techniques have been shown to improve the delivery of topical medications into the paranasal sinuses and this is the recommended approach for managing patients with CRS, especially those who have undergone endoscopic sinus surgery (ESS).[6–11] As such, the off-label use of budesonide respules mixed into high-volume saline irrigations has become a common maintenance strategy during the management of CRS. However, given the off-label nature of this treatment, the safety profile has not been as rigorously defined compared to other U.S. Food and Drug Administration (FDA) approval low-volume metered-dose corticosteroid sprays.[12]

[1]*Division of Otolaryngology–Head and Neck Surgery, Department of Surgery, University of Calgary, Calgary, Alberta, Canada;* [2]*Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada*

Correspondence to: Luke Rudmik, MD, MSc, Division of Otolaryngology–Head and Neck Surgery, Department of Surgery, University of Calgary, Foothills Medical Centre, South Tower Suite 602, 1403 - 29th St. NW T2N 2T9, Calgary, Alberta, Canada; e-mail: lukerudmik@gmail.com

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High-volume sinonasal budesonide irrigations have been shown to be effective and safe in the short-term (less than 8 weeks), including those with challenging phenotypes.[5,13–16] However, the safety of long-term use is less clear. Given that CRS patients often require prolonged daily maintenance therapy using high-volume sinonasal budesonide irrigations to optimize disease control, the objective of this study was to evaluate the impact of long-term budesonide irrigations on the hypothalamic-pituitary-adrenal (HPA) axis.

Patients and methods

Study design

This study was a cross-sectional cohort analysis. Patients who were being managed with twice daily high-volume sinonasal budesonide irrigations for CRS were retrospectively identified and recruited from 2 tertiary level rhinology clinics between March 2014 and July 2015. Inclusion criteria included: (1) adult patients (age greater than 18 years); (2) a history of a guideline-based diagnosis of CRS[17]; (3) previous ESS; (4) twice daily high-volume sinonasal budesonide irrigation (concentration of 1 mg per irrigation; total daily dose of 2 mg); and (5) a minimum of 12 months duration. A total daily dose of 2 mg was chosen as inclusion criteria so the cohort would represent patients on a high dose of budesonide, assuming that a higher dose would be more likely to reveal associated systemic side effects. Patients were placed on budesonide irrigation at the discretion of the treating physician, based on the degree of sinonasal mucosal inflammation. Patients had been increased to twice daily dosing after once daily dosing failed to control these factors. As this is an off-label use of this medication, all patients had previous trialed topical intranasal corticosteroid sprays. Patients were required to have a history of ESS to ensure adequate penetration of irrigations through the paranasal sinuses to ensure sinonasal exposure to budesonide.[11] Patients began budesonide irrigations 1 week postoperatively and as such, the date of the previous ESS was chosen as time 0 (Rudmik et al.[18]).

Exclusion criteria included: (1) systemic corticosteroid use within 3 months of HPA axis testing (ie, within the study period)[19]; and (2) the presence of any of the following comorbid diseases, ciliary dysmotility, cystic fibrosis, oral steroid-dependent inflammatory disease, sarcoidosis, or systemic vasculitis condition. Any systemic corticosteroid use within 3 months has the potential to alter HPA axis testing and provide false positives (ie, patients would appear suppressed when they are not).[19]

The institutional "A pRoject Ethics Community Consensus Initiative" (ARECCI) (formerly The Alberta Research Ethics Community Consensus Initiative) Ethics Screening Tool categorized this project as a quality improvement and evaluation study, and as such was exempt from institutional ethics.

HPA testing

Eligible patients were sent for morning (AM) serum cortisol levels. The normal range for AM serum cortisol testing performed in Alberta Health Services laboratories is 200 to 650 nmol/L. Levels of less than 200 nmol/L warrant further investigation and levels of less than 100 nmol/L are diagnostic of HPA axis suppression. However, in patients on chronic topical steroid therapy, levels of less than 500 nmol/L cannot exclude HPA axis suppression.[19] As such, all patients with AM serum cortisol levels of less than 500 nmol/L were sent for a 250-mg cosyntropin stimulation test to rule out exogenous HPA axis suppression. Cosyntropin stimulation tests were considered normal if the 60-minute cortisol level was greater than 500 nmol/L.[19]

Outcomes

The primary outcome measure was AM serum cortisol levels. Levels greater than 500 nmol/L indicated no evidence of HPA axis suppression. An AM serum cortisol level of less than 500 nmol/L with a normal cosyntropin stimulation test (ie, cortisol level greater than 500 nmol/L at 60 minutes) indicated no evidence of HPA axis suppression. An AM serum cortisol level of less than 500 nmol/L with abnormal cosyntropin stimulation tests (ie, cortisol level less than 500 nmol/L at 60 minutes) were considered diagnostic of HPA axis suppression.[19] Demographic data was retrospectively collected using a chart review and included the following variables: gender, age, asthma history, allergy history, acetylsalicylic acid (ASA) intolerance, smoking history, disease with or without nasal polyposis, 22-item Sino-Nasal Outcome Test (SNOT-22) scores, Lund-Mackay scores, and duration of budesonide use.

Statistical analysis was performed using Stata statistical software (StataCorp LP, College Station, TX). Descriptive statistics (means, SDs, ranges, and frequencies) and distributions were assessed for all outcome variables.

Results

A total of 35 patients met inclusion and exclusion criteria and were enrolled into the study. No eligible patients refused to participate and all of those who were enrolled completed the study. At each follow-up visit, budesonide irrigation compliance was self-reported by the patients—none reported stopping their irrigations. Table 1 outlines the cohort characteristics. The mean duration of high-volume sinonasal budesonide irrigations prior to AM serum cortisol testing was 38.2 months (2.9 years). The mean SNOT-22 score at presentation was 49.1 ± 21.9. At the time of HPA axis testing, the mean SNOT-22 score was 20.5 ± 16.9. Sixty-two percent of patients were taking concurrent inhaled corticosteroids for the treatment of asthma. None of the patients were prescribed concurrent intranasal or ocular corticosteroids. As per study protocol, no patient used systemic corticosteroids in the study period.

HPA axis testing outcomes

The mean serum AM serum cortisol level was 431.2 ± 146.88 nmol/L. Nineteen patients had AM serum cortisol

TABLE 1. Baseline characteristics for cohort with CRS (n = 35)

Characteristic	
Gender, n (%)	
Female	13 (37)
Male	22 (63)
Age (years), mean (range)	49.5 (20–77)
Asthma, n (%)	18 (62)
Allergy, n (%)	13 (45)
ASA intolerance, n (%)	6 (21)
Smoker, n (%)	2 (7)
Nasal polyposis, n (%)	20 (69)
SNOT-22 score presentation, mean ± SD	49.1 ± 21.9
SNOT-22 score follow-up, mean ± SD	20.5 ± 16.9
Sinus CT score (Lund-Mackay), mean (range)	14.3 (4–24)
Duration of budesonide use (months), mean (range)	38.2 (15–96)
Concurrent medication use, n (%)	
Inhaled corticosteroids	18 (62)
Intranasal corticosteroid sprays	0 (0)
Ocular corticosteroid drops	0 (0)
Systemic corticosteroids	0 (0)
Oral contraceptive pills	1 (3)

ASA = acetylsalicylic acid; CRS = chronic rhinosinusitis; CT = computed tomography; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test.

TABLE 2. Hypothalamic pituitary adrenal axis testing (n = 35)

Outcome	
Morning serum cortisol level	
Mean ± SD (nmol/L)	431.2 ± 146.88
Range (nmol/L)	128–808
Normal (n)[a]	16
Low (n)[b]	2
Nondiagnostic (n)[c]	17
250 mcg cosyntropin stimulation test	
Normal (n)[d]	19
Abnormal (n)[e]	0

[a]Normal: greater than 500 nmol/L.
[b]Low: less than 200 nmol/L, greater than 100 nmol/L.
[c]Nondiagnostic: less than 500 nmol/L, greater than 200 nmol/L.
[d]Normal: cortisol greater than 500 nmol/L at 60 minutes.
[e]Abnormal: cortisol less than 500 nmol/L at 60 minutes.
SD = standard deviation.

results less than 500 nmol/L and required cosyntropin stimulation testing. Serum AM cortisol results are detailed in Table 2. Of the 19 patients who required cosyntropin stimulation testing, none had abnormal test results (all cortisol levels greater than 500 nmol/L at 60 minutes).

Discussion

This study examined the effect of long-term (greater than 12 months) high-volume sinonasal budesonide irrigations on HPA axis function in patients with CRS. After a mean of 38.2 months (2.9 years) of twice daily use of 1 mg per irrigation (2 mg daily dose), there were no detected cases of HPA axis suppression on objective testing. The results from this study suggest that the long-term use of sinonasal budesonide irrigations (up to 2.9 years) may be a safe treatment option in patients with CRS after ESS.

The mean serum AM cortisol level was 431.2 nmol/L, with a range of 128 to 808 nmol/L. Of the 35 patients enrolled into this study, 19 had serum AM cortisol levels that could not exclude exogenous HPA axis suppression (less than 500 nmol/L). Seventeen of these patients had serum levels within the normal range, which cannot exclude suppression in patients on prolonged topical steroids. Two patients had low serum AM cortisol levels, which in the general population would have prompted further testing but are not diagnostic of exogenous suppression (less than 200 nmol/L, greater than 100 nmol/L). All 19 of these patients went on to receive normal 250 mcg cosyntropin stimulation tests.

Eighteen patients in this cohort (62%) had a history of concurrent asthma and were taking inhaled corticosteroids. Hypothetically, the systemic effects of multiple corticosteroids may be cumulative and potentially put this subset of patients at higher risk for HPA axis suppression. However, none of these patients had evidence of suppression. None of the patients were concurrently prescribed ophthalmic corticosteroids or intranasal corticosteroid sprays and as such the cumulative effectives of these medications of budesonide irrigations cannot be assessed.

The importance of topical intranasal steroids in the management of CRS is well established.[3,17,20,21] Although the safety profiles for intranasal steroid sprays are well known, the greatest drawback of these low-volume sprays is inadequate delivery into the paranasal sinuses.[5,6,8,9] High-volume irrigation techniques have been shown to optimize delivery of medications into the sinuses and are believed to offer a better maintenance technique to control mucosal inflammation.[6,8–10] High-volume irrigation techniques are now recommended as the primary delivery mechanism for topical intranasal corticosteroid therapy in patients with CRS.[11,22] Unfortunately, they remain limited to off-label agents and lack robust safety profiles.[4]

Prolonged topical steroids are associated with a risk of unintended systemic absorption, which can lead to a variety of adverse effects such as increased intraocular pressure, glaucoma, osteoporosis, avascular necrosis of the hip, and HPA axis suppression.[23] However, HPA axis

suppression can be relatively sinister. As the dose and the duration of corticosteroid therapy increases, the risk of suppression increases. Therefore, as long as the patients continue to receive the corticosteroids, they may not experience any symptoms. When they do, symptoms tend to be nonspecific such as malaise, weakness, and decreased appetite. HPA axis suppression tends to manifest either when patients are placed in an acutely physiologically stressful situation, such as surgery or a significant illness, or when the corticosteroid is abruptly stopped. In these instances, the downregulated HPA axis is unable to mount an appropriate response, which clinically results in an adrenal crisis, a life-threatening condition. As such, identifying patient who have HPA axis suppression is essential in order to appropriate prevent and manage potential complications.[24–26]

Budesonide is a potent topical corticosteroid that is approximately 1000 times more potent than cortisol, which has a reported systemic bioavailability of approximately 35%. It binds to the glucocorticoid receptor and stimulates its anti-inflammatory properties though a variety of mechanisms including: altering the release of arachidonic acid metabolites, inhibiting the accumulation of leukocytes in affected tissue, decreasing vascular permeability, inhibiting neuropeptide-mediated responses, and altering the secretion of glycoproteins from submucosal glands.[5] Budesonide respules added to high-volume saline irrigations provide a total daily dose between 0.25 mg and 2 mg.[5] These relatively higher dosages have raised concerns regarding the potential for increased systemic exposure and complications from high-volume sinonasal budesonide irrigations.[4,5,27]

To date, there have been 3 studies that evaluated the safety of high-volume sinonasal budesonide irrigations.[28–30] Bhalla et al.[28] retrospectively evaluated 18 patients with CRS with nasal polyposis who received a total budesonide dose of 2 mg/day in high-volume irrigations. Serum AM cortisol levels were measured after 8 weeks of use and showed no evidence of HPA axis suppression.[28] Welch et al.[29] prospectively examined 10 patients who received a total daily dose of 1 mg/day in high-volume irrigations. At 6 weeks, serum AM cortisol levels and 24-hour urinary cortisol showed no signs of HPA axis suppression.[29] Seiberling et al.[30] examined the effects of high-volume sinonasal budesonide irrigations (0.5 mg/day) on intraocular pressure and found no effect of intraocular pressure after at least 4 weeks of use. The results from these studies suggest high-volume sinonasal budesonide irrigations are safe for short-term use (4 to 8 weeks).

This is one of the first studies to examine the long-term effects of high-volume sinonasal budesonide irrigations on the HPA axis. After an average of 38.2 months (2.9 years) of daily use, patients receiving a total daily budesonide dose of 2 mg/day showed no evidence of HPA axis suppression. One potential explanation for the lack of systemic effects associated with high-volume sinonasal budesonide irrigations is that the actual retained dose of budesonide is relatively low. Harvey et al.[8] demonstrated that less than 5% of irrigation solution remains in the sinuses after rinsing, suggesting patients' actual budesonide exposure is much lower than the prescribed dose. Regardless, the results from this study suggest that long-term use of high-volume sinonasal budesonide irrigations may not be associated with HPA axis suppression and may be considered safe up to 2.9 years of daily use.

When interpreting the results from this study, the following limitations should be considered. First, the sample size of our cohort is relatively small which predisposes to a type II error by incorrectly accepting the null hypothesis. Therefore, future studies with larger sample sizes should be performed to confirm the findings from this study. Second, the retrospective nature of CRS characteristic data collection does not allow us to examine compliance to medications, which may result in patients receiving less than the intended 2 mg total dose of topical budesonide. Although there is a risk of including patients who were noncompliant with their budesonide irrigations, the cohort of CRS patients evaluated in this study had severe inflammatory phenotypes requiring twice daily budesonide irrigations for longer than 12 months and are followed routinely to ensure disease control is optimized. At each follow-up, compliance to topical therapy was questioned and none reported stopping their budesonide irrigations. Third, there was no control group for this study, which makes it challenging to understand how prolonged high-volume budesonide irrigation therapy compares to patients receiving prolonged low-volume metered dose corticosteroid sprays. However, inhaled budesonide has been FDA approved for the maintenance treatment of asthma and as a prophylactic therapy in children 12 months to 8 years of age with safety reports comparable to FDA approved low-volume intranasal corticosteroid sprays.[31] Fourth, the retrospective nature of the study prevented the ability to obtain "baseline" AM serum cortisol levels which could have been used as a comparison. However, unless the patient had a rare baseline adrenal insufficiency condition, it may be assumed that all patients had normal AM serum cortisol levels prior to beginning treatment. Finally, this study looks specifically at the effects of high-volume sinonasal budesonide irrigations on the HPA axis, and did not evaluate patient-reported outcomes or other systemic effects, such as increased intraocular pressure or osteoporosis. Despite these limitations, we feel the results from this study provide useful outcomes to justify further investigation into the prolonged use of topical high-volume sinonasal budesonide irrigations.

Conclusion

Due to improved sinus access and proven short-term safety, high-volume sinonasal budesonide irrigations have become a popular method of topical corticosteroid therapy during management of CRS. However, the poorly defined safety profile of budesonide irrigations beyond 8 weeks of continuous use represents a gap in our knowledge to counsel patients. Outcomes from this study suggest that after a mean of 38.2 months (2.9 years) of twice daily budesonide

irrigations (total dose of 2 mg per day), there were no detectable cases of HPA suppression in this patient cohort. Future prospective studies with larger sample sizes are needed to confirm the findings from this study to ensure high-volume budesonide irrigations are a safe, long-term therapeutic option for CRS.

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ORIGINAL ARTICLE

Safety analysis of long-term budesonide nasal irrigations in patients with chronic rhinosinusitis post endoscopic sinus surgery

Ethan Soudry, MD[1,2], Jane Wang, NP[1], Reza Vaezeafshar, MD[1], Laurence Katznelson, MD[3,4] and Peter H. Hwang, MD[1]

Background: **Although the safety of topical nasal steroids is well established for nasal spray forms, data regarding the safety of steroid irrigations is limited. We studied the effect of long-term budesonide nasal irrigations (>6 months) on hypothalamic-pituitary-adrenal axis (HPAA) function and intraocular pressure (IOP) in patients post–endoscopic sinus surgery.**

Methods: **This was retrospective case series. Adrenal function was assessed by using the high-dose cosyntropin stimulation test.**

Results: **A total of 48 patients were assessed, with a mean duration of budesonide irrigations of 22 months. Stimulated cortisol levels were abnormally low in 11 patients (23%). None reported to have symptoms of adrenal suppression. Three of 4 patients who repeated the study being off budesonide for at least 1 month returned to near normal levels. Logistic regression analysis revealed that concomitant use of both nasal steroid sprays and pulmonary steroid inhalers was significantly associated with HPAA suppression ($p = 0.024$). Patients with low stimulated cortisol levels were able to continue budesonide irrigations under the supervision of an endocrinologist without frank clinical manifestations of adrenal insufficiency. IOP was within normal limits in all patients.**

Conclusion: **Long-term use of budesonide nasal irrigations is generally safe, but asymptomatic HPAA suppression may occur in selected patients. Concomitant use of both nasal steroid sprays and pulmonary steroid inhalers while using daily budesonide nasal irrigations is associated with an increased risk. Rhinologists should be alerted to the potential risks of long-term use of budesonide nasal irrigations, and monitoring for HPAA suppression may be warranted in patients receiving long-term budesonide irrigation therapy.**

Key Words:
budesonide; corticosteroid; safety; HPAA suppression; intraocular pressure; irrigation; chronic rhinosinusitis

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Corticosteroids are widely used in the management of chronic rhinosinusitis (CRS) to address the underlying inflammatory disorder. To avoid the potential adverse effects of systemic steroids, topical nasal steroids are typically used for long-term maintenance therapy in these patients, often indefinitely, in order to avoid exacerbations. Topical nasal steroid sprays have been shown to have an excellent safety profile in multiple studies[1–4] in terms of hypothalamic-pituitary-adrenal axis (HPAA) suppression and intraocular pressure (IOP).[5–9]

In recent years it has become increasingly common to deliver topical nasal steroids via high-volume saline irrigations (typically 240 mL), specifically in the post–endoscopic sinus surgery (ESS) patient group. Studies have shown that in postsurgical patients there is a significantly improved penetration of the sinus cavities with high-volume low-pressure irrigations compared with nasal sprays or atomizers.[10–13] Budesonide, in the respule form, has been commonly added to these high-volume irrigations in doses ranging from 0.25 mg to 2 mg daily. In comparison, the standard dose of

[1]*Department of Otolaryngology–Head and Neck Surgery, Stanford University School of Medicine, Stanford, CA;* [2]*Department of Otolaryngology–Head and Neck Surgery, Rabin Medical Center, Tel Aviv University, Tel Aviv, Israel;* [3]*Department of Neurosurgery, Stanford University School of Medicine, Stanford, CA;* [4]*Department of Medicine, Stanford University School of Medicine, Stanford, CA*

Correspondence to: Peter H. Hwang, MD, Department of Otolaryngology–Head and Neck Surgery, Stanford University School of Medicine, 801 Welch Road, Stanford, CA 94305;
e-mail: hwangph@stanford.edu

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budesonide delivered via nasal spray metered dose inhaler is significantly lower and typically ranges from 64 μg to 256 μg. Consequently, there has been much interest in studying the safety profile of this delivery method. The vast majority of these studies addressed short term (up to 8 weeks) use of nasal steroid irrigations.[14–19]

In this study we were interested in studying the safety profile (HPAA suppression and IOP) of long-term (6 months or longer) use of budesonide nasal irrigations. HPAA suppression was assessed by the 250 μg cosyntropin stimulation test, which evaluates the response (cortisol production) of the adrenal gland to exogenous adrenocorticotropic hormone (ACTH) administration.

Patients and methods

This study was approved by the Institutional Review Board (IRB) of Stanford University. Since September 2012, we have offered testing of stimulated cortisol levels and IOP to all patients in our clinic who have received budesonide sinus irrigations, 0.5 mg budesonide in 240 mL saline once or twice daily, for at least 6 months. Patients undergoing stimulated cortisol testing were asked to discontinue budesonide rinses 24 to 48 hours prior to the test to allow clearance of any budesonide from the body. The tests were conducted in the early morning (8:00 AM to 10:00 AM) whenever possible. An intramuscular injection of 250 μg of cosyntropin was administered, followed 30 minutes later by blood draw to measure non-fasting serum cortisol and albumin levels. IOP was measured with the Tono-Pen® XL Applanation Tonometer (Reichert Inc., Buffalo, NY) topical anesthesia of the cornea. Patients were questioned for the frequency and dosage of budesonide irrigations and any additional use of other medications. Adverse effects of both irrigations and cortisol stimulation test were recorded as well.

The medical records were reviewed for all patients undergoing cortisol and intraocular pressure testing between 2012 and 2014. Only patients who had undergone ESS were considered. The following information was retrieved: patient demographics, duration and cumulative dose exposure of budesonide irrigation usage, IOP, stimulated cortisol levels, and use of other medications. Exclusion criteria included known pituitary disease, concurrent or recent (<30 days) use of systemic glucocorticoids (oral/intravenous/intramuscular), use of oral estrogens in women, morbid obesity (body mass index [BMI] >38), concurrent pregnancy, and use of medications that affect cortisol production or clearance. Patients found to have low stimulated cortisol levels were re-tested early in the morning if previous measurement had been done in the afternoon. Patients with abnormally low stimulated cortisol levels in the morning were offered re-test when they were 30 days off budesonide rinses.

Statistical analysis

Data were analyzed using IBM SPSS 22.0 statistical software (IBM Corp., Armonk, NY). Chi square was used to analyze statistical differences between categorical variables. An independent 2-tailed t test or Mann-Whitney test were used to analyze continuous variables as determined following normality analysis using the Shapiro-Wilk test. Logistic regression was used for multivariate analysis to identify clinically significant factors associated with HPAA suppression. Values of $p < 0.05$ were considered significant.

Results

A total of 48 patients were included in the study, including 20 females and 28 males. Mean age of patients was 54.5 years (range, 27–77 years); 28 (58%) of our patient were Caucasians, 8 were Asians (17%), 9 were recorded as "other," 1 was African American, and in 2 data was missing. In 40 patients (83%) all sinuses were operated on; in 7 a minimum of bilateral max antrostomy and total ethmoidectomy were performed.

Patients received budesonide irrigations for a mean of 22 months (range, 6–66 months) with a mean daily dose of 0.75 mg. Thirty-two (67%) patients were concurrently using other forms of topical steroids (15, nasal spray; 10, pulmonary inhaler; 1, ophthalmic drops; and 6, both nasal spray and pulmonary inhaler).

Adrenal suppression testing

Of the 48 patients, 11 (23%) had abnormally low stimulated cortisol levels (<18 μg/dL). No patient with an abnormal stimulated cortisol result reported any symptoms of adrenal suppression (weakness, fatigue, dizziness, muscle aches, nausea, vomiting, and diarrhea). Four of these 11 patients repeated the cosyntropin stimulation test being at least 30 days off budesonide irrigations. One remained with low levels and in the other 3 patients stimulated cortisol levels increased significantly (patient #1: 12.2 to 16.4 μg/dL; patient #2: 14.6 to 17.5 μg/dL; and patient #3: 16.6 to 17.6 μg/dL). Interestingly, when patient #1 resumed budesonide rinses, stimulated cortisol levels decreased again to 13.5 μg/dL. All patients with abnormally low cortisol levels were evaluated by an endocrinologist (L.K.) who, based on presenting symptoms, recommended continuation of budesonide irrigations, owing to the symptomatic benefit gained from the therapy, and observation for clinically evident adrenal insufficiency. For the 3 patients who remained with significantly low stimulated cortisol levels (<16 μg/dL), steroid irrigations were maintained, but the patients were also recommended to receive stress dose steroids as needed for medical or surgical indications.[20] To date, there have been no adverse clinical events related to adrenal insufficiency in any of our patients maintained on budesonide irrigations.

Comparison between the group of patients with abnormally low stimulated cortisol levels to those with normal levels did not demonstrate statistically significant differences in terms of duration of budesonide irrigation therapy, average daily budesonide dose, or cumulative budesonide dose. Concomitant use of both nasal steroid sprays

and pulmonary steroid inhalers was significantly higher ($p = 0.021$) in the group of patients with low stimulated cortisol levels. However, concurrent use of only 1 other form of steroid spray or inhaler was not associated with lower stimulated cortisol levels. Although no differences were seen with respect to age, there was a higher proportion of males in the abnormally low stimulated cortisol level group, which reached a nearly significant value of $p = 0.07$. Logistic regression analysis including all of the above parameters revealed that only concomitant use of both nasal steroid sprays and steroid inhalers in addition to the budesonide rinses was significantly associated with HPAA suppression ($p = 0.024$; odds ratio [OR] = 30.4; 95% confidence interval [CI], 1.57 to 588). Albumin levels were within normal limits in all patients, and none of the patients had any documentation of renal insufficiency, thus indicating the reliability of the stimulated cortisol levels.

IOP

IOP was tested in 46 of 48 patients and was found to be within normal limits in all of these patients (range, 13–18 mmHg; mean, 16 mmHg).

Discussion

Topical corticosteroids have been widely used in the treatment of CRS. After ESS, topical nasal steroids have been shown to reduce the rate of polyp recurrence, increase the time to polyp recurrence, reduce systemic steroid rescues, improve ostial patency and improve endoscopy scores.[21–24]

Recent studies have shown that high-volume irrigations have a significantly better penetration of the paranasal sinuses, predominantly in the post-ESS cavity, compared to other delivery methods.[10–13] The addition of budesonide respules to high-volume saline irrigations has been increasingly used in order to improve the topical delivery of these steroids to the sinus cavities. This practice of delivering higher doses of topical steroids intranasally through irrigations and thus minimizing the use of systemic steroids and avoiding their potential systemic adverse effects has gained wide acceptance among rhinologists. Studies have shown that this practice leads to improved post-ESS quality of life scores and endoscopy scores.[25,26] Given that significantly higher doses of steroids are delivered using this method, there has been concern regarding the safety profile of this practice in terms of systemic steroid absorption, HPAA suppression, and elevated IOP.

Budesonide irrigations and HPAA suppression

Identifying patients with HPAA suppression, even if mild, is important because life-threatening hypotension may occur during periods of stress (eg, illness, trauma, surgery) and the condition is totally preventable if supplemental glucocorticoids are administered. Plasma cortisol testing has low sensitivity and is often nondiagnostic due to the cyclical variability of endogenous cortisol levels. Twenty-four–hour urinary free cortisol levels are often nondiagnostic as well, due to lack of sensitivity at low levels; ie, low cortisol excretion may be normal.[27] Consequently, dynamic testing is preferred to diagnose adrenal insufficiency. The advantage of dynamic testing is that it provides information regarding the function, reserve capacity and, hence, the ability of the adrenal gland or of the entire HPA axis to respond to stress. The high-dose cosyntropin test is the most commonly used dynamic diagnostic test.[27–29] A supraphysiologic dose (250 μg) of synthetic ACTH (cosyntropin) is administered via the intramuscular or intravenous routes and cortisol levels are measured either 30 minutes (intramuscular) or 60 minutes (intravenous) after ACTH administration. This is a simple, fast, and inexpensive test that can be performed in the outpatient clinic. At 30 minutes poststimulation, blood cortisol levels above 18 μg/dL are considered normal. In suspected secondary adrenal insufficiency, stimulated cortisol levels below 16 μg/dL have been suggested to better predict abnormal function of the HPAA[29]; nonetheless, the 18-μg/dL cutoff is still more commonly used in many centers.

Multiple studies have assessed HPAA suppression associated with chronic intranasal steroid use.[1–4] Pipckorn et al.[4] investigated HPAA suppression through stimulated cortisol levels and found that intranasal budesonide spray in the dose of 200 to 400 μg/day is safe for up to 5.5 years of treatment of perennial rhinitis.

Intranasal budesonide irrigations have been studied as well, but follow-up times have been limited to 12 months or less. In unoperated patients, doses of up to 2 mg budesonide daily for 4 to 12 weeks were not shown to be associated with HPAA suppression.[14,17,18] In post-ESS patients, Welch et al.[19] found normal serum and urinary cortisol levels in 10 patients after 6 weeks treatment of a total of 1 mg per day budesonide irrigations.[19] Man et al.[15] found normal salivary cortisol levels in 23 patients treated with a total of 6 mg fluticasone daily. Rotenberg et al.[16] studied 20 patients treated with 1 mg budesonide daily for 12 months and found normal ACTH levels. Measurement of ACTH levels alone, however, is considered insufficient in the diagnosis of secondary HPAA suppression.[27]

In our study group we observed that approximately one-quarter of patients receiving long-term budesonide nasal irrigations for the management of CRS developed subclinical adrenal insufficiency. We did not assess baseline adrenal function measurements, so we cannot determine whether the adrenal insufficiency was incidental to or caused by the initiation of budesonide nasal irrigation therapy. Nonetheless, with this relatively high incidence of adrenal insufficiency we can infer that budesonide irrigations had at least some contributing role. Strengthening our assumption were the findings that 3 out of 4 patients with adrenal hypofunction showed significantly increased stimulated cortisol levels after discontinuing budesonide rinses; furthermore, when 1 of these patients resumed budesonide rinses, his stimulated cortisol levels deteriorated again.

Because serum cortisol can be modulated by degree of circulating globulins (including cortisol binding globulin), we measured albumin to serve as a surrogate marker of protein levels.[30] Serum albumin levels were normal in our subjects, suggesting that the serum cortisol was accurately measured.

Our analysis of risk factors for HPAA suppression showed that daily budesonide dosage, duration of use, cumulative dose, and patient demographics were not associated with increased risk, except for a near-significant association with male gender. However, the concomitant use of both nasal and pulmonary topical steroids in addition to budesonide rinses was associated with a significant risk for subclinical HPAA suppression. In patients who are on both nasal and pulmonary steroids in addition to budesonide rinse, close monitoring for HPAA suppression is warranted with a low threshold to discontinue topical steroid treatment. The use of a single additional form of steroid inhaler or spray was not associated with a higher risk of HPAA suppression. Of note, none of our patients with low stimulated cortisol levels complained of fatigue or nausea, or other typical symptoms of adrenal insufficiency.

Budesonide irrigations and IOP

Ocular hypertension, as diagnosed by IOP above 21 mmHg, is associated with a higher risk of developing glaucoma, which is the leading cause of blindness in the United States. Early detection, risk prevention and proper treatment are thus invaluable in reducing the risk for deterioration in vision and blindness. The effect of topical nasal steroids on IOP has been investigated in multiple studies with mixed results. Some studies have shown no association with IOP elevation,[5–9,31] while others show increased risk, particularly in patients with glaucoma or using nasal steroids for longer than 3 months.[11,32,33]

The effect of budesonide nasal irrigations on IOP has been studied as well. Sieberling et al.[31] found that up to 6 months treatment with 0.5 mg budesonide nasal irrigations daily is not associated with elevated IOP. Rotenberg et al.[16] found no effect on IOP following 12 months' use of 1 mg budesonide irrigations daily. In our study group IOP levels remained within normal limits even with up to 66 months use of budesonide nasal irrigations.

Study limitations

Although our study reflects a fairly robust cohort size and mean follow-up time of almost 2 years, it reports a single institution's experience and has the inherent limitations associated with a retrospective case series. Prospective studies on larger cohorts with pretreatment baseline cortisol testing are needed to further corroborate these findings.

Conclusion

A cross sectional analysis of the safety profile of long-term use of budesonide nasal irrigations revealed that in nearly one-quarter of patients, a subclinical HPAA suppression existed with stimulated cortisol levels below 18 μg/dL. In contrast, we did not find an increased risk for IOP elevation in our patient cohort. Statistical analysis revealed that concomitant use of 2 additional forms of topical steroids (nasal and pulmonary) was associated with a higher risk for HPAA suppression. Male gender had a nearly significant higher risk for HPAA suppression. Although no patients presented with clinically overt adrenal insufficiency, these findings should alert rhinologists to the potential risk of subclinical adrenal insufficiency associated with long-term use of budesonide nasal irrigations, particularly in patients receiving other forms of corticosteroid therapy. Laboratory monitoring for HPAA suppression may be warranted given the lack of symptoms reported in patients with objective evidence of HPAA suppression. In our experience, patients with asymptomatic HPAA suppression may continue to use budesonide irrigations successfully under the supervision of an endocrinologist.

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ORIGINAL ARTICLE

Endoscopic endonasal orbital cavernous hemangioma resection: global experience in techniques and outcomes

Benjamin S. Bleier, MD[1], Paolo Castelnuovo, MD[2], Paolo Battaglia, MD[2], Mario Turri-Zanoni, MD[2], Iacopo Dallan, MD[2], Ralph Metson, MD[1], Ahmad R. Sedaghat, MD, PhD[1], S. Tonya Stefko, MD[3], Paul A. Gardner, MD[4], Carl H. Snyderman, MD, MBA[3], Joao Flavio Nogueira, MD[5], Vijay R. Ramakrishnan, MD[6], Luca Muscatello, MD[7], Riccardo Lenzi, MD[7] and Suzanne Freitag, MD[1]

Background: **Endoscopic orbital surgery represents the next frontier in endonasal surgery. The current literature is largely composed of small, heterogeneous, case series with little consensus regarding optimal techniques. The purpose of this study was to combine the experience of multiple international centers to create a composite of the global experience on the endoscopic management of a single type of tumor, the orbital cavernous hemangioma (OCH).**

Methods: **This was a retrospective study of techniques for endoscopic OCH resection from 6 centers on 3 continents. Only primary data from strictly endoscopic resection of OCHs were included. Responses were analyzed to qualitatively identify points of both consensus and variability among the different groups.**

Results: **Data for a total of 23 patients, 10 (43.5%) male and 13 (56.5%) female were collected. The majority of lesions were intraconal (60.9%). The mean ± standard deviation (SD) surgical time was 150.7 ± 75.0 minutes with a mean blood loss of 82.7 ± 49.6 mL. Binarial approaches (26.1%) were used exclusively in the setting of intraconal lesions, which were associated with a higher rate of incomplete resection (31.3%), postoperative diplopia (25.0%), and the need for reconstruction (37.5%) than extraconal lesions. Orthotropia and symmetric orbital appearance were achieved in 60.9% and 78.3% of cases, respectively.**

Conclusion: **Extraconal lesions were managed similarly; however, greater variability was evident for intraconal lesions. These included the laterality and number of hands in the approach, methods of medial rectus retraction, and the need for reconstruction. The increased technical complexity and disparity of techniques in addressing intraconal OCHs suggests that continued research into the optimal management of this subclass of lesions is of significant priority.** © 2015 ARS-AAOA, LLC.

Key Words:
endoscopic; orbital; intraconal; orbital cavernous hemangioma; outcomes

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Endoscopic orbital surgery represents the next frontier in endonasal surgery. The feasibility of endoscopic management of periorbital pathology including orbital[1] and optic nerve decompression[2] were first reported over 25 years ago. Over the next decade the first descriptions of endonasal approaches within the intraconal space began to appear in the literature.[3,4] In subsequent years however, only a limited number of case series from high-volume institutions have been published, which report on a variety of orbital pathologies.[5–10] During the same period, the widespread proliferation of endoscopic skull-base surgery has been mirrored by a body of literature that has

[1]*Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA;* [2]*Department of Biotechnology and Life Sciences, Division of Otorhinolaryngology, University of Insubria, Varese, Italy;* [3]*Department of Ophthalmology, University of Pittsburgh Medical Center, Pittsburgh, PA;* [4]*Department of Neurological Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA;* [5]*Division of Otolaryngology, Hospital Geral de Fortaleza, Forta Leza, Brazil;* [6]*Division of Otolaryngology, University of Colorado, Denver, CO;* [7]*Division of Otorhinolaryngology, General Hospital of Massa, Massa, Italy*

Correspondence to: Benjamin S. Bleier, MD, 243 Charles Street, Boston MA, 02114; e-mail: benjamin_bleier@meei.harvard.edu

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matured from technique papers to larger multicenter outcome studies.[11] A similar rigor must be applied to the endoscopic orbital literature in order to expand the knowledge base in this, still nascent, field.

Orbital cavernous hemangioma (OCH) represents an ideal index lesion to study for a variety of reasons. First, it represents 1 of the most common tumors of the orbit accounting for 5% to 15% of orbital masses. Although OCHs have a predilection for the lateral intraconal space, likely due to a mirroring of ophthalmic arterial vasculature, they may be found throughout the orbit including the medial intraconal and extraconal spaces, as well as the optic canal.[12] Second, the technical complexity of endoscopic dissection is facilitated by the presence of a robust fibrous capsule. Although these lesions tend not to infiltrate into local tissue, they are capable of incorporating adjacent blood vessels and nerves into their capsule as they expand.[13] Histologically, OCHs demonstrate features of slow-growing venous lesions with mature cellular components that do not tend toward dysplasia or hypercellularity. Based on the classification of the International Society for the Study of Vascular Anomalies (ISSVA), these lesions should be characterized as slow-flow cavernous venous malformations. Clinically, OCHs are slow growing with a radiologic growth rate of 10% to 15% per year, resulting in displacement of the globe (axial proptosis for intraconal lesions, nonaxial displacement of the globe for extraconal masses) and, later, visual loss. Expansion is thought to result from a cycle of intravascular clot formation related to vascular stasis, which leads to thrombosis, endothelial cell proliferation, and subsequent recanalization into multiple clefts and vascular channels.[14] Because of the slow growth rate, surgical resection is indicated for symptomatic lesions, whereas smaller, asymptomatic lesions may be observed. The general goal of surgical management is definitive resection because the fate of lesions after partial resection is not well established in the literature.[14]

The purpose of this study was to create a composite of the collective global experience on purely endoscopic endonasal resection of OCHs from primary records. By combining the experience of multiple international centers on addressing a single type of pathology, we have been able to generate a moderate series of an otherwise rare procedure. This, in turn, helps to eliminate the confounders inherently associated with studies that group a range of heterogeneous lesions in order to generate a larger number of cases. Through this effort, our international consortium endeavors to develop some basic recommendations that may be extrapolated to other types of lesions and can serve as a foundation for further growth in this field.

Materials and methods

This was an Institutional Review Board (IRB)-approved, multi-institutional, international, retrospective study of techniques and outcomes in endoscopic orbital surgery, and was performed at the Massachusetts Eye and Ear Infirmary, Boston, MA. A common 25-point questionnaire was sent to 6 highly experienced orbital surgery centers on 3 continents (North America, n = 3; Europe, n = 2; and South America, n = 1). This study had extremely rigid inclusion criteria and accepted only patients who underwent a strictly endoscopic resection of a histopathologically proven OCH, although external methods of medial rectus retraction were permitted. The questionnaires covered specific elements of the preoperative workup, intraoperative techniques, and postoperative outcomes. All data was derived from primary patient records by the operating surgical team. The final data from each center was compiled and analyzed to qualitatively identify points of both consensus and variability in techniques.

Results

Data from a total of 23 patients who underwent an endoscopic endonasal resection of an OCH were collected. The population was comprised of 10 (43.5%) males and 13 (56.5%) females with a mean ± standard deviation (SD) age of 50.9 ± 13.5 years. Fifteen (65.2%) lesions were located on the right side, and 8 (34.8%) were located on the left side. The majority of lesions were located within the intraconal space (60.9%) and the mean follow-up time was 25.3 ± 23.0 months.

The most common presenting symptom was visual impairment (65.2%) followed by proptosis (34.8%). Nearly all patients underwent both computed tomography (CT) (100.0%) and magnetic resonance imaging (MRI) (95.7%) as part of the preoperative workup, whereas only 1 patient (4.4%) underwent preoperative angiography (Table 1).

The mean surgical time was 150.7 ± 75.0 minutes with a mean blood loss of 82.7 ± 49.6 mL. Eleven cases were performed as a team approach including otolaryngology with ophthalmology (26.1%) or neurosurgery (21.7%). The most common approach utilized a single nostril (69.6%). Binarial approaches (26.1%) were used exclusively in the setting of intraconal lesions. Among the intraconal lesions, a 4-handed, binarial approach was utilized in 37.5% of cases in contrast to a strictly 2-handed or 3-handed unilateral approach for patients with extraconal lesions (Fig. 1, Table 2). Bipolar cautery was used for hemostasis in 56.5% of cases, whereas monopolar cautery was avoided in all cases.

The majority of cases (73.9%) achieved a complete resection and did not undergo any subsequent orbital reconstruction. Among orbits that were reconstructed, 83.3% utilized a mucosal graft, whereas 16.7% used fascia lata (Table 3). Similarly, the majority of postoperative outcomes were favorable, with 78.3% of cases resulting in a symmetric eye position. Immediate preservation of binocular vision was achieved in 60.9% of patients (Table 4). All but 1 patient with postoperative diplopia resolved within 2 to 3 months. The etiology of diplopia for this patient with was thought to be inadvertent injury to the inferior rectus muscle.

TABLE 1. Preoperative characteristics

Presenting symptoms, n (%)	
Visual impairment	15 (65.2)
Proptosis	8 (34.8)
Pain	6 (26.1)
Diplopia	5 (21.7)
On-head swelling	1 (4.3)
Location, n (%)	
Intraconal	14 (60.9)
Optic canal	5 (21.7)
Extraconal	3 (13.0)
Mixed	1 (4.3)
Imaging, n (%)	
CT	23 (100.0)
MRI	22 (95.7)
Angiography	1 (4.3)
Tumor size (cm), mean ± SD	
Anterior-posterior	1.57 ± 0.70
Medial-lateral	1.15 ± 0.65
Superior-inferior	1.09 ± 0.48

CT = computed tomography; MRI = magnetic resonance imaging; ON = optic nerve; SD = standard deviation.

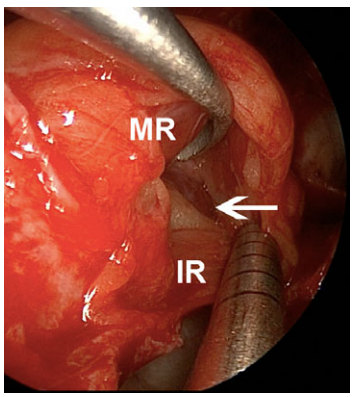

FIGURE 1. Endoscopic view of a right intraconal OCH demonstrating a 3-handed approach for exposure (white arrow represents the OCH). IR = inferior rectus muscle; MR = medial rectus muscle, OCH = orbital cavernous hemangioma.

Intraconal lesions were more likely to be associated with incomplete resection (31.25%) as compared to extraconal lesions (14.29%). Intraconal lesions also carried a higher risk of immediate postoperative diplopia and enophthalmos and were more likely to lead to a decision to reconstruct the orbit (Table 5). Among all patients with postoperative diplopia, only one-half were associated with medial rectus retraction (Table 6).

TABLE 2. Approach vs tumor location

Location	n (%)
Intraconal (n = 16)	
Approach	
Single nostril	10 (62.5)
Binarial	6 (37.5)
Number of hands/surgeons	
2/1	5 (31.3)
3/2	5 (31.3)
4/2	6 (37.5)
Extraconal (n = 7)	
Approach	
Single nostril	7 (100.0)
Binarial	0 (0.0)
Number of hands/surgeons	
2/1	2 (28.6)
3/2	5 (71.4)
4/2	0 (0.0)

Discussion

Although endoscopic skull base and orbital surgery share a common historical origin in time,[3,4] their proliferation has diverged over the subsequent decades. The reasons for this are likely multifactorial and may include the relative paucity of medial intraorbital pathology,[15] the lack of widespread collaborative oculoplastic and rhinology teams, as well as a general unfamiliarity among rhinologists with respect to medial intraconal neurovascular anatomy[16] and intraorbital dissection techniques. As endoscopic skull base techniques have become more widely utilized and accepted, however, approaches to the orbit have experienced a rebirth, with an increasing number of papers being published on the subject in recent years.[13,17] Consequently, this study was conceived in an effort to examine the independent endoscopic techniques developed at multiple experienced institutions to deal with a single type of lesion.

The preoperative workup for OCH was found to be similar among all groups. The vast majority of patients underwent both CT and MRI whereas only 1 underwent angiography. In general, angiography is not necessary because OCHs tend to have characteristic imaging findings that are generally sufficient to make the diagnosis.[14] Furthermore, the majority of procedures were undertaken using image guidance, which may be helpful, particularly when utilizing a limited orbitotomy to identify a small intraconal lesion that is mobile and obscured by periorbital fat.

Intraoperatively, there was general consensus that lesions located in the extraconal space could be sufficiently

TABLE 3. Intraoperative characteristics

	n	%
Team		
ENT	23	100.0
Ophthalmology	6	26.1
Neurosurgery	5	21.7
Use of image guidance		
Yes	19	82.6
No	4	17.4
Approach		
Single nostril	16	69.6
Middle turbinectomy	8	34.8
Binarial	6	26.1
Septal window	4	17.4
Middle turbinate swing[a]	1	4.3
Number of hands/surgeons		
2/1	7	30.4
3/2	10	43.5
4/2	6	26.1
Medial rectus retraction		
None	12	52.2
Double ball probe retraction	3	13.0
Transseptal suture retraction[b]	2	8.7
Blunt dissection	2	8.7
Medial rectus detached	1	4.3
Hemostasis		
Bipolar	13	56.5
None	6	26.1
Warm water	4	17.4
Monopolar	0	0.0
Orbital fat removal		
None	18	78.3
Extraconal	5	21.7
Intraconal	0	0.0
Resection		
Complete	17	73.9
Partial	2	8.7
Biopsy	2	8.7
Decompression	2	8.7
Reconstruction		
None	17	73.9
Mucosal graft	5	21.7
Fascia lata	1	4.3
Packing		
None	12	52.2
Nonabsorbable	10	43.5
Absorbable	1	4.3

[a]Middle turbinate swing: temporary displacement of middle turbinate.
[b]Transseptal suture: a suture or vessel loop is passed above and below the medial rectus muscle belly, allowing for medial retraction through a septotomy.
ENT = ear, nose, throat.

TABLE 4. Postoperative characteristics

	n	%
Eye position		
No change/symmetric	18	78.3
Enophthalmos	5	21.7
Proptosis	0	0.0
Diplopia		
None	14	60.9
Worse	6	26.1
Better	3	13.0
Vision		
Improved	12	52.2
No change	11	47.8
Worse	0	0.0

exposed via a single nostril using 2 or 3 hands. In contrast, intraconal lesions were approached using a variety of both single-nostril and binarial techniques. Although the majority of intraconal OCHs were resected using a 3-handed or 4-handed approach, 31.25% were resectable using only 2 hands. This finding suggests that when performing preoperative planning for tumors located lateral to the medial rectus muscle, strong consideration should be given to providing access for an assisting surgeon, although this is not an absolute requirement. Two of the major challenges associated with endoscopic surgery within the orbit are the presence of copious, mobile, orbital fat and the possibility of bleeding immediately adjacent to critical neurovascular structures including the oculomotor and optic nerves. Extraconal orbital fat can be judiciously shrunk with bipolar electrocautery to improve visualization; however, the safety of removing intraconal fat is controversial. Orbital fat was removed without complication in 21.7%

TABLE 5. Outcomes vs tumor location

Location	n	%
Intraconal (n = 16)		
Results		
Complete resection	11	68.8
Partial resection	1	6.3
Biopsy	2	12.5
Decompression	2	12.5
Morbidity		
New diplopia	4	25.0
New enophthalmos	4	25.0
Reconstruction	6	37.5
Extraconal (n = 7)		
Results		
Complete resection	6	85.7
Partial resection	1	14.3
Biopsy	0	0.0
Decompression	0	0.0
Morbidity		
New diplopia	1	14.3
New enophthalmos	1	14.3
Reconstruction	0	0.0

TABLE 6. Diplopia vs method of medial rectus retraction

Diplopia	Method of retraction	n	%
No	None	13	76.5
	Double ball probe	3	17.6
	Transseptal suture	1	5.9
Yes	None	3	50.0
	External	1	16.7
	Transseptal suture	1	16.7
	Muscle detachment	1	16.7

of our cases; however, this was generally performed in the extraconal space. The removal of intraconal fat to improve visualization should therefore be performed with extreme caution because this may inadvertently traumatize the delicate inferomedial branches of the ophthalmic artery that traverse medially from the main ophthalmic arterial trunk to supply the belly of the medial rectus muscle[16] as well as branches of the third cranial nerve. The use of a saline soaked cottonoid (neuropatty) may be used instead to gently displace a broad area of fat and absorb blood in order to facilitate dissection around the tumor capsule. Both warm water irrigation and bipolar cautery were utilized successfully to provide hemostasis; however, the use of monopolar electrocautery was avoided by all groups. Although the precise current and proximity required to injure the optic nerve is unknown, the literature[18] supports the blanket recommendation to avoid the use of monopolar cautery within the orbit or in proximity to the orbital apex.

Adequate and atraumatic retraction of the medial rectus muscle represents another important consideration when accessing intraconal lesions. Injury to the muscle fibers, neurovascular supply, or medial displacement may all result in postoperative muscle dysfunction and subsequent diplopia. A range of both static and dynamic medial rectus retraction methods were employed among all of the groups. The only external method involved placing a suture around the medial rectus at its insertion on the globe. Although the presence of immediate postoperative diplopia was evenly distributed among patients with or without retraction, the only method not associated with any diplopia was the transseptal double ball technique. In this approach, the right angle of a double ball probe is passed under the inferior border of the muscle, allowing the muscle to be pulled superomedially as needed. Despite this, the numbers are too small to provide a meaningful recommendation regarding the optimal method for medial rectus retraction. Regardless of the method utilized, however, a working knowledge of the course of the oculomotor nerve along the lateral aspect of the medial rectus muscle and its ramification and penetration of the muscle belly approximately one-third of the distance from the annulus of Zinn to its insertion on the globe, will help to protect this nerve from inadvertent traction injury.[16]

A complete resection was possible in the majority of cases of both extraconal and intraconal lesions. This is consistent with the fact that OCHs tend to be well encapsulated and rarely infiltrate adjacent structures.[13] As expected, tumors located within the intraconal space were associated with a greater incidence of incomplete removal and postoperative morbidity including new onset diplopia and enophthalmos. This may be attributed to the fact that approaches to the intraconal space mandate a larger orbitotomy as well as a greater degree of medial rectus instrumentation than extraconal lesions. In light of these technical requirements, it follows that 37.5% of patients with intraconal lesions underwent some form of medial orbital reconstruction as opposed to 0.00% in the extraconal group.

This work represents the largest reported series of purely endoscopic endonasal resection of OCHs. The indications for this approach are currently limited to lesions located medial to the optic nerve. However, it carries multiple advantages over open techniques including improved visualization and illumination while providing direct access to the lesion and reducing trauma and retraction of adjacent normal structures. Consequently, our reported functional outcomes are comparable or better than those reported

in the literature using open techniques.[19,20] Although general consensus existed on multiple aspects of the workup and management of extraconal lesions, several notable areas of variability existed with respect to intraconal lesions. These included the laterality and number of hands in the approach, the methods of medial rectus retraction, and the need for reconstruction. The increased technical complexity of addressing intraconal OCHs coupled with their higher reported postoperative morbidity suggests that continued research into the optimal management of this subclass of lesions is of significant priority. The limitations of this study include the retrospective nature of the data collection as well as the modest sample size that precludes any formal statistical analysis.

Conclusion

Cavernous hemangiomas are among the most common orbital tumors; however, only 23 cases could be gathered from experienced centers for this international study. This reflects, in part, the current lack of widespread collaboration between oculoplastic and rhinologic surgeons. Management of intraconal OCHs exhibited the greatest variability among institutions, suggesting that additional studies are needed to further optimize the approach to lesions in the intraconal space. As a field, we should continue to work to gain a greater familiarity with endoscopic surgery of the orbit, create evidence-based protocols for endoscopic management of orbital pathology, and cultivate the development of collaborative "orbital teams."

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The Laryngoscope

Augmented Real-Time Navigation With Critical Structure Proximity Alerts for Endoscopic Skull Base Surgery

Benjamin J. Dixon, MBBS; Michael J. Daly, MSc; Harley Chan, PhD; Allan Vescan, MD; Ian J. Witterick, MD; Jonathan C. Irish, MD

Objectives/Hypothesis: Image-guided surgery (IGS) systems are frequently utilized during cranial base surgery to aid in orientation and facilitate targeted surgery. We wished to assess the performance of our recently developed localized intraoperative virtual endoscopy (LIVE)-IGS prototype in a preclinical setting prior to deployment in the operating room. This system combines real-time ablative instrument tracking, critical structure proximity alerts, three-dimensional virtual endoscopic views, and intraoperative cone-beam computed tomographic image updates.

Study Design: Randomized-controlled trial plus qualitative analysis.

Methods: Skull base procedures were performed on 14 cadaver specimens by seven fellowship-trained skull base surgeons. Each subject performed two endoscopic transclival approaches; one with LIVE-IGS and one using a conventional IGS system in random order. National Aeronautics and Space Administration Task Load Index (NASA-TLX) scores were documented for each dissection, and a semistructured interview was recorded for qualitative assessment.

Results: The NASA-TLX scores for mental demand, effort, and frustration were significantly reduced with the LIVE-IGS system in comparison to conventional navigation ($P < .05$). The system interface was judged to be intuitive and most useful when there was a combination of high spatial demand, reduced or absent surface landmarks, and proximity to critical structures. The development of auditory icons for proximity alerts during the trial better informed the surgeon while limiting distraction.

Conclusions: The LIVE-IGS system provided accurate, intuitive, and dynamic feedback to the operating surgeon. Further refinements to proximity alerts and visualization settings will enhance orientation while limiting distraction. The system is currently being deployed in a prospective clinical trial in skull base surgery.

Key Words: Image-guided surgery, endoscopic surgery, surgical navigation, virtual endoscopy, skull base surgery, pituitary surgery.

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INTRODUCTION

Endoscopic skull base surgery can be technically demanding and requires a continuous appreciation of the surrounding critical structures.[1] Individual anatomic variations, pathologic processes, and tissue ablation for surgical access can distort or remove landmarks, making navigation in this complex three-dimensional (3D) environment more difficult. Image-guided surgery (IGS) systems are routinely used in many institutions to aid in orientation and facilitate precise, targeted surgery.[2] The cranial base is relatively rigid due to its bony composition, and limited soft tissue deformation occurs during surgery. This allows image registration to be accurate and reliable, especially around the bone–soft-tissue junction.

Various advanced display and feedback options have been developed for IGS systems, but routine clinical implementation of these features is rarely accomplished. Enhanced visualization through virtual views and augmented reality, as well as novel auditory alerts, are among the advancements under investigation.[3–6] Improved computer processing speeds allow these features to be presented effectively in real time with minimal temporal delay.[7] One of the main barriers to clinical implementation is the lack of human factors research focusing on the human–computer interface.[8]

The Guided Therapeutics program at the University Health Network, Toronto has developed a localized intraoperative virtual endoscopy IGS system (LIVE-IGS), which incorporates dynamic 3D virtual views, live tool tracking, and critical structure proximity alert zones.[7]

From the Department of Otolaryngology–Head and Neck Surgery, University of Toronto (B.J.D., I.J.W., J.C.I.); Department of Surgery, University of Melbourne, St. Vincent's Hospital and Peter MacCallum Cancer Institute, Melbourne, Australia (B.J.D.); Ontario Cancer Institute (M.J.D., H.C.); Institute of Medical Science, Princess Margaret Hospital, University of Health Network (M.J.D.); Department of Otolaryngology–Head and Neck Surgery, Mount Sinai Hospital (A.V., I.J.W.); Department of Surgical Oncology (I.J.W., J.C.I.), Toronto, Canada

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Send correspondence to Jonathan C. Irish, MD, 610 University Avenue, 3–954, Toronto, ON M5G 2M9, Canada. E-mail: jonathan.irish@uhn.on.ca

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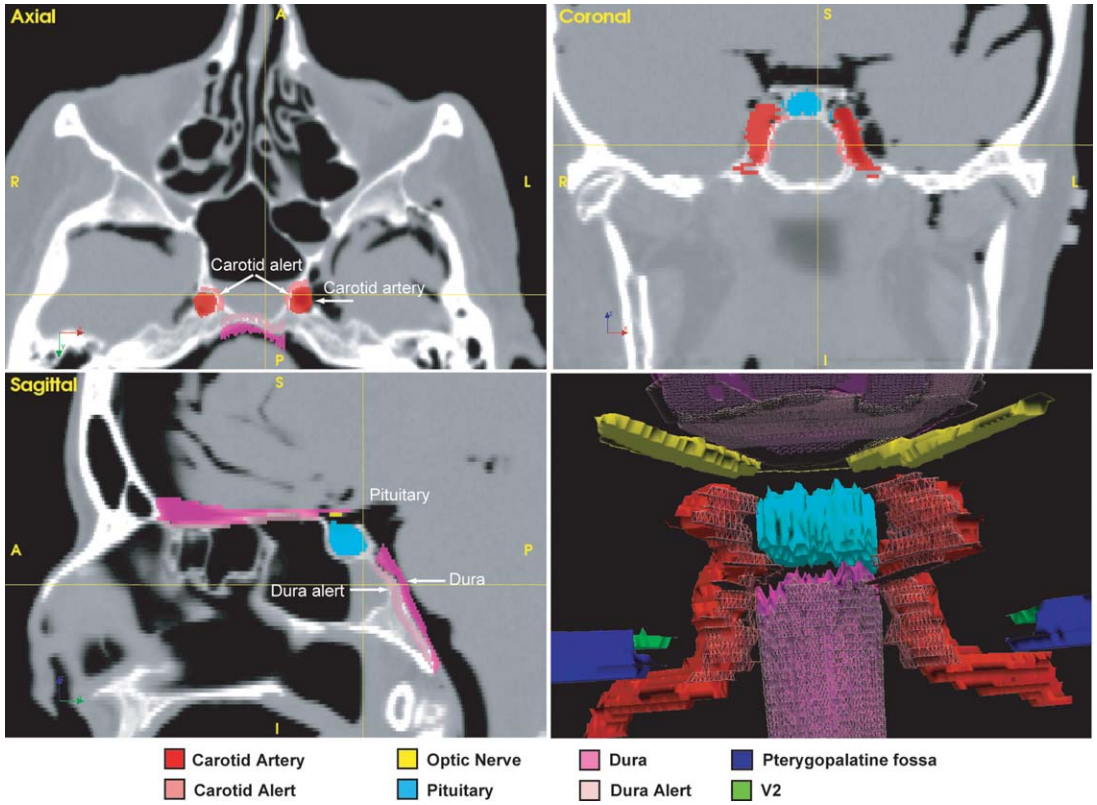

Fig. 1. Manual segmentation of cross-sectional computed tomographic scan images was used to create a three-dimensional virtual view of anatomical structures. A = anterior; I = inferior; L = left; P = posterior; R = right; S = superior.

Contouring pertinent anatomy allows intuitive display of anatomical relationships during surgery. We recognized the need for further interface development and aimed to prepare for clinical introduction of this technology by rigorously testing the system in a preclinical trial. To truly identify the barriers to clinical implementation, we planned an intensive operative exercise in a realistic environment. We elected to exclude inexperienced surgeons or trainees as subjects to avoid results that may not necessarily reflect the true clinical benefits and costs. We restricted participants to fellowship-trained otolaryngologists or neurosurgeons who regularly perform endoscopic skull base surgery. Multi-institutional recruitment was required to achieve an experienced cohort. There was a significant time commitment (around 5 hours) from each participant, and the wet laboratory was designed to replicate the operating room (OR) environment as closely as possible.

Surgeons performed surgical tasks with the LIVE-IGS system and also in a conventional manner so that paired data could be collected. We focused on qualitative feedback to identify interface design issues and target potential improvements. This included visual display settings, auditory alerts, and other ergonomic factors. We intended to update the system in response to feedback throughout the trial. Task workload was assessed to identify whether this technology altered the demands on the surgeon.

MATERIALS AND METHODS

Seven otolaryngology (n = 5) and neurosurgery (n = 2) skull base surgeons from five institutions participated in a cadaver dissection trial. Prior to dissection, each head underwent computed tomographic (CT) scanning followed by critical structure manual segmentation using ITK-SNAP 2.0 software.[9] Structures contoured included the carotid arteries, optic nerves, pituitary gland, dura, and orbits. Alert zones of approximately 2 to 3 mm were manually mapped around the carotid arteries and the dura (Fig. 1). This process was undertaken by the investigating surgeons and took approximately 60 minutes per case. In keeping with clinical protocols, we initially performed magnetic resonance imaging, but the quality of the scans was poor on cadaver specimens and offered no advantage over CT for the purposes of this study. CT angiography could not be performed on cadavers.

The initial surgical approach was performed by the investigators before the subjects started the study task (clivus ablation). Ethmoidectomy, posterior septectomy, and a wide, unified sphenoidotomy were performed, and then the heads were reimaged with a surgical cone-beam CT (CBCT) system.[10] Deformable registration allowed the contours delineated from the preoperative CT to be registered to the intraoperative CBCT imaging.[11]

Optical IGS reflective markers were attached to the head, the 0° endoscope (Hopkins II telescope and IMAGE1 camera; Karl Storz, Tuttlingen, Germany), and the drill (M4 hand-piece; Medtronic, Jacksonville, FL). Registration of the head to the imaging data was then undertaken with an optical tracking system (Polaris; NDI, Waterloo, Ontario, Canada). Fiducial

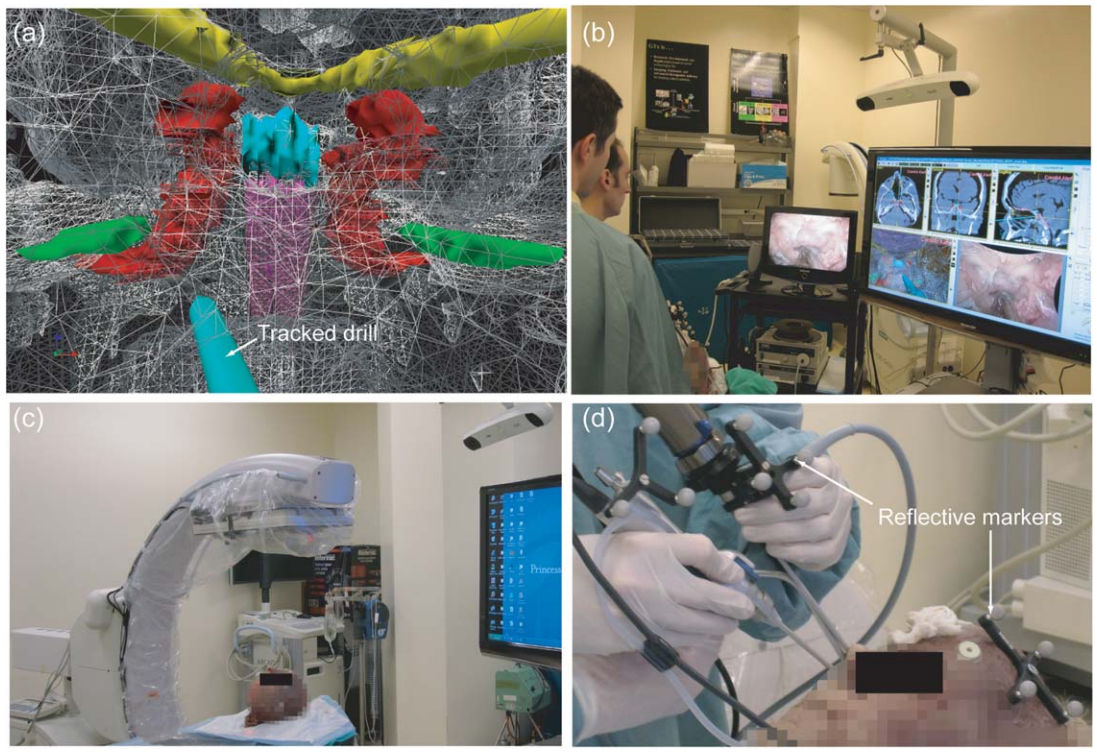

Fig. 2. (a) Three-dimensional virtual view displaying wall-down view of critical structures behind a white mesh overlay of surface contours. The tracked drill is shown. The virtual view updates in real time to provide a view perceptually matched to the endoscopic view. (b) Wet laboratory setup showing the virtual view parallel to the endoscopic monitor in addition to the triplanar views. All images update dynamically as the endoscope and drill are tracked by an image-guided surgery camera located above the display. (c) Cone-beam computed tomography used to update imaging after the initial surgical approach and before clivus ablation. This allowed refinement of the display to show more realistic surface contours. (d) Optical tracking registration markers placed on the head, endoscope, and drill. Orientation of markers was adjusted to limit line-of-sight interference.

registration errors were calculated using a standardized paired-point algorithm. Custom navigation software, developed by our group, provided a real-time 3D virtual view that was displayed on a submonitor adjacent to the endoscopic monitor (Fig. 2a, b).[7] Surface contours were displayed as a mesh and based on intraoperative CBCT imaging (Fig. 2c). A traditional triplanar representation of the updated CT images was placed on the submonitor. The drill was tracked live, and its position was shown on both the virtual and cross-sectional views (Fig. 2d). Auditory feedback was provided through alarms when the tracked instrument (drill) entered a contoured volume representing a critical structure or a proximity alert zone.

Sixteen heads were dissected in total. Two heads were dissected as a pilot by the investigators to establish initial laboratory setup and fine-tune alarm and visualization settings. The seven subjects then performed an endoscopic transclival approach on two heads each; one with the LIVE-IGS system and one in a conventional manner (standard IGS involving a tracked probe and preoperative CT) in random order. The extent of dissection was to each carotid artery laterally and to the dura posteriorly. Ablation extended from the pituitary fossa down to below the level of the petrous segment of the carotid arteries.

The National Aeronautics and Space Administration Task Load Index (NASA-TLX) questionnaire was administered midway through the exercise and again at completion.[12] Open feedback was encouraged during the trial. After completing both dissections, a semistructured interview was carried out and recorded on video. Open responses on general use of the system and each feature were acquired prior to more in-depth questions on specific elements, their potential uses, and recommendations. A seven-point Likert questionnaire pertaining to aspects of the trial was also administered.

The recorded interviews were scrutinized by three investigators. Feedback was categorized, and comments on these features were documented then communicated to an independent observer. Agreement in regard to statements was reached, and these data were entered into a consensus document in subcategories.

Statistical Analysis

Likert questionnaire responses are displayed as medians and interquartile range (IQR). The Wilcoxon signed rank test was used to compare the paired NASA-TLX responses, with $P < .05$ deemed significant.

RESULTS

All seven participants completed the two clivus ablation exercises. A significant amount of time was allocated to become familiar with the navigation system and to explore its capabilities. Fiducial registration errors were consistent with current clinical practice (between 1 mm and 1.8 mm for all cases).

Initial Open Feedback

All subjects were generally impressed by the features displayed, particularly the ability for real-time

TABLE I.
Task Workload Assessment.

	NASA-TLX Scores		
NASA-TLX Subscale	Conventional Mean (SD)	LIVE-IGS Mean (SD)	*P*, Wilcoxon SR Test
Mental Demand	10.6 (4.9)	6.9 (3.3)	.006*
Physical Demand	9.3 (5.6)	7.4 (3.1)	.094
Temporal Demand	6.6 (4.5)	5.1 (2.4)	.19
Performance	5.4 (3.8)	4.6 (2.8)	.496
Effort	9.8 (5.0)	6.1 (3.2)	.011*
Frustration	7.7 (5.5)	4.6 (2.7)	.032*

Lower performance score indicates higher perceived performance.
*Significant improvement with LIVE-IGS ($P < .05$).
LIVE-IGS = localized intraoperative virtual endoscopy image-guided surgery; NASA-TLX = National Aeronautics and Space Administration Task Load Index; SD = standard deviation; SR = signed rank.

navigation of endoscopic and ablative instruments. Accuracy was universally judged to be equal or superior to the current OR standards and sufficient for the applications provided. The main benefit over a conventional system was the speed at which navigation assistance could be provided and interpreted during ablative tasks.

Task Workload

The NASA-TLX scores for mental demand, effort, and frustration were significantly reduced when using the LIVE-IGS system in comparison to conventional navigation ($P < .05$). There was no significant difference in physical demand or perceived performance. Despite open feedback suggesting a potential operative time saving during real cases, no significant change in temporal demand was found during this trial ($P = 0.19$; Table I).

Questionnaire

The seven-point Likert scale questionnaire statements and median (IQR) responses are shown in Table II. No subject disagreed (score 1–3) with any of the statements. One gave a neutral response (score of 4) for question 1. There was universal agreement (score 5–7) for all other questions, with fairly uniform responses across the subjects.

Below is a summary of the feedback gathered for each theme of investigation. Specific responses from each subject are summarized in Supplementary Appendix 1.

Ergonomics

All subjects agreed that the laboratory layout and equipment were consistent with the OR. Minor changes, including mounting the reflective markers to face obliquely opposite the surgeon, were made to minimize optical tracking interference (Fig. 2d). Occasionally, the drill dropped out of vision when it was rotated; however, all of the surgeons were familiar with optical IGS systems and seemed to intuitively recognize when this was a problem.

Visual Display

Image guidance was provided in two ways: a 3D virtual view and cross-sectional, triplanar CT images. Three participants preferentially referenced the virtual view, stating that it was intuitive, allowed faster assessment of proximity to critical structures, and was easier to synthesize. Two preferred the triplanar views, as they were more often used to this display, and thought the virtual view was cluttered or lacked depth information and precision. The other two used both displays fairly equally; the virtual for a quick assessment and the triplanar for fine detail.

The contours were thought to be accurate, and there were mixed opinions as to whether the pixilation

TABLE II.
Questionnaire Responses.

Statements for Questionnaire	Median (IQR)*
I felt it was faster to perform surgery when aided by the virtual view.	6 (5–6)
The system appeared to be sufficiently accurate for its intended use.	6 (6–6)
The dynamic tool tracking allowed me to quickly assess my proximity to critical structures without significantly interrupting dissection.	6 (5.5–7)
Proximity alerts increased my confidence during ablation close to critical structures.	6 (5.5–6)
The current technology is ready for clinical trial without significant changes.	5 (5–6)

*Based on a seven-point Likert scale (7 = strongly agree, 1 = strongly disagree).
IQR = interquartile range.

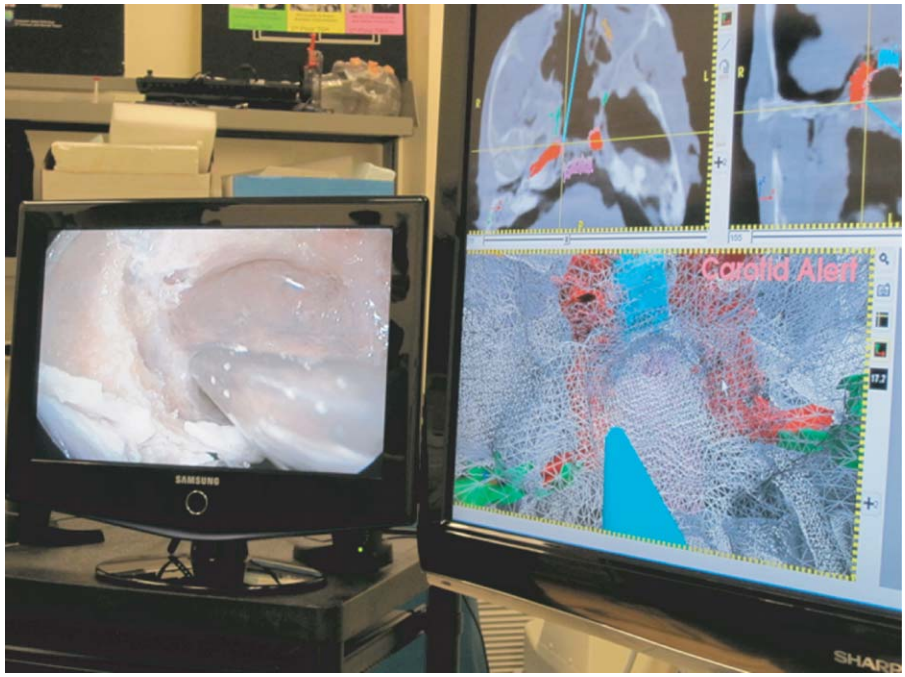

Fig. 3. The drill tip has entered the carotid alert zone as shown in the virtual and cross-sectional views. An auditory alert reminiscent of an arterial Doppler trace is triggered when the drill is positioned in this zone to provide structure-specific proximity information.

of the contours was off-putting. The surface mesh on the virtual view was earmarked as a potential area for further development, with some finding it confusing or distracting; others would have preferred a more lifelike semitransparent surface rendering.

Auditory Alerts

A number of auditory features for critical structure proximity alerts were upgraded during the trial in response to suggestions. Subjects were observed to instinctively shift their gaze toward the source of the alarm. To reduce this interruption, speakers were placed directly next to the endoscopic monitor. The first three participants found the abstract sound alerts (beeps) distracting and often unhelpful. It was difficult to distinguish acoustically which anatomical structure was close and how far away it was. Auditory icons are sounds that in some way relate to the reason for alarm. They should be intuitive and easily learnt. Auditory icons were developed for the dura and carotid arteries to provide more information to the surgeon. For example, the sound chosen to represent proximity to a major vessel (carotid artery) was reminiscent of an arterial Doppler trace. Structure- and distance-specific alarms then gave the operator navigational data without additional visual stimuli or having to look away from the main monitor. Most of the remaining subjects appreciated this new feedback medium.

Alert zones were manually contoured and generally around 2 to 3 mm. There was agreement that this is an appropriate distance. All subjects thought the alarms required some form of customization, especially after a structure had been safely identified. For example, once they had confirmed the position of the carotid, a constant alarm while they were drilling adjacent to it was not helpful. Most suggested being able to turn off the alarms once landmarks and structures were clearly identified.

Applications

There was strong consensus as to the potential clinical applications for this technology. The combination of high spatial demand, reduced or absent surface landmarks, and proximity to critical structures is where image guidance was thought to be particularly useful. Any procedure where there is a significant amount of time spent on a task where these conditions exist would benefit from live navigational feedback and could ultimately reduce operating time, according to our subjects. The main tasks identified during this exercise were drilling adjacent to the carotid, particularly near the clival and petrous portions, and approaching the dura through thick bone (Fig. 3).

Recommendations

All participants thought that the technology was ready for clinical trials, but some improvements were suggested. The ability to customize the settings, particularly the alarm zones, was advised. This included being able to turn individual structure alerts off once the structure was successfully identified. The labor required for anatomical contouring on preoperative imaging was frequently recognized as a barrier to implementation, as it would need to be created, or at least verified, by the operating surgeon.

DISCUSSION

Development of advanced navigational systems is occurring in many centers worldwide for an ever-expanding

number of minimally invasive surgical techniques.[3,13–17] Despite advances in software, computer processing speeds, and registration algorithms, very few of these systems appear to be used during routine procedures. Poor adoption of computer-based assistance through advanced displays has been noted in many industries where technical precision is required.[18,19] Although there is huge potential for this technology, functional deployment has been restricted by limited human factors research investigating interface design.[18]

It was a significant undertaking to create a mock OR with a full set of skull base equipment and recruit experienced skull base surgeons for a 5-hour trial. We wished to make the setting, the procedure, and the subjects (end users) as close to reality as possible to obtain the feedback required to make the system changes necessary for integration into the OR. We gained valuable insight into how different surgeons used the system and noted many similar themes as well as individual differences. Such observations are useful in adapting feedback to be as functional as possible while allowing customization where requested.

The mental demand, effort, and frustration levels were shown to be significantly decreased when using the LIVE-IGS system. All surgeons also appreciated that the overall stress level was much lower operating on a cadaver than a live patient. Drilling adjacent to the carotid or toward the dura in a real operation would be significantly more stressful, and the workload differences may be even greater in a real situation. Subjects commented that it was less demanding to drill when they were some distance (e.g., around 5 mm) away from a critical structure and could quickly check their anatomical position and continue to ablate with confidence. They noted that if they were using traditional style intermittent IGS, or a Doppler probe, they would have checked less frequently, due to the time and interruption required to switch to a different probe, thereby continuing with ablation in a slower and more cautious fashion. We believe that the lower task workload scores reflect this level of reassurance offered by the technology. Incorporating testing of mental workload with tools such as the NASA-TLX has been recommended by other authors, given that traditional outcome parameters such as morbidity and mortality are practically impossible to quantify in this style of translational research.[20] Inferior task performance and a greater number of errors have been noted when mental workload is increased.[21]

When providing a 3D virtual view of anatomical contours, a reference framework must be included to allow surgeons to conceptualize how they relate to the real-life anatomy they are viewing. A mesh surface rendering was presented to place the contours in context. We had mixed reviews on the virtual display, particularly in regard to the mesh. Some wanted less mesh, some wanted a more realistic surface rendering, and others did not use it or found it confusing. There was certainly no consensus on the best way to display 3D contours, and given this we believe allowing customized display settings incorporating various virtual views with adjustable opacity as well as fused augmented reality views may be appropriate.

The integration of live visual displays and auditory alerts involves additional stimuli that inherently demand some attention. Strategies to mitigate unnecessary distraction are important in human–computer interface design.[22–24] Like some other groups, we placed all of the visual augmentation on the submonitor to avoid direct visual stimulation at critical points.[3,25] This design led to most surgeons referencing this data at their discretion rather than forcing their attention through on-screen visual cues. When abstract sound alerts were used as proximity alerts, we noted the surgeon would often scan the submonitor to see why it was alerting. Auditory icons were developed and replaced abstract sounds for the proximity alerts after the first three subjects suggested that individual identification of structures would be preferable. Auditory icons are alarms that bear some relationship to their function and are easily learnt.[26] For the carotid artery, we created an alarm reminiscent of an arterial Doppler trace for the proximity zone and added a beep at the end when the instrument was tracked to be within, or extremely close to, the carotid volume. This was almost instantly recognizable and learnt by surgeons and provided informative feedback on the reason for alarm without disrupting dissection. It was observed that the addition of this feature was associated with decreased scanning of the submonitor, and subjects reported being better informed and less distracted. Driving simulation studies have shown similar results with visual distractions causing more erratic steering than auditory distractions.[27] Sonification, turning data into sound (such as the change in tone with pulse oximetry), can inform without the need to scan for visual data. Investigation in anesthesia simulation showed sonification allowed greater time-sharing performance between a manual and monitoring tasks when compared to visual monitoring.[4] Although auditory icons and sonification show great promise in limiting distraction, the plethora of other alarms and auditory stimuli in the operating environment must be taken into account.[26]

This trial has provided our research group with a better understanding of the issues limiting clinical implementation of this technology as well as the potential clinical uses. We feel that reporting the preclinical development of our system is important to promote efficient progress toward improved surgeon–computer interface design. Although registration accuracy and robustness will always be a concern, this does not appear to be a significant factor restricting adoption, especially within the relatively rigid framework of the skull base. The main barriers appear to relate to interface design and the lack of integration of the elements required to produce the features described. Streamlining the system into a single package that allows intuitive contouring, rapid registration and instrument calibration, and the ability to customize visual display and alarm settings could make this technology only marginally more complex to set up than current IGS systems. We are unsure whether the cost and time required to provide this information would make it suitable for more routine cases such as endoscopic sinus surgery. Further

investigation into behavioral changes and attention shifts created through real-time navigation need further preclinical study.[28] Initial clinical use should be restricted to surgeons who perform advanced cases and already have experience with and a good working knowledge of IGS systems and their potential errors.

CONCLUSION

Real-time surgical navigation systems such as our LIVE-IGS prototype may enhance spatial awareness while reducing task workload during endoscopic skull base surgery. High spatial demand, compromised visual landmarks, and proximity to critical structures combine to create an environment where such technology may be beneficial. Multimodal feedback with novel alarms, such as structure- and proximity-specific auditory icons, could reduce visual stimuli and enhance awareness while limiting distraction.

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The Laryngoscope

Endoscopic Skull Base Reconstruction of Large Dural Defects: A Systematic Review of Published Evidence

Richard J. Harvey, MD; Priscilla Parmar, MD; Raymond Sacks, MD; Adam M. Zanation, MD

Objectives/Hypothesis: Systematically review the outcomes of endoscopic endonasal techniques to reconstruct large skull base defects (ESBR). Such surgical innovation is likely to be reported in case series, retrospective cohorts, or case-control studies rather than higher level evidence.

Study Design: Systematic review and meta-analysis.

Methods: Embase (1980–December 7, 2010) and MEDLINE (1950–November 14, 2010) were searched using a search strategy designed to include any publication on endoscopic endonasal reconstruction of the skull base. A title search selected those articles relevant to the clinical or basic science of an endoscopic approach. A subsequent abstract search selected articles of any defect other than simple cerebrospinal fluid (CSF) fistula, sella only, meningoceles, or simple case reports. The articles selected were subject to full-text review to extract data on perioperative outcomes for ESBR. Surgical technique was used for subgroup analysis.

Results: There were 4,770 articles selected initially, and full-text analysis produced 38 studies with extractable data regarding ESBR. Of these articles, 12 described a vascularized reconstruction, 17 described free graft, and nine were mixed reconstructions. Three had mixed data in clearly defined patient groups that could be used for meta-analysis. The overall CSF leak rate was 11.5% (70/609). This was represented as a 15.6% leak rate (51/326) for free grafts and a 6.7% leak rate (19/283) for the vascularized reconstructions ($\chi^2 = 11.88$, $P = .001$).

Conclusions: Current evidence suggests that ESBR with vascularized tissue is associated with a lower rate of CSF leaks compared to free tissue graft and is similar to reported closure rates in open surgical repair.

Key Words: Systematic review, skull base, septal flap, cerebrospinal fluid leak, dura, pericranium, endoscopic surgery, reconstruction.

Level of Evidence: 3a.

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INTRODUCTION

There has been a rapid evolution of the approach to many ventral skull base pathologies in the last decade. The endoscopic route is now a preferred option for many surgical centers when managing both benign and malignant disease. Endoscopic transnasal transcranial surgery that is now performed was considered highly risky only 10 years ago. Much of the morbidity was associated with the inability to provide a consistent and robust separation of the cranial cavity from the paranasal sinus after the endonasal resection. The reported rates of cerebrospinal fluid (CSF) leaks were as high as 30% to 40%,[1] with significant complications such as meningitis, abscess formation, and ventriculitis. This was seen as an Achilles' heel for endoscopic skull base surgery with dural resections.[2]

The majority of small defects (<1 cm) in the skull base (most commonly encountered during CSF fistula closure following trauma and after iatrogenic injury) are reliably repaired using multilayered free grafts,[3] with rates of success >90% and minimal difference between methods or material used.[3,4] This provides good long-term prevention of further CSF leaks and intracranial infection.[5]

For larger skull base defects (>3 cm), materials used for free graft repairs have included turbinate mucosa,[6] cadaveric pericardium, acellular dermis,[7] fascia lata,[8] and titanium mesh.[9] In general, repair of larger defects with free grafting can lead to a higher rate of CSF leaks than smaller defects,[10] and surgery of larger defects allows unacceptably high leak rates (>30%).[7,11]

In response to these reconstructive failures, the use of local and regional vascularized flaps in the reconstruction of large skull base defects has provided a dramatic shift in our ability to manage such large defects between the cranial and sinonasal cavities. Local vascularized flaps have been developed that can be harvested, tailored, and used in endoscopic endonasal skull base

From the Department of Otolaryngology and Skull Base Surgery (R.J.H., P.P.), St. Vincent's Hospital, Sydney, New South Wales, Australia; the Department of Otorhinolaryngology (R.S.), Concord General Hospital, Sydney, New South Wales, Australia; and the Department of Otolaryngology/Head and Neck Surgery (A.M.Z.), University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, U.S.A.

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Richard J. Harvey, MD, has served on the advisory board for Schering Plough and serves on the speaker's bureau for GlaxoSmithKlein, MSD, and Arthrocare. He is also a consultant for Medtronic and Olympus and grant recipient from NeilMed Pharmaceuticals. Raymond Sacks, MD, is a consultant to Medtronic and Nycomed. The authors have no other funding, financial relationships, or conflicts of interest to disclose.

Send correspondence to Richard J. Harvey, MD, Department of Otolaryngology/Skull Base Surgery, St. Vincent's Hospital, Victoria Street, Darlinghurst, Sydney NSW 2010, Australia.
E-mail: richard@richardharvey.com.au

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surgery,[12–14] and increasingly these vascularized flaps are becoming the repair method of choice for endoscopic skull base reconstruction due to their ease of use, low donor site morbidity, and low complication rates.[13,15]

The aim of this study was to critically and systematically review the data available on the perioperative outcomes of published case series, cohorts, and case-control studies on endoscopic endonasal reconstruction of large dural skull base defects. The primary outcome was overall CSF leak rates in the postoperative period, and a secondary outcome was data stratification with comparison based on avascular grafting versus vascularize tissue reconstructions.

MATERIALS AND METHODS

A systematic review of published literature was performed for the primary outcome of CSF leak rates during endoscopic skull base surgery.

Eligibility Criteria

Published articles in English were eligible. All articles reporting original data on patients undergoing endoscopic skull base reconstruction were eligible, including those with any intervention for the treatment of specific pathologies, such as meningioma and craniopharyngioma, where a large defect would be anticipated. Because this review is of large skull base defects, outcomes of patients undergoing simple closure of CSF fistulae or encephaloceles were excluded because the vast majority of these defects are relatively small. Only studies where an endonasal craniotomy was created as part of a procedure were included. Trials included subjects of any age, with any comorbidity, and of varied duration of follow-up were included. Local and regional flap reconstructions of endonasal skull base surgery series were included. Case series, case-control studies, cohort studies, and randomized controlled trials were included.

Search Criteria

The MEDLINE database was searched from 1950 to November 14, 2010, and the Embase database was searched from 1990 to December 7, 2010. The Cochrane Collaboration database and the National Health Service, Evidence Health Information Resources Web site were also searched. The bibliographies of identified articles were also reviewed and used as an additional data source. No unpublished trials were included. We designed a search strategy to include articles relevant to any aspect of endoscopic surgery and skull base reconstruction. The search strategy used for Embase and MEDLINE databases is shown in Table I.

Once the searches were completed, study selection was performed by two authors (P.P. and R.J.H.) in an unblinded standardized manner. The publications extracted were grouped by title and obvious duplicates were excluded. The abstracts were then reviewed to ascertain whether they met the inclusion and exclusion criteria described above.

TABLE I.
MEDLINE Search Strategy*.

1	Nasal.mp. or Nasal Cavity/
2	nose.mp. or Nose/
3	paranasal sinus.mp. or Paranasal Sinuses/
4	(transnas$ or trans-nas$).mp.
5	(sinonasal or sino-nasal).mp.
6	endoscop$.mp.
7	Endoscopes/
8	Endoscopy/
9	(endonas$ or endosin$).mp.
10	or/1-9
11	Surgical Flaps/ or Reconstructive Surgical Procedures/ or Suture Techniques/
12	reconstruct$.mp.
13	defect.mp.
14	repair.mp.
15	closure.mp.
16	sealing.mp.
17	Cerebrospinal Fluid/su [Surgery]
18	Dura Mater/su [Surgery]
19	or/11-18
20	Ethmoid Sinus/ or Ethmoid Bone/ or ethmoid.mp.
21	Sphenoid Sinus/ or Sphenoid Bone/ or sphenoid.mp.
22	(clivus or clival).mp.
23	anterior cranial fossa.mp. or Cranial Fossa, Anterior/
24	middle cranial fossa.mp. or Cranial Fossa, Middle/
25	posterior cranial fossa.mp. or Cranial Fossa, Posterior/
26	(transethm$ or transsphen$ or transcliv$ or transplan$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
27	(trans-ethm$ or trans-sphen$ or trans-cliv$ or trans-plan$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
28	Craniotomy/ or craniotomy.mp.
29	craniectomy.mp.
30	Skull Base/ or skull base.mp. or skullbase.mp.
31	Brain Neoplasms/ or Pituitary Neoplasms/ or Skull Neoplasms/
32	Sella Turcica/ or Sella Turcica.mp.
33	or/20-32
34	10 and 19 and 33
35	limit 34 to english language

*Similar modified version used in Embase.

Data Extraction

Standardized data sheets were used for each study. Some studies included more than one patient reconstructive group (vascular vs. grafted repair). The primary outcomes were recorded as postoperative CSF leak closure. Secondary analysis of this outcome by reconstruction type was recorded. For each group, the type of reconstruction, pathology, number of patients, success of closure as defined by need for reoperation, and perioperative morbidity relevant to the reconstruction was recorded. The complications recorded included bleeding (epistaxis or intracranial), infectious complications (meningitis, subdural, or intracranial abscess and ventriculitis), persistent pneumocephalus, and any mortality related to the skull base surgery.

Management of Heterogeneity

The large range of methods, study aims, and pathologies were reported qualitatively in the data (Tables II–IV). Studies were deemed suitable for inclusion only if they described dural

TABLE II.
Characteristics of Included Studies by Endoscopic Reconstruction Type (Vascular Flap or Mixed).

Study	Year	Study Focus, Flap or Pathology	No.	No. With Defect	Repair Type	Age, yr (SD or Range)	% Female	Defect Size, Longest Axis	Defect Location	Lumbar Drain Use, % (Days)	Prior Radiotherapy
El-Sayed[28]	2008	Local flap, posterior septal	30	20	Vascular flap	52 (18–86)	50	1.86 cm^2	E, P, C, ITF	55 (4)	20%
Fortes[31]	2007	Local flap, ITF	4	4	Vascular flap	52.8 (4)	50	NR	C, P	NR	NR
Fortes[30]	2007	Regional flap, TPF	2	2	Vascular flap	NR	NR	NR	C	NR	100%
Hackman[34]	2009	Regional flap, palatal	1	1	Vascular flap	70	100	NR	C	NR	100%
Hadad[12]	2006	Local flap, posterior septal	43	43	Vascular flap	NR (22–74)	28	NR	F, E, P, C	NR	NR
Harvey[13]	2009	Local flap, septal and ITF	30	30	Vascular flap	45.5 (20.2)	43	24.9 mm	E, P, C, O	0	NR
Horiguchi[35]	2010	Local flap, posterior septal	21	14	Vascular flap	58 (20–78)	43	NR	P, C	7	NR
Kassam[37]	2008	Local flap, posterior septal	75	55	Vascular flap	47 (4–80)	37	NR	E, P, C, ITF, O	100 (4)	NR
Luginbuhl[41]	2010	Mixed benign and malignant neoplasms, CSF leak	16	16	Vascular flap	NR	NR	NR	E, P, C	25–50 (7)	NR
Madhok[42]	2010	Rathke cysts	35	3	Vascular flap	34 (12–67)	NR	NR	P	NR	NR
Nyquist[43]	2010	Mixed benign neoplasms	5	5	Vascular flap	56.4 (31–72)	60	NR	P, C	20 (1)	NR
Patel[44]	2010	Regional flap, pericranial	10	10	Vascular flap	NR	NR	NR	E, P	NR	30%
Shah[45]	2009	Local flap, posterior septal pediatric	6	6	Vascular flap	13 (2.5)	NR	NR	E, P	NR	NR
Stamm[46]	2008	Craniopharyngioma	4	4	Vascular flap	23.4 (16.3)	25	NR	E, P,C	0%	NR
Zanation[15]	2009	Local flap, posterior septal	70	70	Vascular flap	NR	NR	>20 mm in 60%	E, P, C	93 (3)	23%
Greenfield[33]	2010	Mixed benign and malignant neoplasms, CSF leak	44	33	Mixed	55.4 (17-85)	61	NR	F, E, P	NR	NR
Ceylan[19]	2009	Mixed benign and malignant neoplasms	13	13	Mixed	47 (12.3)	62	NR	E, P, C	31	NR
Cavallo[18]	2009	Craniopharyngioma	22	22	Mixed	49.4 (18–80)	32	NR	P	61	27%
Folbe[29]	2009	Olfactory neuroblastoma	23	19	Mixed: 1 flap, 18 free	56.6 (15–79)	30	NR	E, P	NR	NR
de Divitiis[25]	2008	Meningioma	11	11	Mixed: 3 flap, 8 free	56.1 (44–80	64	29.8 mm	E, P	NR	NR
Dehdashti[26]	2008	Chordoma	12	9	Mixed: 5 flap, 7 free	49.4 (15.8)	33	40.3 mm	C	NR	25%

SD = standard deviation; E = transethmoid/cribriform; P = transplanum; C = transclival; ITF = transpetrous, ptyergoid or infratemporal fossa; NR = not reported; TPF = temporparietal flap; O = transodontoid; CSF = cerebrospinal fluid.

TABLE III.
Characteristics of Included Studies by Endoscopic Reconstruction Type (Free Grafting).

Study	Year	Study Focus, Flap or Pathology	No.	No. With Defect	Repair Type	Age (SD or Range)	% Female	Defect Size (Longest Axis)	Defect Location	Lumbar Drain Use, % (Days)	Prior Radiotherapy, %
Batra[16]	2010	Mixed benign and malignant neoplasms	31	17	Free	57.5 (14–84)	42	16 mm	F, E, P	47	19
Cavallo[18]	2007	Suprasellar: Men, CP, AD, RC, glioma	21	21	Free	NR	NR	NR	P	5 (7)	5
Chen[20]	2006	Mixed malignant neoplasms	7	1	Free	52.7 (33–79)	29	NR	E, P	NR	NR
Church[21]	2003	Iatrogenic post-ESS defects	3	3	Free	43.7 (10.6)	0	>20 mm	E, P	67	0
de Divitiis[23]	2007	Suprasellar: Men, CP, AD, RC, AC	20	20	Free	49.5 (24–70)	55	NR	P	15	NR
de Divitiis[22]	2007	Craniopharyngioma	10	10	Free	57.2 (26–70)	40	52.8 mm^2	P	NR	NR
de Divitiis[24]	2007	Meningioma	6	6	Free	56.1 (44–70)	50	24.7 mm	P	0	0
El-Banhawy[27]	2008	Meningioma (from mixed group)	3	3	Free	42.5 (40–45)	0	14 mm	E, P	NR	NR
Esposito[9]	2007	Mixed: Men, CP, AD, Ch, RC, malignant neoplasms	620	58	Free	46 (5–86)	59	NR	P, C	100	NR
Gardner[1]	2008	Meningioma	35	35	Free	55 (39–79)	83	NR	E, P	100	6
Germani[32]	2007	Mixed benign and malignant neoplasms, CSF leak	56	55	Free	NR	NR	29% 4–20 mm, 29% >20 mm	E, P	20	NR
Horiguchi[35]	2010	Control patients: free grafts	11	10	Free	52 (27–79)	27	NR	E, P, C	90	NR
Kassam[36]	2007	Mixed benign and malignant neoplasms, CSF leak	25	11	Free	11.9 (5.3)	52	NR	E, P, C	NR	NR
Laufer[38]	2007	Suprasellar: Men, CP, RC	10	10	Free	54 (12.4)	NR	26.5 mm	P	50	NR
Leng[39]	2008	Mixed: Men, CP, Ch, CSF leak	10	10	Free	NR	NR	NR	E, P, C	50	10
Leong[40]	2006	Mixed benign and malignant neoplasms	14	10	Free	57.4 (26–84)	43	4–40 mm	E, P	70 (5)	29
Luginbuhl[41]	2010	Control patients: free grafts	24	24	Free	NR	NR	17 mm	E, P, C	33	NR
Stamm[46]	2008	Craniopharyngioma: free grafts	3	3	Free	23.4 (16.3)	33	NR	P	0	NR
Vergez[47]	2009	Adenocarcinoma	17	5	Free	68 (44–82)	0	NR	C, P	NR	NR
Villaret[48]	2010	Mixed malignant neoplasms	62	14	Free	61.7 (25–84)	29	NR	E, P	47	19

F = transfrontal; E = transethmoid/cribriform; P = transplanum; CP = craniopharyngioma; AD = adenoma; RC = Rathke's cyst;, NR = not reported; ESS = endoscopic sinus surgery; AC = astrocytoma; Ch = chordoma; C = transclival; CSF = cerebrospinal fluid; Men = meningioma.

TABLE IV.
Perioperative Outcomes of Included Studies by Endoscopic Reconstruction Type.

Study	Year	No.	No. With Defect	CSF Leak	Pneumocephalus	Epistaxis	Intracranial Bleed	Meningitis	Other Intracranial Infective	Sinusitis	PE/DVT	Mortality
Vascular flap reconstructions												
El-Sayed[28]	2008	30	20	0	0	0	1	0	0	0	0	0
Fortes[31]	2007	4	4	0	0	0	0	0	0	0	0	0
Fortes[30]	2007	2	2	0	0	0	0	0	0	0	0	0
Hackman[34]	2009	1	1	0	NR	NR	NR	NR	NR	NR	NR	0
Hadad[12]	2006	43	43	2	NR	1	0	0	0	0	NR	o
Harvey[14]	2009	30	30	1	0	2	0	0	0	1	0	0
Horiguchi[35]	2010	21	14	2	NR	NR	NR	NR	NR	NR	1	0
Kassam[37]	2008	75	55	8	NR	1	NR	0	0	NR	NR	0
Luginbuhl[41]	2010	16	16	1	NR	NR	NR	NR	NR	NR	NR	NR
Madhok[42]	2010	35	3	0	NR	NR	NR	NR	NR	NR	NR	0
Nyquist[43]	2010	5	5	0	NR	0	0	0	0	0	0	0
Patel[44]	2010	10	10	0	NR	NR	NR	NR	NR	NR	NR	0
Shah[45]	2009	6	6	1	NR	NR	NR	NR	NR	NR	NR	NR
Stamm[46]	2008	4	4	0	NR	0	0	0	0	0	0	0
Zanation[56]	2009	70	70	4	NR	NR	NR	NR	NR	NR	NR	0
Free graft reconstruction												
Batra[16]	2010	31	17	2	1	1	0	1	0	1	1	0
Cavallo[17]	2007	21	21	2	NR	NR	NR	0	NR	1	NR	0
Chen[20]	2006	7	1	0	NR	NR	NR	NR	NR	NR	NR	0
Church[21]	2003	3	3	0	0	0	0	0	0	0	0	0
de Divitiis[23]	2007	20	20	1	1	NR	NR	NR	NR	1	NR	NR
de Divitiis[22]	2007	10	10	2	0	0	2	0	0	1	NR	1
de Divitiis[24]	2007	6	6	2	NR	0	1	NR	NR	NR	NR	1
El-Banhawy[27]	2008	3	3	0	NR	NR	NR	NR	NR	NR	NR	0
Esposito[9]	2007	620	58	7	NR	NR	NR	2	NR	NR	NR	0
Gardner[1]	2008	35	35	14	1	NR	1	0	NR	1	3	0
Germani[32]	2007	56	55	3	0	1	0	0	1	0	NR	0
Horiguchi[35]	2010	11	10	3	NR	NR	NR	NR	NR	NR	NR	NR
Kassam[36]	2007	25	11	2	NR	NR	NR	0	NR	NR	NR	0
Laufer[38]	2007	10	10	1	NR	NR	NR	NR	NR	NR	NR	0
Leng[39]	2008	10	10	0	NR	NR	NR	NR	NR	NR	NR	0
Leong[40]	2006	14	10	0	NR	1	0	2	0	2	1	0
Luginbuhl[41]	2010	24	24	10	NR	NR	NR	NR	NR	NR	NR	0
Stamm[46]	2008	3	3	2	NR	0	0	0	0	0	0	0
Vergez[47]	2009	17	5	0	0	0	0	1	0	NR	0	0
Villaret[48]	2010	62	14	8	NR	NR	NR	1	0	NR	NR	0
Mixed reconstructions												
Greenfield[33]	2010	44	33	4	NR	0	NR	0	2	5	NR	0
Ceylan[19]	2009	13	13	5	NR	NR	1	NR	NR	NR	NR	1
Cavallo[18]	2009	22	22	3	0	0	0	0	0	1	0	0
Folbe[29]	2009	23	19	4	0	1	0	0	0	0	0	0
de Divitiis[25]	2008	11	11	3	0	0	1	0	0	0	0	1
Dehdashti[26]	2008	12	9	4	1	0	1	0	0	0	0	0

CSF = cerebrospinal fluid; PE/DVT = pulmonary embolus/deep vein thrombus; NR = not reported.

defect reconstructions or could providef enough information to separate extradural surgery from those that had obvious arachnoid to sinonasal communication. This ensured a study population that was not confounded by patients who did not have a significant risk of postoperative CSF leak.

Statistical Assessment

Statistical assessments were performed primarily with descriptive data. Case-by-case analysis was performed for summary data. Assessment of different pathologies was performed as nominal data and analyzed using χ^2 and Fishers

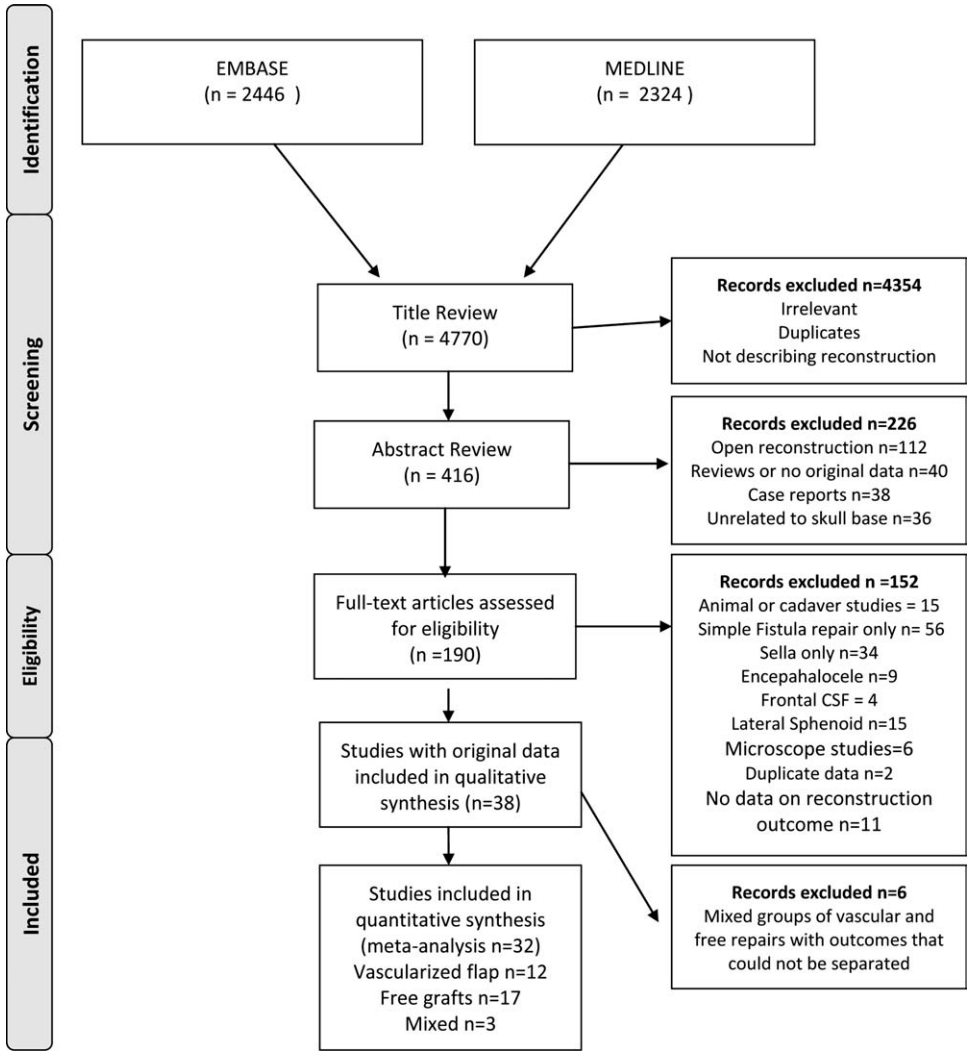

Fig. 1. Article selection process from the Embase and MEDLINE database searches.

exact tests via SPSS version 17 software (SPSS Inc., Chicago, IL).

RESULTS

The search of Embase and MEDLINE produced a total of 4,770 studies written in English. After exclusion of duplicates, 1,088 studies remained. A title search found 416 articles on skull base surgery. Of the 416 abstracts reviewed, 268 described endonasal skull base surgery. Of these, 40 (15%) were reviews of endoscopic or endonasal techniques and 38 (14%) were simple case reports. These studies were excluded from analysis. The selection process is outlined in Figure 1.

The abstract search found 190 articles directly relating endoscopic skull base repair or the management of conditions in which reconstruction would be required. Those studies that described sella-only reconstruction (n = 34), encephalocele management (n = 9), and unique locations of simple fistula (n = 9) were excluded. The full-text analysis produced 38 studies with extractable data regarding endoscopic skull base reconstruction with large dural defects.[1,9,12,15,16–49] Of these, 12 articles described a vascularized reconstruction,[12,13,15,28,30,31,34,37,42–45] 17 described free graft repairs,[1,9,16,17,20–24,27,32,37–40,47,48] and nine were mixed reconstructions.[13,18,19,25,26,29,33,35,41] Three of these had mixed data levels in clearly defined patient groups that could be used for comparison in this systematic review.[13,35,41]

The study characteristics of the 38 articles included are described in Tables I through IV. Perioperative outcomes were defined as CSF leak, revision surgery, infectious complications (meningitis, intracranial abscess, sinusitis), hemorrhagic complications (epistaxis, intracranial bleeding), thromboembolic events, respiratory events, and mortality. Of all these, only CSF leaks were consistently reported among all 38 studies.

CSF Leak Outcomes Results

There were 609 patients with large dural defect reconstructions included in the meta-analysis from the 38 articles. A total of 326 patients (54%) underwent a free graft reconstruction, and 283 patients (46%) had vascularized reconstruction. The overall rate of CSF leak was 11.5% (70/609). This was represented as a 15.6% leak rate (51/326) for free grafts and a 6.7% leak rate (19/283) for the vascularized reconstructions ($\chi^2 = 11.88$, $P = 0.001$).

TABLE V.
Intranasal and Regional Vascular Flaps Available for Skull Base Reconstruction.

Location	Vascular Tissue Flap	Pedicle	Comments/Limitations
Intranasal vascular tissue flap	NSF[13,54]	Sphenopalatine artery	Ideal for all skull base reconstructions
	ITF[14]	Inferior turbinate artery*	Good for small clival defects, cannot reach ACF or sella
	MTF[55]	Middle turbinate artery*	Good for small ACF or transphenoidal defects, small in size, thin mucosa, difficult to elevate
Regional vascular tissue flap	PCF[44]	Supraorbital and supratrochlear artery	Hearty flap with versatile dimensions, extends from ACF to sella but not to posterior skull base
	TPFF[30]	Superficial temporal artery	Good for clival or parasellar defects, 90° pedicle rotation limits reconstruction of ACF
	PF[34]	Greater palatine artery	Theoretical flap that reaches all areas of skull base, 3-cm pedicle but difficult to dissect, experience

*Terminal branch of posterior lateral nasal artery of the sphenopalatine artery.
NSF = nasoseptal flap; ITF = inferior turbinate flap; ACF = anterior cranial fossa; MTF = middle turbinate flap; PCF = pericranial flap; TPFF = temporoparietal fascia flap; PF = palatal flap.

The included studies stratified by reconstruction type are listed in Table IV. The vascularized reconstruction group compares favorably to the published rates in a report of an international collaborative study on craniofacial surgery (6.5%–25%).[49]

Other Complications

Only CSF was routinely reported from the included studies. The reported nonleak perioperative morbidity is described in Table IV. However, the lack of uniform reporting makes for an unreliable meta-analysis and is reported as descriptive only.

DISCUSSION

Early reconstructive techniques in skull base surgery evolved from endoscopic repair of defects following spontaneous CSF leaks and accidental or iatrogenic trauma. Many articles and a meta-analysis have validated the reconstruction of small CSF fistulas, with a wide variety of free grafting techniques achieving success in more than 95% of patients that can be successfully revised if necessary.[3,5] The application of such techniques to the larger defects, as a result of intradural procedures, proved to be inadequate. Additional layering and collagen matrixes had reduced the CSF leak rate, but failure remained unacceptably high.[7,11,50]

Larger defects pose additional challenges of a wide dural resection, intra-arachnoid dissection, and exposure to high-flow CSF within the cisterns. But perhaps the most significant influence is the larger nonvascularized reconstructive bed—CSF on one side and sinus cavity (air) on the other. The posteriorly pedicled septal flap is the workhorse of most endoscopic intradural skull base surgery.[13,51] Other vascular pedicled flaps provide alternatives to address skull base defects of various sizes and locations when the posterior septal flap is unavailable. A summary of these vascularized local and regional flap options and limitations are summarized in Table V.

The endonasal approach may appear attractive to many anteriorly based pathologies. However, there is associated sinonasal morbidity associated with such an approach. Although endoscopic skull base surgery differs greatly from functional endoscopic sinus surgery, the final cavity left behind from the approach still needs to be functional. Crusting and short-term nasal morbidity is likely to be underreported in trials. de Almeida et al. reported nasal crusting the most common (98%) symptom, followed by nasal discharge (46%), whereas loss of smell was reported by only 9.5% of patients.[52] Crusting was short lived, with half of the patients achieving a crust-free nose by 101 days (95% confidence interval, 87.8-114.2 days).[52] Sinonasal function does appear to improve over time for these patients.[53] Loss of smell is often permanent, and although olfactory loss may be the consequence of an open approach, the risk should be considered when choosing the endonasal route.

Advancements in endoscopic skull base reconstruction have evolved with the ever-increasing size and complexity of lesions that are approached and resected. The principles of multilayer reconstructions and the routine use of vascularized flaps in expanded endonasal surgery have reduced postoperative CSF leak rates of between 5% and 10% (6.7% in this meta-analysis). In this review, vascularized skull base reconstructions for large dural defects had a clear and significant ($P = .001$) advantage over free grafting in the prevention of postoperative CSF leaks. Future advances will help us to understand and manage patients at high risk for a postoperative CSF leak, especially those who have been previously irradiated and/or require revision surgery. Additionally, our knowledge of reconstruction donor site morbidity, sinonasal quality of life, and methods to reduce patient postoperative recovery will continue to advance.

CONCLUSION

Current evidence in this systematic review suggests that skull base repair with vascularized tissue is associated with a lower rate of CSF leak compared to free tissue graft and is similar to reported closure rates in open surgical repair.

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CLINICAL REVIEW

Sublingual Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and Asthma

A Systematic Review

Sandra Y. Lin, MD
Nkiruka Erekosima, MD, MPH
Julia M. Kim, MD, MPH
Murugappan Ramanathan, MD
Catalina Suarez-Cuervo, MD
Yohalakshmi Chelladurai, MBBS
Darcy Ward, BA
Jodi B. Segal, MD, MPH

Importance Allergic rhinitis affects up to 40% of the US population. To desensitize allergic individuals, subcutaneous injection immunotherapy or sublingual immunotherapy may be administered. In the United States, sublingual immunotherapy is not approved by the Food and Drug Administration. However, some US physicians use aqueous allergens, off-label, for sublingual desensitization.

Objective To systematically review the effectiveness and safety of aqueous sublingual immunotherapy for allergic rhinoconjunctivitis and asthma.

Evidence Acquisition The databases of MEDLINE, EMBASE, LILACS, and the Cochrane Central Register of Controlled Trials were searched through December 22, 2012. English-language randomized controlled trials were included if they compared sublingual immunotherapy with placebo, pharmacotherapy, or other sublingual immunotherapy regimens and reported clinical outcomes. Studies of sublingual immunotherapy that are unavailable in the United States and for which a related immunotherapy is unavailable in the United States were excluded. Paired reviewers selected articles and extracted the data. The strength of the evidence for each comparison and outcome was graded based on the risk of bias (scored on allocation, concealment of intervention, incomplete data, sponsor company involvement, and other bias), consistency, magnitude of effect, and the directness of the evidence.

Results Sixty-three studies with 5131 participants met the inclusion criteria. Participants' ages ranged from 4 to 74 years. Twenty studies (n=1814 patients) enrolled only children. The risk of bias was medium in 43 studies (68%). Strong evidence supports that sublingual immunotherapy improves asthma symptoms, with 8 of 13 studies reporting greater than 40% improvement vs the comparator. Moderate evidence supports that sublingual immunotherapy use decreases rhinitis or rhinoconjunctivitis symptoms, with 9 of 36 studies demonstrating greater than 40% improvement vs the comparator. Medication use for asthma and allergies decreased by more than 40% in 16 of 41 studies of sublingual immunotherapy with moderate grade evidence. Moderate evidence supports that sublingual immunotherapy improves conjunctivitis symptoms (13 studies), combined symptom and medication scores (20 studies), and disease-specific quality of life (8 studies). Local reactions were frequent, but anaphylaxis was not reported.

Conclusions and Relevance The overall evidence provides a moderate grade level of evidence to support the effectiveness of sublingual immunotherapy for the treatment of allergic rhinitis and asthma, but high-quality studies are still needed to answer questions regarding optimal dosing strategies. There were limitations in the standardization of adverse events reporting, but no life-threatening adverse events were noted in this review.

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ALLERGIC RHINITIS AFFECTS approximately 20% to 40% of the US population.[1] Currently, 2 forms of specific immunotherapy (subcutaneous immunotherapy and sublingual immunotherapy) are used clinically in the United States. Considerable interest has emerged in sublingual immunotherapy, which involves placement of the allergen under the tongue for local absorption to desensitize the allergic individual over an extended treatment period to diminish allergic symptoms. Compared with subcutaneous immunotherapy, sublingual immunotherapy is easy to administer, does not involve administration of injections, and may be administered at home, avoiding the inconvenience of office visits. The opportunity for home-based therapy makes it potentially suitable for use in medically underserved areas.

In 1996, a World Health Organization Task Force on Immunotherapy cited the

For editorial comment see p 1297.

CME available online at www.jamanetworkcme.com and questions on p 1299.

Author Affiliations: Division of General Pediatrics and Adolescent Medicine (Dr Kim), Departments of Otolaryngology-Head and Neck Surgery (Drs Lin and Ramanathan), Medicine (Drs Erekosima, Suarez-Cuervo, Chelladurai, and Segal and Ms Ward), and Pediatrics (Dr Kim), Johns Hopkins University School of Medicine, Baltimore, Maryland.
Corresponding Author: Sandra Y. Lin, MD, Johns Hopkins University School of Medicine, 601 N Caroline St, Ste 6254, Baltimore, MD 21287 (slin30@jhmi.edu).
Clinical Review Section Editor: Mary McGrae McDermott, MD, Contributing Editor. We encourage authors to submit papers for consideration as a Clinical Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

emerging clinical data on sublingual immunotherapy, and recognized its potential as a viable alternative to subcutaneous therapy.[2] In Europe, approximately 45% of specific immunotherapy consists of sublingual immunotherapy, with up to 80% in Southern Europe.[3] Sublingual tablet and aqueous immunotherapy have been approved by European regulatory authorities.

In the United States, there are no sublingual forms of immunotherapy approved for use by the Food and Drug Administration. However, some physicians in the United States use subcutaneous aqueous allergens, off-label, for sublingual desensitization. Physicians are supported in using this desensitization approach by the European Medicines Agency's approval of certain sublingual products; however, due to the differing standardization of potency in Europe and the United States, doses are hard to compare among countries.

The primary objective of this systematic review was to review the clinical efficacy and safety of sublingual immunotherapy delivered as an aqueous solution as can potentially be done in the United States. This study was derived from work done for an evidence report commissioned by the US Agency for Healthcare Research and Quality to determine effectiveness of specific immunotherapy for allergic rhinitis and asthma (Agency for Healthcare Research and Quality publication 13-EHC061-EF).

METHODS

A protocol for this review was developed and posted online (http://effectivehealthcare.ahrq.gov/ehc/products/270/665/SIT_Protocol_20110824.pdf), following guidelines for systematic review.[4,5] We searched the following databases: MEDLINE (from 1950 to December 22, 2012), EMBASE (from 1947 to December 22, 2012), LILACS (from 1982 to December 22, 2012), and the Cochrane Central Register of Controlled Trials (inception to December 22, 2012) with a specific search strategy (eMethods at http://www.jama.com).

Titles, abstracts, and articles were reviewed independently by at least 2 separate investigators from the study team, with various study members assigned to review portions of the literature, and disagreements were resolved by consensus. We searched for English-language randomized controlled trials (RCTs) reporting on the effects of sublingual immunotherapy. We required that the RCTs enrolled patients with allergic rhinoconjunctivitis and/or allergic asthma due to airborne allergens confirmed with skin or specific immunoglobulin E blood testing, and clearly stated the dose of allergen delivered. Allowed comparators were placebo, other sublingual immunotherapy regimens, or pharmacotherapy. Studies were excluded if they did not report on our outcomes of interest (eTable 1). Studies also were excluded for which similar formulations are not obtainable in the United States, even for off-label use.

The primary outcomes of interest included symptom scores (for rhinitis, conjunctivitis, or asthma), medication scores, combined symptom and medication scores, quality of life, safety or harms, and adverse events. Asthma outcomes were extracted only if patients in the study were diagnosed as having asthma by using objective criteria (such as pulmonary function testing), or according to established clinical guidelines. Secondary outcomes included pulmonary function test results and provocational test results (allergen challenge).

Standardized forms for data extraction were completed independently by paired investigators. Data were abstracted from the published text or tables, and if necessary, from figures. Differences in opinion were resolved through consensus adjudication and by discussion during team meetings. For studies that recorded outcomes at multiple time points, we used the data from the final time point reported. For studies that treated and assessed patients during a single season, we extracted the outcomes at peak pollen seasons when available. Articles were also reviewed from duplicative data, and studies reporting follow-up data from an earlier study were abstracted with the original report.

The risk of bias was assessed using a modification of the Cochrane Collaboration Tool for Assessing Risk of Bias from the *Cochrane Handbook for Systematic Reviews of Interventions*.[5] We assessed 6 categories of potential bias: random allocation, lack of allocation concealment, inadequate blinding, incomplete data reporting, sponsor participation in the study design or interpretation of data, and other sources of bias. Studies were categorized as having a low, medium, or high risk of bias depending on their performance across these 6 categories (eMethods).

Studies were summarized by allergens, comparators, and outcomes producing detailed evidence tables. We graded the quantity, quality, and consistency for each primary outcome by adapting an evidence grading scheme recommended by the GRADE Working Group's guide for conducting comparative effectiveness reviews.[6] The grading incorporated the risk of biases, the consistency of the direction of the effect across studies for a given comparison and outcome, the relevance of the collection of trials to the question of interest (directness), and the magnitude of the effects reported in the trials. We could not comment on the precision of the effect size because there were seldom measures of variability within the individual studies. The magnitude of effect in a trial was classified according to the percentage difference in the post-to-pre change (<15% difference defined as weak, a 15%-40% difference defined as moderate, and >40% difference defined as a strong effect), comparing the sublingual immunotherapy group with the comparator group.

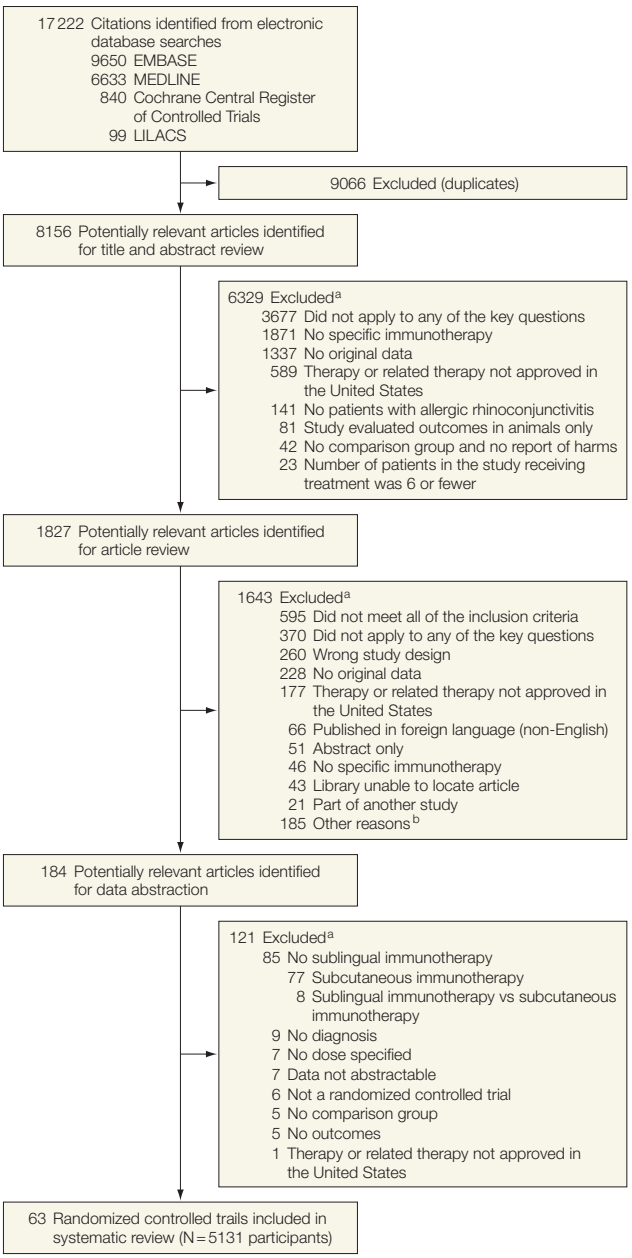
The evidence for each primary outcome was graded as (1) high grade: high confidence the evidence reflects the true effect; (2) moderate grade: moderate confidence that the evidence reflects the true effect and future research may change the estimate, (3) low grade: low confidence that the evidence reflects the true effect and further research is likely to change the estimate, or (4) insufficient evi-

dence.[7] The following system was used to assign grade when looking at the overall evidence for each outcome: high-grade evidence required a minimum of 2 or more trials with low risk of bias, and at least 1 strong magnitude of effect in the context of largely consistent overall evidence. Moderate-grade evidence required 1 or more trials with low risk of bias or strong magnitude of effect, or 1 trial with low risk of bias or moderate magnitude plus 1 trial with medium risk of bias or strong magnitude. Evidence was low grade if it did not meet any of these categories. Insufficient evidence was assigned if there were no relevant trials. The team reviewed and came to consensus on the grades. The evidence regarding indirect outcome measures (pulmonary function test results and provocation tests) was not graded.

A meta-analysis was not performed due to the extreme heterogeneity of the included studies. There was a wide range of clinical diversity in the types of participants, their allergies, allergens treated, and geographic treatment locations. The extreme variability of the published RCTs in dosing and treatment schedules confounds meta-analysis. Methodological diversity was evident in the study designs, quality, and systems for measured outcomes. The statistical reporting was incomplete in most studies and information such as confidence intervals was rarely reported.

To reduce the risk of publication bias in our results, we searched public registries of clinical trials and requested scientific information packets from relevant pharmaceutical companies to search for unpublished trials. Because measures of variance were not reported in most of the included studies, we could not produce a meaningful funnel plot to look for evidence of publication bias.

Figure. Flow Diagram of Sublingual Immunotherapy Studies



[a] Articles were excluded by 2 reviewers at this level so this number is exceeded by the total for all of the exclusions listed.
[b] The possible other reasons included control group is a healthy population, routes of administration not included (eg, oral, nasal, lymph node), abandoned interventions, outcomes not reported, no comparator group, continued medical education reports, editorials or reviews, studies about mechanism of action, other allergies (eg, food, aspirin), study in animals or in vitro, or fewer than 6 patients per treatment group.

RESULTS

We identified 8156 potentially relevant citations. After applying exclusions and triage to other topics, 63 RCTs remained for this systematic review (FIGURE). We identified 63 RCTs testing sublingual immunotherapy with 5131 participants included. Participants' ages ranged from 4 to 74 years. Twenty-six studies (41%) enrolled adults only, 17 (27%) included both adults and children,[8-24] and 20 (32%) exclusively studied children (<18 years of age; n = 1814 patients).[25-44]

The study comparator groups were placebo (46 studies; 73%), another sublingual intervention without a placebo group (9 studies; 14%), and conventional treatment (pharmacotherapy) without placebo

(8 studies; 13%). All studies allowed either conventional or rescue medications in all treatment groups. The maintenance dosing varied from daily to weekly, with treatment duration ranging from 3 months to 5 years. There was great heterogeneity in the reporting of the maintenance or cumulative dose delivered, and a variety of units to report dosing. Forty-three studies (68%) were assessed as having a medium risk of bias. There was a low risk of bias in 13 studies (21%) and a high risk of bias in 7 studies (11%). The reporting of outcomes was heterogeneous with diverse systems and scores for reporting on primary outcomes (eTable 2). A formal assessment of publication bias could not be performed due to lack of variability estimates from most included trials.

Evidence for Use of Sublingual Immunotherapy

We found moderate evidence across outcomes to support the use of sublingual immunotherapy to improve clinical outcomes (TABLE 1).

Asthma. Thirteen studies (n=625) evaluated sublingual immunotherapy for the control of asthma symptoms. The majority of studies (7; 54%) evaluated dust mite allergen.[25-27,35-37,42] All but 1 study were placebo-controlled studies, and all allowed pharmacotherapy for symptom relief. The placebo-controlled studies demonstrated statistically significant improvement in asthma symptoms in the sublingual immunotherapy group relative to the placebo group. The magnitude of the association was strong in 9 of these studies (69%). The remaining study, which compared sublingual immunotherapy with inhaled steroids, showed comparable improvement in both groups. The risk of bias was medium for the majority of studies (8; 62%), and favored sublingual immunotherapy in all of the studies. We graded the strength of evidence as high in support of sublingual immunotherapy for improving asthma symptoms.

Rhinitis. Rhinitis or rhinoconjunctivitis symptom scores were reported in 36 placebo-controlled studies* involving 2985 participants. The most frequently studied allergens were grass mix (10 studies; 28%) and dust mite (8 studies; 22%). The majority of studies (94%) demonstrated greater improvement in the sublingual immunotherapy groups vs placebo. The overall risk of bias was medium for this group. The magnitude of association was moderate or strong in 14 studies (39%). We concluded that the strength of evidence was moderate in support of using sublingual immunotherapy for improving rhinitis or rhinoconjunctivitis symptom scores.

Conjunctivitis. Conjunctivitis outcomes were reported in 13 studies involving 1074 patients.† All but 1 study demonstrated an improvement compared with the placebo group; and the majority of studies (11; 85%) had medium or low risk of bias. A strong magnitude of association was demonstrated in 3 studies (23%). We concluded that the evidence was of moderate strength in support of sublingual immunotherapy for treating allergic conjunctivitis.

Medication Scores. Medication scores were reported in 41 studies involving 2162 patients.‡ Grass mix (10 studies; 24%) and dust mite (9 studies; 22%) were the most commonly studied allergens. Thirty-eight studies (93%) demonstrated greater improvement in symptoms in the sublingual immunotherapy group vs the comparator group, with 16 studies demonstrating a strong magnitude of association. We graded the strength of evidence as moderate in support of sublingual immunotherapy for decreasing medication use.

Quality of Life. Disease-specific quality of life was reported in 8 studies involving 819 patients.[14,29,32,51,54,65,67,68] Half of these studies showed statistically significant gains in quality of life after treatment with sublingual immunotherapy compared with placebo. All used validated disease-specific instruments. These studies demonstrated a medium risk of bias overall, with 7 of 8 demonstrating a favorable change with sublingual immunotherapy. Two studies (25%) had a strong magnitude of association. We concluded that the strength of evidence was moderate in support of sublingual immunotherapy to improve disease-specific quality of life.

Other Outcomes. Some studies reported outcomes as a combined score: (1) medication use plus symptom scores§ and (2) asthma plus rhinitis or rhinoconjunctivitis symptoms.[41,43,45,61-63] The evidence was graded as moderate to support the use of sublingual immunotherapy for these outcomes. Indirect outcomes such as pulmonary function[8,26,27,33,36,42,66] and allergen challenges‖ were not graded, but sublingual immunotherapy was consistently associated with improvements in both.

Outcomes in Children. Evidence was similar in strength to support the use of sublingual immunotherapy in children (<18 years of age) for allergic rhinitis and asthma. The strength of evidence was high to support sublingual immunotherapy use for the improvement of asthma in children based on 9 studies[25-27,35-38,41,42] involving 471 participants. A strong magnitude of association for asthma outcomes was identified in 6 of 9 pediatric studies (67%) compared with 3 of 4 mixed-age/adult studies (75%). Rhinitis or rhinoconjunctivitis outcomes were reported in 12 trials[28-32,35-39,41,42] involving 1065 children, with moderately strong evidence to support sublingual immunotherapy use; strong magnitude of effect was present in 2 of 12 pediatric studies (17%) compared with 7 of 23 mixed-age/adult studies (30%). However, the strength of the evidence in children dif-

*References 9-12, 14-17, 19, 24, 28-32, 35-39, 41, 42, 46, 49-60.

†References 10-12, 14, 19, 29, 36, 39, 41, 48, 52, 55, 56.

‡References 10-12, 14-17, 19, 22-32, 35, 37-39, 41, 43-46, 50, 52, 54-58, 60-66.

§References 8, 14, 15, 22, 23, 31, 34, 43, 50, 52-54, 57, 63-65, 67-70. ‖References 9, 20, 23, 30, 34-36, 46, 56, 58, 60, 62-64, 66, 71, 72.

fered in 2 outcomes from our larger report. First, there was insufficient evidence to grade disease-specific quality of life based on 2 studies[29,32] involving 461 participants. Second, the data for the evidence for the combined symptom plus medication score were graded as low based on 2 studies[31,34] involving 329 participants. A comprehen-

Table 1. Sublingual Immunotherapy Evidence Summary

Outcome	No. of Participants	No. of Studies	Allergens	Comparators	Summary of Grading Data	Findings	Strength of the Evidence
Asthma symptoms	625	13	Dust mite[25-27,35-37,42] *Alternaria*[22,45] Grass mix[46] Tree mix[41] Birch[47] *Parietaria*[48]	Sublingual immunotherapy vs placebo[22,25-27,35-37,42,45,47,48] vs inhaled steroids[46] vs placebo-controlled trial of sublingual immunotherapy[41]	Two studies with low risk of bias and strong magnitude of effect.[25,35]	All placebo-controlled studies demonstrated greater improvement in the sublingual immunotherapy group. The study[46] of sublingual immunotherapy vs inhaled steroids showed improvement in both groups.	High
Rhinitis or rhinoconjunctivitis symptom scores	2985	36	Grass mix[11,12,16,17,19,31,32,46,49,50] Dust mite[15,28,29,35-37,42,51] *Parietaria*[30,38,48,52] Cedar[53-55] Timothy grass[56] Ragweed[10,57] Birch[47,58] Olive[39] Cat[59] Tree mix[41] Multiple allergens[14,60]	Sublingual immunotherapy vs placebo[10,12,14-17,19,28-32,35-37,39,42,47-52,54-57,59] vs pharmacotherapy[46,58] vs placebo-controlled trials of sublingual immunotherapy[11,41,57,60]	One study with low risk of bias and strong magnitude.[11] Six studies with medium risk of bias and strong magnitude.[16,39,42,46,49,50]	The majority of studies showed greater improvement in symptoms in the sublingual immunotherapy group vs placebo.	Moderate
Asthma symptoms plus rhinitis or rhinoconjunctivitis symptom scores	515	6	*Alternaria*[45] Birch[61] Tree mix[41] Grass mix[43] Dust mite[62] Multiple allergens[63]	Sublingual immunotherapy vs placebo[4,45,61] vs 2 placebo-controlled and 1 pharmacotherapy-controlled trials of sublingual immunotherapy[41,62,63]	Two studies with medium risk of bias and strong magnitude.[41,63] One study with medium risk of bias and moderate magnitude.[61] Two studies with medium risk of bias and insufficient data to determine magnitude of effect.[45,62] One study with low risk of bias and moderate magnitude of effect.[43]	Five studies demonstrated greater improvement in the sublingual immunotherapy group.[41,43,45,61,63] One placebo-controlled study[62] found no improvement in symptoms.	Moderate
Conjunctivitis symptom scores	1074	13	Grass mix[11,12,19] Dust mite[29,36] *Parietaria*[48,52] Timothy grass[56] Ragweed[10] Cedar[55] Olive[39] Tree mix[41] Multiple allergens[14]	Sublingual immunotherapy vs placebo[10-12,14,19,29,36,39,48,52,55,56] vs a placebo-controlled trial of sublingual immunotherapy[41]	Five studies with low risk of bias[11,14,36,48,56]; 1 of these had strong magnitude.[11] Six studies with medium risk of bias[10,12,19,39,41,52]; 1 of these had strong magnitude.[41] Seven studies with insufficient data to determine magnitude of effect.[10,12,19,29,48,52,56]	All but 2 studies showed greater improvement in symptoms in the sublingual immunotherapy group vs placebo. One study showed greater improvement with placebo.[10] The direction of change could not be determined in 1 study.[48]	Moderate

(continued)

sive description and subanalysis of the pediatric studies are available in the full Agency for Healthcare Research and Quality report on effectiveness of specific immunotherapy for allergic rhinitis and asthma.

Safety Outcomes. The studies did not uniformly or consistently report safety information, although 47 studies (75%)

Table 1. Sublingual Immunotherapy Evidence Summary (continued)

Outcome	No. of Participants	No. of Studies	Allergens	Comparators	Summary of Grading Data	Findings	Strength of the Evidence
Medication use scores	2162	41	Grass mix[11,12,16,17,19,31,32,43,46,50] Dust mite[15,25-29,35,37,62] *Parietaria*[30,38,52,64] Cedar[54,55,65] *Alternaria*[22,45] Tree mix[23,41] Timothy grass[56,60] Ragweed[10,57] Birch[58,61] Olive[39] Rye[44] Multiple allergens[14,24,63]	Sublingual immunotherapy vs placebo[10,12,14-17,19,22,24-32,35,37-39,43-45,50,52,54-56,58,64,65] vs pharmacotherapy[23,46,61,66] vs 5 placebo-controlled trials of sublingual immunotherapy[11,41,57,60,62]	Ten studies with low risk of bias[11,14,25,30,32,38,56,57,60,64]; 2 of these had strong magnitude of effect[11,25]; 2 had weak magnitude.[14,60] Twenty-two studies with medium risk of bias[10,12,15-17,19,23,24,26,28,35,37,39,41,45,46,50,52,54,61,63,65]; 7 of these had strong magnitude,[12,23,24,45,46,52,61]; 6 of these had weak magnitude of effect.[10,15,50,54,62,65] Six studies with high risk of bias[22,27,29,31,55,58]; 3 of these had strong magnitude.[22,55,58] Ten studies with insufficient data to determine magnitude of effect.[16,17,25,29-32,35,39,56]	Sublingual immunotherapy did better than comparator in all but 1 study.[32] The direction of change could not be determined in 1 study.[30] There was a strong magnitude of effect in 16 studies.[11,12,22,23,25,27,37,44-46,52,55,57,58,61,63]	Moderate
Medication use plus symptom scores	1669	20	Cedar[53,54,65,67,68] Grass mix[31,43,50,69] *Parietaria*[52,64,70] Dust mite[15] *Alternaria*[22] Ragweed[57] Tree mix[23] Multiple allergens[8,14,34,63]	Sublingual immunotherapy vs placebo[14,15,22,43,50,53,54,64,65,67-70] vs pharmacotherapy[23,52] vs no treatment[31,34] vs sublingual immunotherapy (1 placebo-controlled trial,[57] 1 pharmacotherapy-controlled trial,[63] and 1 trial vs no treatment[8])	Four studies with low risk of bias[14,57,64,67]; 1 of these had strong magnitude[57]; 2 had low magnitude.[14,64] Eleven studies with medium risk of bias[8,15,23,34,50,52-54,63,65,69]; 5 of these had strong magnitude.[8,43,52,63,69] Four studies with high risk of bias.[22,31,68,70] Eight studies with insufficient data to determine magnitude of effect.[2,23,31,53,54,65,67,70]	All studies but one[67] (in which direction of change could not be determined) showed greater improvement with sublingual immunotherapy than comparator. Six studies demonstrated a stong magnitude of effect.[8,34,52,57,63,69]	Moderate
Disease-specific quality of life	819	8	Cedar[54,65,67,68] Dust mite[29,51] Grass mix[32] Multiple allergens[14]	Sublingual immunotherapy vs placebo[14,29,32,51,54,65,67,68]	Four studies with medium risk of bias[14,54,65,68]; 2 of these had strong magnitude.[14,65] Two studies with low risk of bias and insufficient data to determine magnitude of effect.[2,67] Five studies with insufficient data to determine magnitude of effect.[29,32,51,65,67]	Four studies reported significant improvement in disease-specific quality of life vs placebo.[54,65,67,68] Two studies reported significant improvement with sublingual immunotherapy when comparing the initial with the final quality-of-life scores.[14,51]	Moderate

mentioned safety.¶ The lack of a standard grading system and the heterogeneous reporting systems used by the different studies required that safety outcomes be presented descriptively. We concluded that the evidence was insufficient to comment further about safety (TABLE 2). Because our safety review was limited to RCTs, the safety data presented herein should not be considered representative of all the existing sublingual immunotherapy safety literature.

¶References 8-15, 17-19, 21, 24, 25, 27-36, 38, 39, 41, 43-45, 49-51, 53-56, 59-63, 66, 68, 69, 73-75.

Local reactions were more frequent in patients receiving sublingual immunotherapy (range, 0.2%-97%) than in the comparator groups (range, 3%-38.5%). Systemic reactions were rarely reported, but were more common in the groups receiving sublingual immunotherapy than in comparator groups. There were no reported episodes of anaphylaxis, life-threatening reactions, or death in any treated patients across studies.

COMMENT

We found that the evidence is of moderate strength overall and it supports the position that aqueous sublingual immunotherapy is associated with improvement in allergic rhinitis and asthma outcomes. By definition in this review, moderate grade indicates moderate confidence that the evidence reflects the true effect. However, future research may change this estimate. Standardization of safety data reporting was lacking across studies, but there were no reports of life-threatening adverse events in this review. The results of this systematic review are applicable to patients with allergic rhinoconjunctivitis and/or asthma because we included only

Table 2. Sublingual Immunotherapy Safety Summary of Studies Reporting Adverse Events

		Adverse Events			
				Severity	
	Total No. of Patients	No. of Patients[a]	Range of Patients, %[a]	Description	% of Total Reported Events
Local reactions by allergen[b]: grass mix,[11,12,17,19,30,31,33,43,49,50,60,69] dust mite,[9,15,25,29,35,51,62,66] trees,[39,41,53-55,61,68,73] multiple allergens,[13,14,21,24,34,63] *Parietaria*,[30,48] *Alternaria*,[45] ragweed,[10] cat[59]					
Sublingual immunotherapy groups (n = 39 studies)	2520	681	0.2-97	Unspecified Mild Moderate	45 54 1
Placebo groups (n = 24 studies)	933	191	3-38.5	Unspecified Mild	26 74
Local reactions to Timothy grass[56,c]					
Sublingual immunotherapy group	28	380 reactions	4.75 events per patient	Mild	100
Control group	28				
Upper respiratory reactions by allergen[d]: grass mix,[11,12,17,32,43,49,50] dust mite,[9,29,36] trees,[41,55,73] *Parietaria*,[30] multiple allergens[8,21,24]					
Sublingual immunotherapy groups (n = 19 studies)	1201	347	3-92	Unspecified Mild Severe	73 25 2
Control groups (n = 12 studies)	572	228	1.6-93	Unspecified Mild Moderate	94 5 1
Lower respiratory reactions by allergen[e]: grass mix,[11,17,32,43,49,50] dust mite,[29,36,51,62] trees,[55] cat,[59] *Parietaria*,[30] multiple allergens[13,34]					
Sublingual immunotherapy groups (n = 16 studies)	1229	197	0.3-69 of doses	Unspecified Mild Moderate Severe	93 5 1 1
Control groups (n = 10 studies)	522	145	3-67 of doses	Unspecified Mild Moderate Severe	94 4 1 1
Cutaneous reactions by allergen[f]: grass mix,[17,31,43,50] dust mite,[29,36,66] trees,[53,55] multiple allergens[13,14,24,34]					
Sublingual immunotherapy groups (n = 15 studies)	1336	151	0.7-57	Unspecified Mild	93 7
Control groups (n = 6 studies)	535	135	2-65	Unspecified Mild	96 4

(continued)

studies that confirmed the diagnosis of allergy with testing.

Our systematic review is the most comprehensive in 2 aspects: it reports on the widest breadth of allergic symptom outcomes compared with previous reviews, and it includes a significantly larger number of RCTs compared with previous reviews because the search extends to December 2012. Our systematic review included RCTs of all age groups and all environmental allergens, evaluated the efficacy of sublingual immunotherapy, and performed grading of evidence for the largest number of direct (n=7) and indirect (n=2) clinical outcomes. Prior to our current review, the largest scale systematic reviews of sublingual immunotherapy, which reported on 2 primary outcomes, were performed in 2003,[76] updated in 2010,[77] and published in the Cochrane Collaboration Database. Our study included RCTs through December 2012, which allowed inclusion of 11 new RCTs not included in the last large Cochrane review.[77] Our findings are congruent with previous reviews of sublingual immunotherapy,[76-79] which found sublingual immunotherapy to be an effective treatment without serious adverse events, with all authors noting the wide heterogeneity in the literature.

Some prior systematic reviews have focused on a single outcome, such as allergic conjunctivitis[78] or asthma.[79] A review published in 2008 concluded that sublingual immunotherapy was associated with efficacy for treatment of asthma, but the magnitude of association was not large.[79] Our analysis found high-grade evidence to support that sublingual immunotherapy was associated with improved asthma symptoms. Of note, our study included 5 studies[22,43,45-47] published after 2008 that were included for asthma evidence grading in which 3 had strong magnitude of association,[22,46,47] which may explain the greater evidence in our report.

Table 2. Sublingual Immunotherapy Safety Summary of Studies Reporting Adverse Events (continued)

		Adverse Events			
				Severity	
	Total No. of Patients	No. of Patients[a]	Range of Patients, %[a]	Description	% of Total Reported Events
Gastrointestinal reactions by allergen[g]: grass mix,[12,17,19,31-33,43,49,50] dust mite,[9,29,36,62] trees,[41,55] *Parietaria*,[30] ragweed,[43] multiple allergens[13,24,34]					
Sublingual immunotherapy groups (n = 20 studies)	1704	281	0.3-74	Unspecified Mild Moderate	91.0 8.9 0.1
Control groups (n = 11 studies)	636	244	3-73	Unspecified	100
Cardiovascular reactions by allergen[h]: grass mix,[49] tree (cypress)[55]					
Sublingual immunotherapy groups (n = 2 studies)	65	2	2-4	Mild	100
Control group (n = 1 study)	30	1	2-4	Mild	100
Ocular reactions by allergen[i]: grass mix,[11,32,43,69] dust mite,[29,36] trees,[39,73] *Parietaria*,[30] multiple allergens[21,24]					
Sublingual immunotherapy groups (n = 11 studies)	763	308	1.5-73.4	Unspecified Mild Severe	98 1 1
Control groups (n = 7 studies)	428	182	3-65	Unspecified Mild Moderate	98 1 1
General symptoms by allergen[j]: grass mix,[11,19,32,33,49,50] dust mite,[25,27-29,35] *Parietaria*,[48] trees,[41] Timothy grass,[56] multiple allergens[14,21]					
Sublingual immunotherapy groups (n = 17 studies)	763	149	1-60	Unspecified Mild Moderate	74 22 4
Control groups (n = 10 studies)	435	21	6-67	Unspecified Mild Moderate	86 13 1

[a] Unless otherwise indicated.
[b] There were 25 studies that reported adverse events in the control (placebo) group.
[c] Based on 1 study that did not report the number of injections.
[d] Thirteen studies reported adverse events in the control (placebo) group; 2 studies had adverse events only in the placebo group.[15,62]
[e] Ten studies reported adverse events in the control (placebo) group; 1 study had adverse events only in the placebo group.[15]
[f] Nine studies reported adverse events in the control (placebo) group; 1 study had adverse events only in the placebo group.[12]
[g] Eleven studies reported adverse events in the control (placebo) group; 1 study with 60 patients did not report the number of doses or the number of events so the percentage or range of adverse events was not quantifiable and severity was 100% unspecified.[33]
[h] One study reported adverse events in the control (placebo) group.
[i] Nine studies reported adverse events in the control (placebo) group; 1 study had adverse events only in the placebo group.[55]
[j] Ten studies reported adverse events in the control (placebo) group; 1 study had adverse events only in the placebo group[62]; 2 studies with 116 patients did not report the number of doses or the number of events so the percentage or range of adverse events was not quantifiable and severity was 50% modified and 50% unspecified.

Other systematic reviews of sublingual immunotherapy have focused on a particular allergen such as dust mite[80] or grass.[81] Our review similarly found that sublingual immunotherapy treatment for these allergens was associated with improvement in a variety of outcomes.

Challenges

We encountered several challenges during our review process. We included only RCTs in this review; however, the studies varied substantially in their risk of bias. Among 46 studies (73%) that received industry support, few described the extent of involvement of their sponsors. For these reasons, most studies were considered to have a moderate or high risk of bias.

The literature was heterogeneous. The inconsistent scoring and lack of standardized reporting systems for clinical outcomes and harms made comparisons difficult among studies. The studies used varying criteria for diagnosing asthma and assessing asthma severity. The use of combined scores such as asthma plus rhinitis may not accurately reflect the degree of control for both disease processes. Studies with multiple allergens presented a similar dilemma; response to 1 allergen may have determined the overall clinical score, with little effect from a second allergen. The heterogeneity of the data on symptoms and medication use precluded pooling the data for further analysis.

Most challenging to this review was the extreme variability in the dosing and treatment schedules from study to study. The doses were reported in varying units (biological units, index of reactivity units, standardized quality units, micrograms, bioequivalent allergy unit, specific treatment units, etc). Indeed, without a common unit of dose measurement, it is impossible to compare dose effect among studies. In several studies, major allergen content was not reported. To illustrate, dust mite was the most widely used sublingual allergen in 5 studies. When considering the dosing for dust mite in micrograms per month, the highest dose used was more than 50 times greater than the lowest dose, yet clinical efficacy was reported at both ends of the spectrum (eTable 2). The extreme variability in sublingual doses and treatment schedules makes it impossible to comment on the strength of the evidence regarding dosing and treatment schedule.

Another significant limitation of the current review in regard to dosing was the difficulty in comparing European allergens with US allergens.[82] In the United States, the Food and Drug Administration establishes for each standardized allergen an in vitro potency test that all manufacturers must use to compare their extracts; in Europe, each allergen manufacturer has its own reference standards rather than a European standard. Another difference is that the in vivo potency in the United States is quantified by intradermal testing methods, which is not the case in Europe. This current review has attempted to express, when possible, sublingual dosing in micrograms of major allergen (eTable 2). However, it must be emphasized that due to these differences between allergen standardization and potency in the United States vs Europe, caution must be exercised when attempting to translate European dosing to the United States.

There were deficiencies in the statistical reporting provided in the included studies. Most of the studies had small sample sizes and small amounts of relevant statistical information on the outcomes reported because scores were frequently unavailable (such as standard deviation, standard error, or confidence intervals). Therefore, precision of the point estimates could not be assessed.

As in most fields, there may be publication bias in the sublingual immunotherapy literature, with studies reporting positive results being more likely to be published than studies reporting negative results. Our study aimed to overcome publication bias by searching for registered and yet unreported clinical trials and requesting scientific information packets from relevant pharmaceutical companies to look for unpublished trials; however, our report includes studies in the periods before clinical trial registration was required. The incomplete statistical reporting in the majority of included studies made it impossible to prepare a meaningful funnel plot to further assess publication bias. One of the major limitations when considering the validity of the conclusions of this systematic review is the potential for publication bias.

Future Research

Additional RCTs are needed to examine the efficacy and safety of sublingual immunotherapy. There is a particular need for additional high-quality studies that directly compare sublingual with subcutaneous immunotherapy. Future studies should use standardized methods to report and score symptoms, adverse events, and dosing. Studies including patients with asthma should describe how asthma was diagnosed and how severity was determined. This will allow assessment of whether there is a particular subgroup of patients with asthma that may benefit from sublingual immunotherapy. In addition, the target maintenance dose, dosing strategies, duration of treatment, and use of single vs multiple allergen therapy have not been fully determined.

CONCLUSIONS

Our review found moderate strength in the evidence to support the use of sublingual immunotherapy for allergic rhinitis and asthma. This indicates moderate confidence that the evidence reflects a true efficacy. However, future research could change the estimate. High-quality studies are needed to answer questions of optimal dosing strategies. There were limitations in the standardization of adverse event reporting, but no life-threatening adverse events were noted.

Author Contributions: Dr Lin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Lin, Suarez-Cuervo, Ward, Segal.

Acquisition of data: Lin, Erekosima, Kim, Ramanathan, Suarez-Cuervo, Chelladurai, Ward.
Analysis and interpretation of data: Lin, Erekosima, Kim, Ramanathan, Suarez-Cuervo, Chelladurai, Segal.
Drafting of the manuscript: Lin, Erekosima, Chelladurai, Ward.
Critical revision of the manuscript for important intellectual content: Lin, Erekosima, Kim, Ramanathan, Suarez-Cuervo, Chelladurai, Segal.
Statistical analysis: Lin, Erekosima, Ramanathan, Chelladurai.
Obtained funding: Lin, Segal.
Administrative, technical, or material support: Ramanathan, Suarez-Cuervo, Chelladurai, Ward.
Study supervision: Lin, Erekosima, Segal.

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Task force report

Sublingual grass and ragweed immunotherapy: Clinical considerations—a PRACTALL consensus report

James T. Li, MD, PhD,[a] David I. Bernstein, MD,[b] Moises A. Calderon, MD, PhD,[c] Thomas B. Casale, MD,[d] Linda Cox, MD,[e] Giovanni Passalacqua, MD,[f] Oliver Pfaar, MD,[g,h] and Nikolaos G. Papadopoulos, MD[i] *Rochester, Minn, Cincinnati, Ohio, London, United Kingdom, Tampa and Fort Lauderdale, Fla, Genoa, Italy, Wiesbaden and Mannheim, Germany, and Athens, Greece*

Sublingual allergen immunotherapy provides a new option for patients with allergic rhinitis in the United States. The efficacy of these sublingual immunotherapy tablets in the treatment of allergic rhinitis has been firmly established in large multicenter clinical trials. In addition, the clinical benefits of sublingual immunotherapy might persist after treatment is discontinued. Local reactions, such as gastrointestinal or oropharyngeal symptoms, are common. However, severe anaphylaxis is rare, and therefore the immunotherapy tablets can be administered at home. Sublingual immunotherapy for allergic rhinitis has been used successfully for years in Europe, and these products might be appropriate for patients who do not do well with standard drug therapy or for those who prefer a disease-modifying approach. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: *Sublingual, immunotherapy, ragweed, sublingual immunotherapy*

Abbreviations used
AIT: Allergen immunotherapy
FDA: US Food and Drug Administration
PI: Package insert
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual allergen immunotherapy

For the first time in more than 100 years, a new form of allergen immunotherapy (AIT) has been introduced in the United States. In early 2014, the US Food and Drug Administration (FDA) approved 3 sublingual AIT products (Table I[1-3]) based on their demonstrated safety and efficacy in multicenter, multicountry clinical trials with large patient populations and supported by years of real-life use in Europe. The safety of sublingual allergen immunotherapy (SLIT) allows for home administration, and this might be attractive for patients with allergic rhinitis that is not well controlled with standard pharmacotherapy and who prefer a disease-modifying approach but cannot commit the time required for subcutaneous immunotherapy (SCIT) to be administered in a medically supervised setting.

From [a]the Division of Allergic Diseases, Mayo Clinic, Rochester; [b]the University of Cincinnati; [c]Imperial College London; [d]the University of South Florida, Tampa; [e]Nova Southeastern University, Fort Lauderdale; [f]Allergy and Respiratory Diseases, University of Genoa; [g]the Center for Rhinology and Allergology, Wiesbaden; [h]the Department of Otorhinolaryngology, Head and Neck Surgery, Universitatsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim; and [i]the Allergy Research Center, Athens.

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Corresponding author: James T. Li, MD, PhD, Mayo Clinic, 200 First St, Rochester, MN 55905. E-mail: li.james@mayo.edu.

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TABLE I. Characteristics of SLIT tablets available in the United States[1-3]

Brand name	Components	Clinical indications	Doses	Regimens	Updose	Observe first dose	Children	Sustained benefit
Grastek	Timothy grass	Allergic rhinitis/rhinoconjunctivitis with/without controlled asthma in patients with specific IgE antibodies to relevant allergens	Daily tablet	Precoseasonal (start ≥12 wk before season) or year-round	No	Yes	5-17 y	For sustained effectiveness for 1 season after treatment cessation, take daily for 3 y
Oralair	Sweet vernal, orchard, perennial rye, timothy, Kentucky bluegrass	Allergic rhinitis/rhinoconjunctivitis with/without controlled asthma in patients with specific IgE antibodies to relevant allergens	Daily tablet	Precoseasonal (start 4 mo before onset of season)	Yes, for first 3 d	Yes	10-17 y	No indication
Ragwitek	Short ragweed	Allergic rhinitis/rhinoconjunctivitis with/without controlled asthma in patients with specific IgE antibodies to relevant allergens	Daily tablet	Precoseasonal (start 12 wk before onset of season)	No	Yes	No	No indication

The purpose of this document is to offer practical guidance informed by long-term experience in Europe for the use of SLIT in the United States. Responses to the following key clinical questions provide a basis for rational decision making for the use of these new options in the management of allergic diseases.

WHAT ARE THE CLINICAL INDICATIONS FOR SLIT?

The 3 sublingual allergen tablets approved in the United States, 5-grass (Oralair; Stallergenes, Antony, France), short ragweed (Ragwitek; Merck & Co, Whitehouse Station, NJ), and timothy grass (Grastek; Merck & Co), are indicated for "the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies"[2] for the allergens contained in the specific product (see Boxes 1 and 2). In Europe the indication is for "allergic rhinitis with/without asthma." The decision to use SLIT depends on practical considerations, experience of the prescribing allergists/immunologists with the respective treatment form, cost, convenience, and patient preference.

The majority of studies for SLIT were conducted in patients with allergic rhinitis/rhinoconjunctivitis. Because pivotal studies were not designed to study asthma, none of the FDA-approved tablets list asthma as an indication. However, the pivotal SLIT tablet trials included patients with controlled asthma, and beneficial effects on asthma symptoms were demonstrated in those studies.[4] A systematic review of AIT for allergic rhinoconjunctivitis and asthma yielded 63 studies with 5131 participants who met the inclusion criteria.[4] Thirteen studies evaluated SLIT (aqueous solution) for the control of asthma symptoms. Those studies demonstrated statistically significant improvement in asthma symptoms in the SLIT group relative to the placebo group, with a "strong" association in 69% of the studies. There is also evidence suggesting a reduction in asthma symptoms in children treated with SLIT (also see the section entitled "Is SLIT effective and safe for children?").[5]

Nevertheless, neither the US- nor European Medicines Agency–licensed package inserts (PIs) include asthma alone as a clinical indication, and all PIs state that the tablets have not been studied in "subjects with moderate or severe asthma."

Similar to SCIT, the US SLIT tablet PI warning states that it might not be "suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction" or for patients "who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta blockers."[2,3]

With respect to pregnancy, there are very limited data on the safety of any form of AIT. The PIs for the 3 SLIT tablets state the following, as for SCIT: "Because systemic and local adverse reactions with immunotherapy may be poorly tolerated during pregnancy, [the product] should be used during pregnancy only if clearly needed."

HOW DOES SLIT'S EFFECTIVENESS COMPARE WITH THAT OF SCIT?

In the United States SCIT is administered through the subcutaneous route, and extracts are often mixed in a physician's office, whereas SLIT is administered through the sublingual route, with tablets produced by manufacturers. Other countries might have different SCIT and SLIT products available. There is insufficient evidence to do a meaningful comparison of efficacy between SCIT and SLIT; however, existing evidence suggests both routes are effective in reducing symptom scores and medication use in patients with allergic rhinitis and asthma compared with placebo. Several systematic reviews and meta-analyses of randomized controlled trials of SCIT, SLIT, or both versus placebo (indirect and indirect comparison) suggest that SCIT might provide greater clinical and immunologic efficacy (Table II).[6-11]

The main outcomes used to evaluate efficacy in those studies were reduction of symptoms, need for rescue medication, combined symptom and medication scores, and improvement in quality of life.

A comparison of Cochrane meta-analyses suggests that the clinical effect size for SCIT might be greater than for SLIT, but the findings are not definitive.[12-14] Comparisons of effect size are hampered by substantial methodological and clinical heterogeneity between studies and lack of standardization of clinical outcomes, dosages, schedules, and duration of treatment. Studies directly comparing the 2 treatment modalities are limited by study size and power (Table III).[14-25] In one study directly comparing the efficacy of SLIT and SCIT by using timothy extract produced by the same company (SCIT: Alutard SQ and SLIT: Grazax; ALK-Abelló, Hørsholm, Denmark), there was a significant chance in in nasal challenge threshold only in the SCIT-treated subjects.[26]

TABLE II. Systematic reviews comparing sublingual and subcutaneous immunotherapy

	Indirect		Head to head	
Key findings	**Di Bona et al, 2012[7]**	**Dretzke et al, 2013[8]**	**Chelladurai et al, 2013[9]**	**Kim et al, 2013[10]**
No. of RCTs	17 SCIT vs placebo 22 SLIT vs placebo	17 SCIT vs placebo 11 SLIT vs placebo	8 SCIT vs SLIT	3 SCIT vs SLIT, pediatric only
Symptom score	SMD = SCIT vs placebo, −0.92 (95% CI, −1.26 to −0.58) SMD = SLIT-D vs placebo, −0.25 (95% CI, −0.45 to −0.05) SMD = SLIT-T vs placebo, −0.40 (95% CI, −0.54 to −0.27)	SSD = SCIT vs SLIT, 0.35 (95% Crl, 0.13 to 0.59) Favoring SCIT	Moderate-grade evidence Favoring SCIT	Low-grade evidence Favoring SCIT
Medication score	SMD = SCIT vs placebo, −0.58 (95% CI, −0.86 to −0.30) SMD = SLIT-D vs placebo, −0.37 (95% CI, −0.7 to 0.0) SMD = SLIT-T vs placebo, −0.30 (95% CI, −0.44 to −0.16)	SSD = SCIT vs SLIT, 0.27 (95% Crl, 0.03 to 0.5) Favoring SCIT	Low-grade evidence, no difference in treatment effectiveness between SCIT and SLIT	Low-grade evidence Favoring SCIT
Safety	SCIT: 0.86 AEs/patient SLIT: 2.13 AEs/patients Anaphylactic episodes SCIT/SLIT: 12/1	NR	Local reactions (frequency) SCIT: 20% SLIT: 7% to 56% Anaphylactic episodes SCIT: 1 SLIT: 0	Local reactions (patients) SCIT: 3 SLIT: 3 Systemic reactions (patients) SCIT: 4 SLIT: 0 Anaphylactic episodes SCIT: 1 SLIT: 0

Adapted from Chelladurai and Lin.[11]

AE, Adverse event; *Crl*, credible interval; *NR*, not reported; *RCTs*, randomized controlled trials; *SLIT-D*, sublingual immunotherapy drops; *SLIT-T*, sublingual immunotherapy tablets; *SMD*, standardized mean difference; *SSD*, standardized score difference.

IS SLIT MORE EFFECTIVE THAN ALLERGY MEDICATIONS?

No direct head-to-head studies comparing the efficacy of SLIT with medications in the treatment of seasonal or perennial allergic rhinitis have been published because all SLIT trials have allowed for rescue medication use. Therefore only indirect comparisons are possible. An indirect comparison was conducted through a meta-analysis of large (>100 patients), double-blind, placebo-controlled trials evaluating the efficacy of SLIT 5-grass pollen/timothy grass tablet or allergy medications for seasonal allergic rhinitis.[27] Twenty-eight publications on symptomatic medication trials and 10 publications on SLIT trials met the inclusion criteria and were evaluated (total n = 21,223). The authors stated the following: "The SLIT tablets had a greater mean relative clinical impact than second-generation antihistamine and montelukast and much the same mean relative clinical impact as nasal corticosteroids."[27] This indirect comparison suggests that SLIT can be as good or better than as-needed medications.

In addition to providing a similar magnitude of improvement, SLIT can provide sustained benefits for 2 years after discontinuation after 3 years of continuous treatment.[28] Whereas the medications for allergic rhinitis only alleviate symptoms and do not provide sustained benefits after discontinuation,[29] SLIT is a disease-modifying approach that has the potential to affect the course of the condition over time.

WHAT ARE EFFECTIVE DOSE REGIMENS FOR SLIT? WHAT HAPPENS IF A DOSE IS MISSED?

The 3 US-licensed products showed comparable efficacy within the investigated dose ranges. Therefore we recommend following the instructions in the product PIs, keeping the following points in mind:

- Doses are expressed in allergy units that are different for each product and not comparable. See Table IV[30-36] for various optimal maintenance doses in micrograms based on dose-ranging studies.
- The 5-grass product is available in 2 strengths (100 and 300 IR). For children and adolescents aged 10 to 17 years, the dose is increased over the first 3 days ("updosing"): on day 1, a 100-IR tablet is given; on day 2, two 100-IR tablets are given; and on day 3 and after, the 300-IR tablet (same as for adults) is given. For the ragweed and timothy grass products, children and adults take the same dose (ie, a single tablet daily over the prescribed time period) with no updosing.
- Treatment with the ragweed and timothy products is initiated at least 12 weeks before the expected onset of the season and continued throughout the season, and treatment with the 5-grass product is initiated at 16 weeks before the expected onset of the season and continued throughout the season (ie, the "precoseasonal" regimen). Some studies suggest that benefits might be seen if treatment is started at 8 weeks before or at onset of season.[37-39] The timothy product has an option of continuous year-round treatment. According to the PI, "for sustained effectiveness for one grass pollen season after cessation of treatment, [the product] may be taken daily for three consecutive years."

Regarding missed doses, the PIs for the short ragweed and timothy grass products state that "data regarding the safety of restarting treatment after missing a dose of [the product] are limited. In the clinical trials, treatment interruptions for up to seven days were allowed." No data on missed doses are available for the 5-grass product. The medication guide for patients for all 3 products states the following: "If you forget to take [the product], do not take a double dose. Take the next dose at your normal

TABLE III. Randomized trials comparing the clinical effects of SCIT and SLIT

Study, year	Allergen (duration)	Patients enrolled/dropouts	Age range (y)	Main results
Piazza et al,[15] 1993	Mite (2 y)	SCIT = 17/0 SLIT = 14/0 LNIT = 12/0 Control = 14/0	15-60	SLIT: decrease in symptoms at 3 mo but not 12-24 mo SCIT: decrease in symptoms at 3, 12, and 24 mo; IgE, IgG, and IgG_4 changed only in SCIT. No change at all in LNIT.
Quirino et al,[16] 1996*	Grass (1 y)	SCIT = 10/0 SLIT = 15/0	18-60	Significant reduction in symptom and drug intake score in both groups vs baseline. No change in IgE level. Increase in IgG level and reduction of skin reactivity only in the SCIT group.
Mungan et al,[17] 1999	Mite (1 y)	SCIT = 15/0 SLIT = 10/0 Placebo = 11/0	18-65	Reduction in rhinitis score for SLIT and SCIT. Asthma score reduction only for SCIT. Reduction in drug score for both SLIT and SCIT. Reduction in SPT diameter only in the SCIT group.
Khinchi et al,[18] 2002*	Birch (2 y)	SCIT = 24/5 SLIT = 23/9 Placebo = 24/9	18-60	Reduction in rhinitis score in SLIT and SCIT. No significant difference between the 2 treatments, both superior to placebo. Medication scores SLIT and SCIT decreased vs placebo. No change in QoL.
Mauro et al,[19] 2007	Birch (4 mo)	SCIT = 23/8 SLIT = 24/5	18-65	During pollen season, no SLIT-SCIT difference in symptoms plus drug scores. Specific IgG_4 levels significantly increased with SCIT only.
Antunez et al,[20] 2007	Mite (2 y)	SCIT = 12/1 SLIT = 11/1	8-17	Improvement in subjective evaluation and VAS in both groups. Increase in IgG_4 levels only for SCIT. Decreases IgE/IgG_4 levels in both.
Tahamiler et al,[21] 2008	Mite (3 + 3 y)	SCIT = 96/NR SLIT = 97/NR	NR (adults)	Decrease in symptom score and nasal provocation scores in both groups after 3 y of treatment (greater in SCIT). Improvement maintained after 3 y only in SCIT.
Ventura et al,[22] 2009	Cypress (1 y)	SCIT = 10 SLIT = 10	18-65	Decrease in symptom scores in both groups (no value given): decrease in nasal eosinophil counts in SLIT.
Eifan et al,[23] 2010	Mite (1 y)	SCIT = 16/2 SLIT = 16/1 Drug = 16/2	5-12	Significant reduction in total rhinitis and asthma scores, medication scores, VAS scores, and skin reactivity for both SCIT and SLIT. No difference between routes of administration.
Yukselen et al,[24] 2011	Mite (1 y)	SCIT = 10/1 SLIT = 11/1 Placebo = 11/0	7-14	Significant reduction in symptom and medication score vs baseline with both treatments. SCIT is better than SLIT vs placebo.
Keles et al,[25] 2011*	Mite (1 y)	SCIT = 15/2 SLIT = 15/2 SCIT + SLIT = 15/1 Drugs = 15/3	5-12	Decreased asthma attacks and use of steroids at 4, 12, and 18 mo for SCIT and SCIT plus SLIT at 12 mo only for SLIT. No change in VAS score for asthma with SCIT or SIT alone.

QoL, Quality of life; *NR*, not reported; *SCIT*, subcutaneous immunotherapy; *SLIT*, sublingual immunotherapy; *SPT*, skin prick test; *VAS*, visual analog scale.
*Double-blind double-dummy.

TABLE IV. Optimal maintenance doses of allergen based on available dose-ranging studies

Author, year	Total patients randomized	Allergen/preparation	Optimal maintenance dose
Durham et al,[34] 2006	855	Timothy grass/tablets	15 μg of Phl p 5/d
Didier et al,[35] 2007	628	5-Grass mix tablets	25 μg/mL group 5/d
Creticos et al,[30] 2014	784 AR/ARC	Ragweed tablets	12 μg of Amb a 1/d
Bergmann et al,[31] 2014	AR/ARC	Dust mite	28 μg of Der p 1, 120 μg of Der f 1 (500 IR)
Mosbech et al, 2014[32] and 2015[36]	Asthma 604 AR 204	Dust mite tablet	6 SQ-HDM 6 SQ-HDM
Nolte et al,[33] 2015	124	Dust mite tablets	12 DU*

AR, Allergic rhinitis; *ARC*, allergic rhinoconjunctivitis; *HDM*, house dust mite.
*Same product as the Mosbech et al studies but different dosing units.

scheduled time the next day. If you don't take [the product] for more than one day, contact your health provider before restarting."[2,3,40]

CAN SLIT ALLERGENS BE COMBINED?

The European experience suggests that distinct SLIT tablets (grass and ragweed) can be administered separately to the same patient. One open-label, controlled, 4-parallel-group, randomized study showed favorable results in patients sensitized to grass and birch with 2 SLIT products[14]; another reported favorable results in patients given SLIT with grass plus olive extract.[27] Ongoing studies suggest that dual administration of SLIT products can be well tolerated. However, there are no published data on the concomitant use of the 3 products approved in the United States with each other or with SCIT, and the PIs state that concomitant dosing might increase the likelihood of local or systemic adverse reactions to either SCIT or SLIT.

WHAT ADVERSE EVENTS CAN OCCUR WITH SLIT?

Adverse reactions associated with SLIT can be local or systemic. Local reactions, such as oral or mild gastrointestinal symptoms, are fairly common, affecting up to

Box 1. Tablet administration for adults

For all 3 SLIT products, the tablet should be placed under the tongue immediately after removal from the blister packet and allowed to dissolve completely. The first dose should be administered in the office under the supervision of a physician with experience in the diagnosis and treatment of acute allergic reactions. The patient should be observed for at least 30 minutes after administration for signs or symptoms of a severe systemic or local reaction. According to the PIs, the tablet should not be taken with food or beverage, and no food or beverage should be ingested for 5 minutes after taking the tablet.

Box 2. Tablet administration in children

In children SLIT doses should be administered under the direct supervision of an adult. It is important that the tablet remain under the tongue for at least 1 minute until fully dissolved. There is no evidence that premedication with an antihistamine will prevent local reactions. Parents should be prepared for the likelihood of local reactions before their child starts SLIT and instructed to contact the office if local reactions persist and are troublesome.

75% of SLIT-treated patients.[41] Itching or irritation affecting the lips, tongue, ears, or throat are the most common reported symptoms. Isolated gastrointestinal symptoms associated with SLIT, such as abdominal pain or nausea, can be considered local reactions caused by swallowing the tablet contents. If gastrointestinal symptoms occur in conjunction with other systemic symptoms, they would be considered systemic reactions.

The European Academy of Allergy and Clinical Immunology allergy immunotherapy guidelines recommend withholding SLIT in patients with acute gastroenteritis,[42] and the US PIs for all 3 SLIT products recommend treatment discontinuation in patients who experience severe or persistent gastroesophageal symptoms. In the nearly 3 decades of SLIT use globally, a greater safety risk in patients with inflammatory gastrointestinal conditions, such as eosinophilic esophagitis or inflammatory bowel disease, has not been apparent. To date, 2 case reports of pollen SLIT–associated eosinophilic esophagitis have been reported.[43,44]

A framework for grading local side effects of SLIT is available and might be helpful. This 3-grade classification system for SLIT local reactions based on the patient's subjective accounting was developed with the intent of "improving and harmonizing the surveillance and reporting of the safety of SLIT."[45] A framework for grading possible but rare systemic reactions is also available.[46]

Most SLIT-induced local reactions occur shortly after treatment initiation and cease within 2 weeks without any medical intervention. The duration of local reactions generally does not exceed 10 days.[47] There have been no studies evaluating the effect of antihistamine premedication on the incidence or severity of SLIT-induced local reactions, but expert opinion would support the use of antihistamines in the treatment of a local reaction. Although the overall dropout rate in double-blind, placebo-controlled trials was similar between groups, dropouts because of adverse events (mostly because of persistent local reactions) were significantly greater in the SLIT groups compared with the placebo groip.[41,48]

Patients should be educated about SLIT-induced local reactions before therapy initiation. Patient education regarding treatment-related adverse events might improve adherence and decrease early withdrawal from treatment. Patients should be instructed to contact the physician's office if local reactions persist or if they have gastrointestinal symptoms, an asthma exacerbation, difficulty breathing, or signs and symptoms of anaphylaxis.

The incidence of fatal and near-fatal systemic reactions with SCIT and SLIT suggests that the SLIT systemic reaction rate is significantly lower and severe systemic reactions are relatively uncommon when compared with SCIT. A comprehensive review of 104 SLIT studies published through October 2005 found that the systemic reaction rate was 0.056% of doses administered.[41] In a *post hoc* analysis of randomized controlled trials of timothy tablet that included 3314 adults and 881 children, there was no evidence of increased systemic allergic reactions or severe local allergic swelling in the adults or children with asthma (24 and 31%, respectively) compared with the subjects without asthma.[49]

Severe anaphylaxis (World Allergy Organization grade 4) is rare with SLIT. The European experience suggests that after administration of more than a billion doses, no SLIT-related fatalities have occurred. Although the prescribing information for FDA-approved SLIT products recommends that patients have an epinephrine autoinjector, epinephrine autoinjectors usually are not prescribed in other parts of the world.

Because SLIT generally is administered in a setting without direct medical supervision after the initial dose, patients should be given instructions regarding recognition and management of adverse reactions and when SLIT should be withheld (eg, asthma exacerbation and acute gastroenteritis).

IS SLIT EFFECTIVE AND SAFE FOR CHILDREN?

The efficacy and safety of SLIT in children is similar to the efficacy and safety in adults.[3] In Europe 3 large, pivotal, multicenter double-blind, placebo-controlled trials, each with more than 200 children and adolescents with grass pollen allergy, consistently demonstrated an effect size comparable with the data in the adult trials.[19,50,51] The frequency of local and systemic reactions was similar to that of adults taking SLIT.

In North America a double-blind, placebo-controlled trial in children with grass pollen allergy aged 5 to 17 years was conducted with 282 patients in 41 American and 8 Canadian sites.[52] Preseasonal and coseasonal SLIT treatment with timothy grass tablets resulted in a 26% reduction in mean total combined score relative to placebo. A single mild systemic reaction to the grass tablet was reported on day 1 of treatment.

Also, in North America a randomized, placebo-controlled trial of timothy grass tablets in 1501 polysensitized children with grass allergy and adults aged 5 to 65 years found reductions in symptoms over the entire season and in the peak pollen season, confirming previous research. Efficacy was similar in children and adults.[49]

The timothy grass SLIT tablet has been demonstrated to be safe and effective in treating children and adolescents aged 5 to 17 years. The 5-grass product has been approved for patients aged 10 to 17 years, although a subanalysis of one of the trials demonstrated that the 5-grass tablet in schoolchildren aged between 5 and 11 years had an efficacy similar to that in the subgroup of adolescent patients aged between 12 and 17 years.[53] The grass pollen tablets gained European market authorization for ages 5 years and up. However, additional evidence of efficacy and safety in children aged 5 to 9 years is required by the FDA before approval for that age group can be granted (also see the section on long-term benefits of SLIT below).

ARE THERE LONG-TERM BENEFITS TO SLIT?

Studies show that the clinical benefits of SLIT can continue after treatment is discontinued.[28,31,54,55] Randomized, double-blind, placebo-controlled trials with grass SLIT showed that after 3 years of active treatment, both clinical and immunologic benefits were demonstrated for at least 2 subsequent years.[28,37] The pivotal trials leading to US approval of timothy tablets showed that 3 years of continuous treatment resulted in a sustained increase in antigen-specific IgG_4 levels during the treatment period and for an additional 2 years,[28] and the PI for the timothy tablets states that "for sustained effectiveness for one grass pollen season after cessation of treatment, [the product] may be taken daily for three consecutive years" ("continuous" regimen).[2]

Although data from 5-grass tablet clinical trials also showed sustained clinical benefits for at least 2 more years after a 3-year of preseasonal/coseasonal therapy course,[55] the FDA did not give the product an indication for sustained use. No data on the sustained effectiveness of the ragweed product are available.

A prospective, open, controlled 15-year study of patients with respiratory allergy who were monosensitized to mites evaluated the duration of SLIT efficacy after discontinuation in relationship to treatment duration.[54] In patients who received SLIT continuously for 3 years, the clinical benefits persisted for about 7 years.[54] In those receiving SLIT for 4 or 5 years, the clinical benefits persisted for 8 years. New sensitizations occurred in all the control subjects over 15 years and in less than a quarter of the patients receiving SLIT for 3, 4 to 5, and 15 years (21%, 12%, and 11%, respectively).

With respect to children, for whom allergic rhinitis is a risk factor for asthma, the evidence suggests that SLIT might decrease the development of future asthma. For example, an open study of 113 children aged 5 to 14 years with grass pollinosis found the development of asthma after 3 years was 3 times more frequent in the control subjects compared with those who received SLIT.[56] SLIT also was associated with less medication use in the second and third years of therapy, and symptom scores tended to be lower. In an open randomized study of 216 children with allergic rhinitis, SLIT treatment was associated with a significant reduction in new allergen sensitization and onset of persistent asthma.[57] Data from double-blind, placebo-controlled studies on these preventive effects of SLIT are not available yet, but one large trial has been initiated in Europe.[58]

ARE THERE DIFFERENCES BETWEEN THE TIMOTHY AND 5-GRASS SUBLINGUAL TABLETS?

There are no discernible differences in efficacy or safety between the timothy and 5-grass (sweet vernal, orchard, perennial rye, timothy, and Kentucky bluegrass) tablets in treating adults sensitized to grass pollen during the grass pollen season. Sustained efficacy for up to 2 years has been demonstrated for both, although only the timothy product has FDA approval for sustained benefits. However, no comparative studies between the US-approved grass SLIT products have been done. See Table I for specific dosing and regimens for the timothy, 5-grass, and ragweed products.

Ragweed, timothy, and other grasses are prevalent in different regions during specific months. It is the prescribing physician's obligation to know what pollens and aeroallergens are predominant in their locales and how best to use this information to guide therapy, including the use of SLIT.

WHERE DOES SLIT FIT AMONG ALL MANAGEMENT OPTIONS FOR ALLERGIC RHINITIS?

The management of allergic rhinitis is highly individualized. No single treatment program will be right for all patients. As with other chronic diseases, response to treatment, experience with adverse effects, cost, access, and patient preference are all relevant to management decisions. Unique features of the management of allergic disease include exposure history and patient-specific/allergen-specific sensitization. The optimal management of allergic rhinitis should integrate all these factors through shared (patient-physician) decision making. A detailed allergy history, allergy testing, and physician-patient discussion of management options are essential.

Allergen avoidance is often included in the management plan, but complete avoidance is rarely feasible, and clinical effectiveness is variable. Pharmacologic options include antihistamines (oral and intranasal), intranasal corticosteroids, and leukotriene modifiers. When effective and well tolerated, these agents can be considered first-line options. However, they are not effective for all patients, might generate unacceptable adverse effects, and do not have disease-modifying properties.

SLIT might be an appropriate first-line treatment when a disease-modifying approach is preferred or for patients who value the potential benefits of immunotherapy (eg, long-term immunomodulation), as well as for those for whom standard drug therapy is ineffective or poorly tolerated. If symptoms are not reduced within 2 years, the patient should be re-evaluated. Those who respond can expect benefits to last up to 2 years after treatment.

The safety and efficacy of various SLIT formulations has been demonstrated in 85 randomized, double-blind, placebo-controlled trials published through April 2015.[30,32,33,45,54,59-63] SLIT might be a suitable therapeutic option when a patient presents with a single clinically relevant sensitization (eg, grass or ragweed), when AIT administration outside the physician's office is preferred, and when the lower risk of anaphylaxis is valued. Generally, patients can expect a reduction in symptoms and concomitant medication over time, as well as improved quality of life during the peak allergy season.

HOW DOES SLIT ADHERENCE COMPARE WITH ADHERENCE TO SCIT OR MEDICATIONS?

Adherence to both SLIT and SCIT outside of double-blind, placebo-controlled trials has been shown to be relatively poor, and adherence rates with SLIT are in line with those for most self-administered treatments for other chronic diseases.[64] Strategies that can enhance SLIT adherence include appropriately educating patients about their illness and treatment; discussing goals and expectations[65,66] with a view toward shared decision-making[67]; follow-up telephone calls, letters, and visits[66,68]; and text messages and other forms of electronic reminders. A general reminder at the beginning of the allergy season could also be helpful.

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REVIEW ARTICLE

Improvement and prevention of asthma with concomitant treatment of allergic rhinitis and allergen-specific therapy

David J. Mener, MD, MPH and Sandra Y. Lin, MD

Background: **Asthma and allergic rhinitis are 2 of the most prevalent chronic medical diseases. Asthma is estimated to affect 8% of adults and 9% of children, with nearly 300 million people affected worldwide. Poorly controlled allergic rhinitis may be associated with worsening asthma symptoms over time. Various treatments have been proposed in the improvement and prevention of asthma in children and adults with allergic symptoms, which have included pharmacotherapy with antihistamines and topical intranasal corticosteroids, as well as allergen-specific immunotherapy.**

Methods: **Articles were selected through PubMed and personal knowledge of the authors based on a comprehensive literature review examining whether treatment of allergic rhinitis improves and/or prevents concomitant symptoms of asthma. The largest and highest-quality studies were included in the literature review. The search selection was not standardized. Articles written in a language other than English were excluded.**

Results: **Clinical trials have showed improvement in asthma symptoms with concomitant treatment of allergic rhinitis with antihistamines and topical intranasal corticosteroids, though improvement in objective pulmonary function parameters has not been uniformly demonstrated with antihistamine use alone. There is very strong evidence to suggest that subcutaneous and sublingual immunotherapy may in addition prevent the progression of asthma in high-risk atopic patients by inducing immunological tolerance.**

Conclusion: **Traditional pharmacotherapy with antihistamines and topical intranasal steroids has been shown to improve allergic rhinitis symptoms with concomitant allergic asthma; however, only allergen-specific immunotherapy offers long-term control in improving asthma symptoms, exacerbations, and likely ultimate prevention in developing asthma.**

Key Words:
allergic rhinitis; asthma; allergen-specific immunotherapy; sublingual immunotherapy; subcutaneous immunotherapy; intranasal corticosteroids; antihistamines

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Asthma and allergic rhinitis (AR) are 2 of the most prevalent chronic medical diseases, with asthma affecting nearly 8% of adults, 9% of children,[1] and encompassing nearly 300 million persons worldwide.[2] The prevalence of AR has nearly doubled since 1970[3] and is estimated to cost more than 2 billion dollars annually in the United States.[4] Nearly 80% of patients with typical asthma symptoms also report general nasal symptoms, with 40% of rhinitis patients reporting coexisting asthma.[5]

Department of Otolaryngology–Head and Neck Surgery, Johns Hopkins School of Medicine, Baltimore, MD

Correspondence to: David J. Mener, MD, MPH, Johns Hopkins University, Department of Otolaryngology–Head and Neck Surgery, 601 N. Caroline Street, 6th Floor, Baltimore, MD 21287; e-mail: david.mener@gmail.com

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AR encompasses symptoms consistent with an allergic cause such as clear rhinorrhea, nasal congestion, pale nasal mucosa, red and watery eyes in response to inhaled allergens.[6] Asthma is a condition that encompasses chronic inflammation of the lower airway resulting in expiratory obstruction, with recurrent attacks consisting of cough, wheezing, and chest tightness. Bronchial hyperreactivity may represent an intermediate phase along the disease spectrum leading from nasal AR to asthma.[7] Asthma and AR both affect the mucosa of the respiratory tract and may share a common TH2 immunologic-mediated imbalance.[8] In addition, AR has been shown to be a 2-fold to 7-fold risk factor for development of asthma,[9,10] with more than 20% of all patients with asthma suffering from rhinitis[11] and 40% of infants with atopic dermatitis[12] developing asthma ultimately.[11,12] Both conditions may be exacerbated by re-exposure of airborne allergens. This may lead

to subsequent mast cell sensitization, release of inflammatory mediators, cytokines (interleukin [IL]-4, IL-5, and IL-6), and cysteinyl leukotrienes, which may cause chronic mucosal inflammation,[8,13] vascular permeability, vasodilation, and rhinorrhea.[14] This subsequently results in ongoing inflammation by antigen-mediated activation of mast cells, basophils, and eosinophils.[15] In a more prolonged late-phase response occurring 4 to 8 hours after the initial immunoglobulin E (IgE)-mediated reaction to the allergen exposure, nasal congestion and lower airway obstruction ensue, with increased bronchial hyperresponsiveness to airborne allergens and irritants.[16] Thus, poorly controlled AR may be associated with worsening asthma symptoms over time.[17]

Repeated exposure to inhaled antigens (such as seasonal pollens, mold, and perennial indoor allergens) in patients with allergic predisposition may be the underlying etiology leading to advancement of the allergic march.[18] The link between AR and asthma has been explained by various mechanisms, which include elicitation of the nasal-bronchial reflex, preferential increase in oral vs nasal inhalation due to nasal obstruction, reduction in filtration/humidification of the nose, and postnasal drainage of inflammatory material into the lower airways;[19] however, the latter has not been well supported.[20] Primary mouth breathing is hypothesized to bypass the nasal mucociliary filtration system that naturally entraps particles (ie, potential allergens) and irritants, thereby reducing exposure to the lower airways.[16] Prevention of nasal congestion and rhinorrhea resulting from the early allergic response may reduce bronchial hyperresponsiveness. Current treatment for AR consists of pharmacotherapy with antihistamines, topical intranasal steroids, and immunotherapy.

Concomitant improvement and prevention of asthma with treatment of AR with allergen-specific therapy has been observed to be an additional beneficial consequence.[21] This may be because of reduced nasal inflammation, suppression of histamine-driven immunologic changes, and immunomodulation leading to a more TH1-dominated vs TH2-dominated response.[22] Interestingly, as ambient grass pollen increases above 19 grains/m^3, the risk of children presenting to the emergency department for asthma exacerbations increases; this association appears to be dose-responsive.[23] Various treatment strategies have been proposed in the prevention and development of asthma in children and adults with allergic symptoms, which have included allergen avoidance, pharmacotherapy (namely antihistamines and topical intranasal steroids), and allergen-specific immunotherapy (ASI).[15]

Antihistamines in the improvement and prevention of asthma

Histamine has been shown to increase vascular permeability, facilitate plasma proteins and leukocytes extravascularly, produce cough by direct stimulation of H1 receptors, lead to mucous production by direct stimulation of H2 receptors, and cause bronchoconstriction through direct muscle stimulation; this cascade ultimately leads to lower and upper airway mucosal edema and inflammation.[17,24] Elevated histamine levels after allergen-specific challenge have been noted in early and late bronchoconstriction responses during spontaneous acute asthma episodes.[17] The clinical practice guidelines for AR make a strong recommendation that clinicians recommend oral second-generation antihistamines for patients with AR and primary complaints of sneezing and itching.[6]

Cetirizine and loratadine are the 2 most highly studied second-generation antihistamines in regard to concomitant use in AR and asthma. Cetirizine is a highly specific H1 receptor antagonist that infrequently crosses the blood-brain barrier.[25] Cetirizine also may inhibit the infiltration of tissues by eosinophils after allergen challenge,[26] as well as reduce neutrophil and monocyte chemotaxis in the nose, lungs, and skin,[24] which may help with concomitant asthma.[26] Unlike older conventional antihistamines that may cause severe sedation and cognitive impairment, cetirizine is only reported to have modest sedation and anticholinergic effects at doses necessary to improve bronchodilation;[27] terfenadine, an older antihistamine that has since been removed from the market due to safety concerns, was only effective at ameliorating asthma symptoms at high doses.[28]

Cetirizine (10 mg daily) given to patients with pollen-induced asthma has been shown to eliminate asthma symptoms of dyspnea and wheezing in 32% percent of patients within 3 months and reduce pharmacotherapy use, with no patients noted to have incapacitating acute asthma attacks.[29] Furthermore, cetirizine appears to have an additive bronchodilatory effect when combined with albuterol[30] and improve bronchial hyperresponsiveness within 6 hours after nasal allergen challenge.[13] Moderate doses (20 mg daily) and standard doses (10 mg daily) of cetirizine have been shown to significantly reduce asthma symptoms of chest tightness, wheezing, shortness of breath,[25,31] and nocturnal asthma in patients with mild to moderate asthma[25] in as early as 6 weeks.[31] Not surprisingly, a dose-responsive relationship has been noted with cetirizine, with higher doses (20 mg daily) generally more effective in improving forced expiratory volume in 1 second (FEV1), peak expiratory flow rate, forced expiratory flow rate, and vital capacity than lower doses (10 mg and 5 mg daily).[30] A large randomized prospective clinical trial (Early Treatment of the Atopic Child [ETAC] trial) in infants with a history of atopic disease treated with cetirizine (0.25 mg/kg twice daily) for 18 months interestingly reduced the incidence of asthma in 50% of infants sensitized to grass pollen and 40% of infants sensitized to dust mites.[32]

Low-dose loratadine (5 mg daily), another highly potent and specific H1-histamine antagonist, given for 2 to 6 weeks has been shown in patients with AR to decrease asthma symptom severity scores, cough, shortness of breath, chest tightness, need for pharmacotherapy, peak expiratory flow

rates, and FEV1.[33–35] Improvement in asthma scores has been noted as early as day 1 of treatment.[34] Desloratadine, the active metabolite of loratadine, has been shown in patients with grass-pollen AR to decrease circulating eosinophils and bronchial symptom scores in as early as 1 week.[36]

The effectiveness of antihistamines improving subjective and objective asthma parameters in patients with AR has not been consistently demonstrated. Improvement in pulmonary function with objective clinical parameters such as methacholine challenge and pulmonary function tests with antihistamine use has not been demonstrated universally with loratadine or cetirizine.[13,25,36,37] Although improvement in cough and sputum production, reduced pharmacotherapy, increased mean expiratory flow and FEV1[34] have been noted with cetirizine,[29] these results were not statistically significant.[25,31] Furthermore, although desloratadine has been shown to reduce systemic eosinophilia in patients treated for 7 days, there was no reduction in eosinophilia in the nasal or bronchial mucosa.[36] Last, some physicians have been reluctant in practice to use antihistamines in patients with AR and asthma because of concerns about mucous inspissation from anticholinergic effects.[38]

When evaluating the addition of a variety of antihistamines to existing asthma therapy with leukotriene receptor antagonists, several studies have reported that patients receiving antihistamines reported no significant changes in overall asthma symptoms,[37,39] dyspnea, or satisfaction with treatment,[39] with only a clinically small (4.5%) but statistically significant improvement in forced end vital capacity.[40] A large multicenter clinical trial among children with atopic dermatitis was unable to demonstrate a reduction in the development of asthma with cetirizine treatment.[32] It has been postulated that antihistamines, even at higher doses, may only be effective in mild or moderate persistent asthma rather than in severe persistent asthma.[17]

Nasal steroids in the improvement and prevention of asthma

Potent topical nasal steroids are considered first-line therapy for AR,[38] are strongly recommended by the current clinical practice guidelines[6] for long-lasting chronic nasal cavity inflammation, and may be more effective than antihistamines in controlling symptoms.[41] Topical nasal steroids may improve lower airway inflammation in patients with established AR and asthma as follows: reduction in nasal inflammation, improvement in nasal airflow, reduction in the nasopulmonary reflex,[42,43] decrease in IL-4 and IL-5 expression, promotion of transforming growth factor (TGF)-beta expression, decreased influx of eosinophils into the nose,[42] and promotion of epithelial reconstitution.[44] Improvement in bronchial responsiveness from intranasal steroids has been theorized to occur because of reduction of postnasal rhinorrhea, mild systemic absorption, and inhalation into the bronchial lower airway.[42] Remarkably, a Mayo Clinic study demonstrated that topical nasal steroid treatment with beclomethasone in patients with ragweed AR and coexisting asthma unexpectedly improved both AR and asthma symptoms.[45]

Initial treatment of children with chronic nasal obstruction attributed to AR with intranasal budesonide resulted in decreased asthma scores and reduced exercise induced bronchoconstriction; however, the study was unable to exclude the possibility of intranasal intrapulmonary deposition of steroids.[46] More recently though, intranasal corticosteroids have been shown to likely improve asthma symptoms by improving nasal function rather than a direct effect on the lungs because less than 2% is delivered to the lung, and only a small amount is swallowed and absorbed through the gastrointestinal tract.[47]

Recent clinical trials have shown that topical nasal steroids reduce inflammation, polyposis, and may improve concomitant asthma symptoms.[48] Treatment with intranasal aqueous beclomethasone in patients with AR and concomitant asthma for as few as 4 weeks improved bronchial hyperreactivity and evening/morning asthma symptom scores.[47] This is further supported by evidence that patients with asthma and AR were observed to improve bronchial hyperresponsiveness with nasal beclomethasone after exposure to ragweed pollen[48] within 6 weeks of therapy; compared to patients treated with intranasal beclomethasone, patients in the placebo group had significantly worse bronchial responsiveness to inhaled methacholine.[48] Intranasal and oral inhaled budesonide, when combined, have been shown to improve peak expiratory flow, rescue inhaler requirement, asthma score, and daily activity score.[49] Improvement in lower airway disease symptoms, need for pharmacotherapy, bronchial hyperresponsiveness, and FEV1 has been duplicated with intranasal mometasone,[50] fluticasone,[42] and triamcinolone.[51] Improvement has been observed in patients as early as the first day of treatment.[50]

Extraordinarily, patients with pollen-induced AR who received mometasone intranasal therapy, training on the proper use of nasal sprays, and a lesson on the relationship of AR and asthma had significantly fewer asthma symptoms and required less pharmacotherapy than patients without detailed training.[52] Furthermore, improvement in asthma symptoms may be extrapolated to reduce utilization of health care services. A retrospective cohort of children and adult patients aged 12 to 60 years treated with intranasal corticosteroids for AR resulted in one-half the risk of asthma-related events such as hospitalizations compared to untreated patients.[53] Last, analysis of health insurance claims in a large cohort of patients showed the greatest reduction in emergency department visits for patients with asthma occurred in those who received the greatest number of prescriptions for topical nasal steroids.[54]

Most studies examined have shown clinical improvement in asthma with concomitant use of intranasal steroids

for AR. However, the Preventive Allergy Treatment (PAT) study demonstrated in a multicenter open clinical trial that the use of nasal steroids was lowest in children who ultimately did not develop asthma.[55] Although intranasal corticosteroids are generally considered to be safe and well-tolerated, a recent meta-analysis demonstrated concerns regarding decreased knemometry growth in children with as short as 4 weeks of treatment,[56] potentially limiting long-term use for children with concomitant AR and asthma.

ASI in the improvement and prevention of asthma

ASI should be strongly considered in patients with allergic diseases, those who prefer to potentially avoid long-term pharmacotherapy, and those who desire to alter immunological tolerance to improve asthma symptoms, bronchial hyperresponsivness, and pulmonary function. With ASI, small, controlled doses of allergens are given to patients over a period of time and titrated to doses necessary to promote immune tolerance.[57] The mechanism of action of ASI is likely the result of a switch from TH2-mediated to TH1-mediated immunity with a subsequent reduction in the production of IL-4, IL-5, and IL-13 cytokines, resulting in reduced upper and lower airway inflammation.[58] ASI may prevent progression from AR to asthma.[59] Clinicians should refer patients with AR for immunotherapy who have had an inadequate reduction in symptoms with standard pharmacotherapy according to current practice guidelines.[6]

Subcutaneous immunotherapy (SCIT) has been shown to improve asthma symptoms, pulmonary function, and reduce pharmacotherapy intake in a large meta-analysis consisting of prospective, randomized controlled trials involving 962 patients suffering from asthma.[60] A Cochrane review studying SCIT specific to dust mite, pollen/grass, animal dander, and mold evaluated 88 studies consisting of 3459 subjects with asthma, and found that SCIT improved asthma symptoms, reduced pharmacotherapy use, and decreased bronchial hyperresponsiveness[61] against dust mite and pollen allergens. The overall conclusion was that treatment of 3 asthma patients with allergen SCIT would prevent an asthma exacerbation in 1 person, and treatment of 4 asthma patients would decrease pharmacotherapy use and bronchial hyperresponsiveness in 1 person; however, there was no consistent effect of immunotherapy on lung function or reduction of asthma symptoms when using animal dander extracts.[61] Long-term prevention of asthma in allergy sensitized children with immunotherapy has also been shown. Over an observation period of 14 years, 72% of children with asthma treated with ASI compared with 22% of children treated with placebo were free of asthma.[62] Long-term prevention of asthma has been shown at follow-up at 5 years[63] and 10 years[15] despite 2-year termination of immunotherapy.

The development of sublingual immunotherapy (SLIT) in the 1980s was an important advancement, with reduction in systemic side effects from SCIT and improved tolerance in pediatric patients.[8] SLIT has also been studied extensively; 2 large meta-analyses consisting of 256 children and 1000 adults and children showed significant improvement in asthma symptom and medication requirement scores.[21,64] Similarly, the Efficacia nella rinite allergica di SlitOne (EFESO) trial in Italy demonstrated that adults with AR who later developed asthma were significantly less likely to have been treated with 2 years of SLIT compared to individuals taking traditional pharmacotherapy.[65] A comprehensive systematic review found modest evidence to support that SLIT improves asthma symptoms.[66] The cumulative strength of evidence has been suggested to be class 1a for SCIT and class 1b for SLIT in preventing the subsequent development of asthma[67,68] by inducing immunological tolerance with continued clinical improvement despite cessation of treatment. Despite the overwhelming evidence, there are no sublingual aqueous forms of immunotherapy approved for use by the U.S. Food and Drug Administration (FDA), but tablet forms were approved in 2014 for ragweed and grass pollen.[66]

Dust mites

Two large meta-analyses consisting of 441 children and 452 children with asthma showed that treatment with dust mite SLIT resulted in decrease in symptom and medication scores compared to placebo.[69,70] Nearly one-half of patients allergic to house dust mites that were treated with *Dermatophagoides pteronyssinus* extract encapsulated in liposomes showed decreased symptom and medication scores after only 1 year of therapy.[71] In addition, children and adults with asthma exacerbations attributed to house dust mite allergies have demonstrated significant reductions in asthma exacerbations, decrease need for pharmacotherapy, and decreased bronchial hyperreactivity after treatment with allergen-specific SCIT for 3 years.[22,72,73]

In children aged 6 to 17 years with asthma and allergies to house dust mites, SCIT resulted in mean daily fluticasone propionate reductions from 330.3 μg to 151.5 μg compared to no reduction in the control group. Surprisingly, patients treated with SCIT to *D. pteronyssinus* in a 6-week cluster accelerated regimen were observed to have faster decreases in asthma symptoms compared to patients in the conventional 12-week schedule.[74] A small randomized controlled trial consisting of children with mild persistent asthma and rhinitis treated with 12 months of SLIT, SCIT, or standard pharmacotherapy, showed significant decreases in total asthma scores in children treated with immunotherapy.[75] Children receiving 12 months of sublingual immunotherapy to standardized *D. pteronyssinus* and *Dermatophagoides farinae* also showed improvement in forced expiratory flow, bronchial hyperactivity, reduction in the number of acute asthma exacerbations, and significant reduction in the need for pharmacotherapy; clinical improvement was even noted as early as 6 months.[76] However, a recent Cochrane review found only a

borderline reduction in asthma symptoms among studies treating patients with dust mite immunotherapy.[61]

Pollen

Overall, a recent Cochrane review demonstrated superior reduction in asthma symptoms with immunotherapy extracts of pollen compared to dust mites.[61] Grass pollen SCIT given to asthma patients aged 3 to 16 years over 2 seasons have showed decreased asthma symptoms scores, decreased need for pharmacotherapy, and improvement in bronchial reactivity to allergens.[77] A large multicenter clinical trial (the PAT study), the first prospective long-term follow-up study testing the hypothesis of whether ASI may reduce the development of asthma, showed that ASI in children with grass and/or birch allergy for 3 years resulted in significantly fewer asthma symptoms after 5 years[55] and 10 years[15] despite treatment termination after 2 years. However, bronchial responsiveness to methacholine showed no significant improvement, attributed to possibly the natural history of improvement in control patients from infancy to adulthood.

Tree pollen SLIT for over 2 years has likewise been shown to decrease asthma symptoms, decrease pharmacotherapy use, increase force expiratory volumes, and decrease rescue medication usage.[78,79] In Italy, SCIT to *Parietaria judaica* pollen reduced development of new asthma symptoms from 47% to 14%, reduced prevalence of asthma by 12%, and the need for rescue medications; however, bronchial hypersensitivity and sputum eosinophilia were unchanged.[59] It is estimated that 6.6 patients with AR need to undergo immunotherapy with *Parietaria* to prevent 1 patient from subsequently developing asthma.[59] Long-term asthma prevention was shown at follow-up 6 years after termination of immunotherapy, with none of the patients initially presenting with rhinitis developing asthma.[79] Similar findings have been demonstrated in children with seasonal allergic rhinoconjunctivitis caused by allergy to birch and grass pollen; children treated with specific immunotherapy with grass[81] and birch allergens[55] were over 3 times less likely to develop asthma after 3 years.[80] It has been estimated that atopic children not undergoing immunotherapy are 3.8 times more likely to develop asthma than similar children undertaking ASI.[80] A large meta-analysis of 441 children with asthma showed that treatment with pollen SLIT reduced symptom and medication scores compared to placebo.[69] Patients undergoing SLIT with birch and *Parietaria* showed improvement in methacholine sensitivity/bronchial hyperresponsiveness,[81] pulmonary function, and nasal eosinophil counts as early as 12 months, likely due to the estimated 12-fold increase in cumulative dose compared to SCIT.[78]

Conclusion

There is a very strong anatomic, functional, and immunologic relationship between the nasal upper airway and bronchial lower airway. Nasal stimulation by airborne allergens induces nasal obstruction and edema, thereby reducing nasal breathing and filtration, leading to bronchial inflammation and lower airway obstruction. A common mechanism proposed includes local irritation of the nasal mucosa leading to upregulation of inflammatory mediators within the respiratory tract.[82] Asthma may be the most significant potential morbidity in patients suffering from AR. Understanding the critical environmental risk factors influencing AR to later manifest as bronchial asthma is crucial to implementing effective pharmacotherapy. Traditional pharmacotherapy with antihistamines and topical intranasal steroids has overall been shown to improve the symptoms of AR with concomitant allergic asthma; however, only ASI offers long-term control and outcomes in improving asthma symptoms, reduces exacerbations, and likely prevents development of asthma. The mechanism of action of ASI is likely the result of a switch from TH2-mediated to TH1-mediated immunity with a subsequent decrease in IL-4, IL-5, and IL-13 cytokines, resulting in reduced upper and lower airway inflammation. Treatment of AR proactively has been shown to reduce asthma symptoms, bronchial hyperreactivity, and reduce the need for pharmacotherapy. Additional studies are necessary to examine whether early treatment of AR may ultimately prevent the progression to asthma, though clinical studies to date seem to support this hypothesis as well.

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REVIEW ARTICLE

Comorbidities of asthma and the unified airway

Robert J. Stachler, MD, FACS[1,2]

Background: **Asthma is a comorbid condition that may be seen by otolaryngic allergists when treating their patients with allergic rhinitis (AR). Often asthma is overlooked when aggressive treatment could prevent the development or progression of early disease.**

Methods: **This article is a retrospective review of the current literature on asthma as a comorbidity of the unified airway. The unified airway and asthma are clearly defined. The epidemiology, morbidity, mortality, pathophysiologic mechanisms, and the chronicity of asthma are reviewed.**

Results: **The otolaryngic allergist will become familiar the unified airway concept and the close relationships between AR, chronic rhinosinusitis, and asthma.**

Conclusion: **Otolaryngologists should be aware of the unified airway in order to most effectively treat their patients with AR. Knowledge of the close relationships between asthma and AR will help prevent progression of disease, identify early asthma, and improve the outcomes and quality of life for our patients.**

Key Words:
asthma; unified airway; allergy; rhinitis; chronic rhinosinusitis; allergic rhinitis

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Asthma is perhaps the most overlooked diagnosis in the field of otolaryngology–head and neck surgery. Clinicians need to be able to recognize the complex interrelationships that coexist between asthma and allergy due to the unified airway. Both diseases are very similar, and if managed appropriately, stop the progression to more advanced disease.

The unified airway model

The unified airway concept[1–3] has been popular over the last 20 years. This concept closely links the middle ear, nose, and paranasal sinuses, all the way down to the distal bronchioles, as one functional group or unit. Rhinitis, sinusitis, and asthma are closely linked epidemiologically and pathophysiologically. There is shared inflammation that occurs due to close communication among cellular and humoral components of the immune system.[4,5] Braunstahl et al.[4] showed propagation and sustained responses locally, regionally, and systemically when one discrete area of the respiratory tract was stimulated. Distal inflammatory effects subsequently ensued, far away from the initial inciting event. This implies that exacerbations of disease in one area will lead to concurrent or subsequent worsening of disease in other respiratory units.[6] Allergic respiratory disease thus affects the entire upper and lower aerodigestive tract, linking allergic rhinitis (AR) with asthma in various severities.[6] Patients with upper airway disease have a higher prevalence of lower-tract disease. Conversely, those with lower-tract disease have an increased incidence of upper airway involvement. Thus, any intervention in either tract will influence symptoms in the other.[3]

Asthma defined

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms, such as wheezing, shortness of breath, chest tightness, and cough, that vary over time and in intensity, together with variable expiratory airflow limitation.[7] The symptoms and airflow limitation may vary over time and in intensity. These variations can be caused

[1]*Department of Otolaryngology–Head and Neck Surgery, Henry Ford Medical Group, Detroit, MI;* [2]*Department of Otolaryngology–Head and Neck Surgery, Wayne State University, Detroit, MI*

Correspondence to: Robert J. Stachler, MD, FACS, Department of Otolaryngology–Head and Neck Surgery, 2799 West Grand Blvd, K8, Detroit, MI 48202; e-mail: rstachl1@hfhs.org

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by many inciting events, such as exercise, allergen or irritant exposure, change in weather, or viral respiratory infection. The symptoms and airflow limitation can resolve and respond to medications, or may be very subtle and not be noticed for some time. Episodic flare-ups can occur, which can be life threatening. Asthma is associated with airway hyperresponsiveness to direct or indirect stimuli. In some cases, a complex process is initiated involving inflammatory mediators, eosinophils, mast cells, T lymphocytes, neutrophils, and epithelial cells. Chronicity of the condition, if it occurs, leads to advanced disease and airway remodeling. This may lead to irreversible pulmonary mucosal changes. These changes, inflammation with ensuing airway obstruction, can result in the classic symptoms of wheezing, chest tightness, coughing, and breathlessness.[8] Clinicians need to focus primarily on the inflammatory component of the disease to prevent the chronic changes that can occur, while treating the reversible increased bronchial reactivity. Uncontrolled asthma or suboptimal management may result in the chronic changes the clinician is trying to avoid.

TABLE 1. Similar histopathologic findings in CRS and asthma

Mucosal edema
Vasodilation
Cellular (eosinophil and lymphocyte) infiltration
Major basic protein deposition
Thickening of the basement membrane
Hyperplasia of the goblet cells
Mucous gland hypertrophy
Angiogenesis
Collagen deposition
Epithelial damage
Subepithelial fibrosis

CRS = chronic rhinosinusitis.

Relationships between asthma and upper airway disease

Asthma has been noted to be closely related to AR. Corren,[9] in 1997, reviewed this relationship and found that 78% of asthmatics have nasal symptoms. Thirty-eight percent (38%) of patients with rhinitis (AR and non-AR) will have asthma. His data also suggests that rhinitis often precedes the development of asthma. Other authors[10,11] have shown a 3-fold increase in asthma over a 20-year period in allergic patients when compared to nonallergic controls. Guerra et al.'s study[10] also showed that patients with higher serum immunoglobulin E (IgE) levels at the onset of the study had a 5-fold increase in their risk of developing asthma. Shaaban et al.,[12] in a longitudinal population-based study noted that the presence of AR increases the relative risk for asthma to 3.53 (95% confidence interval [CI], 2.11 to 5.91). The relative risk for asthma in patients with non-AR was 2.71 (95% CI, 1.64 to 4.46). AR clearly is often discovered concurrently with asthma, and predisposes one to develop asthma over time.

Asthmatic Nordic children with AR had a higher risk of hospital readmissions and more hospital days per year compared to asthmatic patients without rhinitis.[13] Nasal symptoms have been associated with asthma. Patients with nasal complaints (congestion, itching, and rhinorrhea), should be carefully evaluated for asthma. Bronchial hyperactivity has been demonstrated in patients with AR who were unaware of their pulmonary condition.[14,15] Clinicians, otolaryngologists, pulmonologists, and primary care physicians need to consider asthma on a more regular basis when evaluating patients with severe nasal complaints.

AR has been shown to worsen the overall prognosis of asthma.[16] Those who have asthma and AR have more severe lower respiratory disease and account for more costs to the healthcare system. Tight control of the AR leads to improved asthma control and vice versa.[16–18]

Chronic rhinosinusitis, histopathologically, appears similar to asthma.[19] The nasal mucosa remodels and thickens in a similar manner seen with chronic changes in the bronchial mucosa. Under the microscope the findings are nearly indistinguishable (Fig. 1). Remodeling is due to mucosal edema, submucosal gland and bronchial smooth muscle hypertrophy, collagen deposition, basement membrane thickening, and subepithelial fibrosis in the lamina reticularis (Table 1). The only finding that is different is the mucosal thickening is not as noted in the nose in rhinitis as it is in the bronchial airway in asthma patients.

Nasal polyposis is associated with rhinitis and asthma. It is one of the diagnostic criteria for allergic fungal rhinosinusitis.[20] Aspirin-sensitive respiratory disease is another condition with a strong association of polyps, rhinosinusitis, and asthma. It occurs when one has an allergy to aspirin or other nonsteroidal anti-inflammatory agents. Aspirin ingestion leads to an intense inflammatory response of the upper and lower airways, exacerbations of rhinosinusitis, and asthma (Samter's triad).[21] Awad et al.[22] reported that aspirin-intolerant asthmatics had statistically superior asthma outcomes with endoscopic sinus surgery for chronic rhinosinusitis compared to aspirin-tolerant sinus surgery patients.

Chronic rhinosinusitis patients with asthma have a higher rhinosinusitis severity score (Lund-Mackay score) than nonasthmatic patients and more nasal polyps regardless of atopic status, indicative of a strong relationship between chronic rhinosinusitis severity and chronic airway inflammatory diseases, asthma, and nasal polyps.[23] Asthmatic patients with coexistent symptomatic chronic sinusitis have greater asthmatic severities requiring more aggressive management to gain control of the condition.[24–31] Both medical and surgical treatment of chronic rhinosinusitis has been

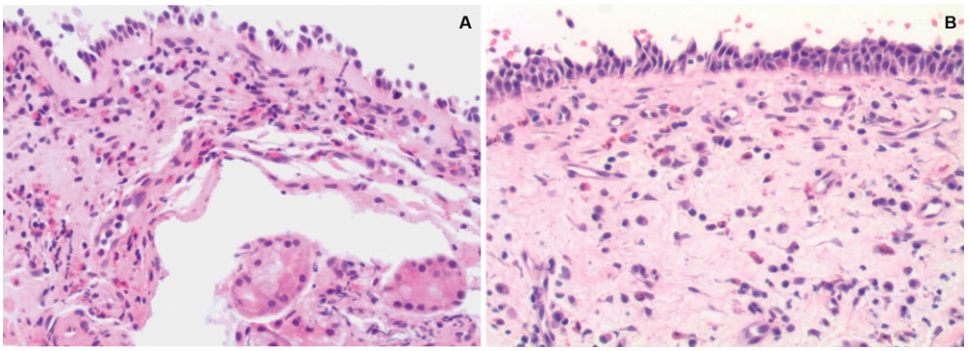

FIGURE 1. (A) Bronchial airway: asthma. (B) Chronic rhinosinusitis: sinonasal epithelium. Note the similarities and the chronic inflammatory infiltrates with increased numbers of eosinophils in both A and B. Note the remodeling and narrowing of the airway in A.

associated with subjective and objective improvements in asthma.[24,32]

Epidemiologic relationships

AR has a prevalence of between 15% and 40%.[33,34] Asthma affects 7% to 8% of the population.[33,34] Between 75% and 80% of atopic and nonatopic people with asthma have rhinitis. Rhinitis is also a risk factor for developing asthma.[35] In children aged 6 to 11 years the male to female ratio of asthma is 3:2 for affected individuals. Older children (aged 12 to 17 years) have a male to female ratio of 8:5.[36] It is theorized that males have smaller airways for a given lung size than females.[37] The smaller airways may predispose males to more wheezing and lower respiratory illnesses. As the males grow older, the ratio normalizes then reverses later in life, resulting in a larger female component.

The development of atopy in early childhood, before 6 years of age, is a risk factor for increased bronchial hyperresponsiveness in late childhood.[37] The presence of AR predisposes one to a greater risk of bronchial hyperactivity even before asthma is diagnosed. Eleven percent (11%) to 32% of patients who have seasonal AR will have bronchial hyperresponsiveness with a methacholine challenge outside of their allergic season. During the season, 48% will have a positive methacholine challenge test.[38] About 50% of patients with perennial AR without asthma showed hyperresponsiveness to bronchial challenge. Only 25% of sensitized individuals sensitized to 1 or more allergens go on to develop asthma.[39] Linneberg et al.[40] showed that sensitivity to perennial allergens significantly increases one's risk of developing asthma compared to those sensitized to seasonal allergens. Seasonal AR patients had a 10-fold greater risk of developing asthma, compared to a 50-fold increase in risk for those who have perennial allergies.[41]

Certain risk factors have been noted for the development of asthma. Tobacco exposure is a significant risk factor in the development of asthma in children[42] and the morbidity of asthma in adults.[43] Obesity is a risk factor for development of and the expression of asthma.[44] Recurrent viral throat infections, ie, respiratory syncytial virus (RSV), increases a child's risk of developing asthma later in childhood.[45] Other factors including prematurity, air pollution, and atopy help to contribute to the development of asthma.

Morbidity and mortality

There were 13.9 million outpatient visits for asthma in 2002. Most visits were in children under the age of 18 years (687 per 10,000) compared to those older than 18 years (181 per 10,000).[36] The utilization of emergency room (ER) services is increasing over time. Unscheduled visits to the ER increased to 1.9 million in 2002. Children under the age of 4 years were most affected. African American children were 4 times as likely as Caucasian children to go to the ER for their asthma. Hospitalizations for asthma increased 200% in children and 50% in adults from 1960 to 1980.[45] The cost of asthma continues to climb over time. Per person costs per year for asthmatics are $1300. Asthma-related costs have risen over 50% from 1984 to 1994. The direct and indirect costs in the United States were $12 billion. Only 10% to 20% of patients have severe asthma, which accounts for 50% of the total cost of treatment rendered to this population.

Fortunately, asthma deaths are rare under the age of 15 years. The 1978 mortality rate from asthma was 0.8/100,000, and increased to 2.0/100,000 in 1989. It went up to 2.1/100,000 in 1994. A drop in the year 2000, to 1.6/10,000, was noted. The 2002 mortality rate for asthma was noted to be 1.5 per 100,000. The African American mortality rate is 200% higher than the rate in Caucasian children at 3.7 per 100,000.[36] Clearly some racial disparity exists between the patients afflicted with this disease.

Pathophysiology

There are 2 key mechanisms that are proposed to explain the pathophysiology of asthma: inflammatory mechanisms, which include local reactions and distal crosstalk in the airway; and systemic, neurogenic mechanisms.

Inflammatory mechanisms

Local inflammation occurs when an inhaled antigen causes an IgE-mediated type 1 hypersensitivity reaction. This initiates an inflammatory cascade, characterized by mast cell degranulation. Preformed mediators including histamine, kinins, and proteases are released, which causes chemotaxis and migration of other sensitized mast cells, neutrophils, basophils, eosinophils, T lymphocytes, and macrophages across a mucosal endothelium into the local area (nose or bronchial mucosa) and submucosa. Vascular leakage and interstitial edema occur, causing pruritis, rhinorrhea, nasal congestion, and sneezing.[46] This response is linked by upregulated systemwide inflammatory mediators at distal sites in the respiratory tract (lined by pseudostratified columnar epithelium).[41,47–49] Braunstal et al.[41,48,49] and Georgopoulos et al.[47] noted in a series of studies that antigens placed in the nose resulted in upregulation of inflammatory mediators in the distal bronchi. Similarly, they noted that antigen placement into the bronchi with a bronchoscope resulted in upregulation of inflammatory mediators in the nose. Interactions between inflammatory cells, mast cells, alveolar macrophages, eosinophils, lymphocytes, neutrophils, basophils and associated mediators, histamine, leukotrienes, prostaglandin D_2, and platelet-activating factor cause bronchial smooth muscle contraction.[7,50] This late-phase response will occur several hours after an initial response because it requires an influx of inflammatory cells and can lead to chronic changes. The eosinophils seem to have the greatest increase in proportion to other inflammatory cells in this timeframe.[50,51] These reactions show that allergic changes in one area can effect the whole unified airway. This links the allergic reactions to distal locations in the unified airway.

Eosinophils and their release of their cationic proteins (major basic protein [MBP], eosinophil cationic protein [ECP], peroxidase, and eosinophil-derived neurotoxin [EDN]) is the cardinal feature of allergic pathophysiology.[52–54] The eosinophil is drawn to the inflammatory reaction by the T helper 2 (TH2) cytokine interleukin 5 (IL-5).[55] IL-5 mediates eosinophil expansion, priming, recruitment, and prolonged tissue survival in allergic reactions.[55] IL-5, IL-4, IL-13, and eotaxins (eosinophil-specific chemokines) are responsible for promoting the eosinophil-mediated inflammatory responses.[55] Endothelial adhesion proteins, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM1) assist in the migration of neutrophils, lymphocytes, and eosinophils from the intravascular space into the airway.[50,56–59] Other cells in the inflammatory process, mast cells, release their mediators and histamine causing leukotrienes to be created, which cause bronchoconstriction. The eosinophil release of the toxic proteins causes endothelial cell damage and airflow obstruction.[50] Histologically, these processes create the mucosal edema, submucosal gland and bronchial smooth muscle hypertrophy, mucous hypersecretion, basement membrane thickening, and fibrosis classically seen in asthma.[50,60–62]

Systemic, neurogenic mechanisms

Neuronal stimulation in the nose can result in the release of cholinergic neurotransmitters and contraction of the bronchial smooth muscle.[63,64] This reaction links a local response to a systemic, distal location. Furthermore, there is strong evidence that links the distribution of inflammatory mediators from an initial inflammatory site to lymphoid tissue[65] and marrow, amplifying the inflammatory responses across the nasal passages, sinuses, and lower airways. Increased blood eosinophil and IL-5 levels in the upper and lower airways were shown when a single antigen challenge was administered to nonasthmatic subjects with seasonal allergy.[66] Bronchial hyperresponsiveness was noted when atopic patients with AR and asthma were given a nasal challenge.[67] Nasal challenges in allergic patients without asthma resulted in increased bronchial expression of adhesion molecules (VCAM-1, ICAM-1, and endothelial-leukocyte adhesion molecule 1). As discussed previously in the inflammatory mechanisms section, these molecules are responsible for assisting in the transport of the eosinophil from the circulation into the airway, reducing the peak expiratory airflow[41] as the numbers of the cells in the area increase and the inflammation from the reaction begins to augment.

Bronchial challenge with antigens, in nonasthmatic, allergic patients, resulted in an intense nasal inflammatory reaction causing immune cell degranulation, and increased IL-5 levels in peripheral blood.[49] This suggests that stimulation can occur anywhere within the unified airway.

Neuroregulatory mechanisms from vagal nerve activation may cause bronchoconstriction of the bronchial smooth muscle. Neuromediators, substance P and calcitonin gene–related peptide, modulate the release of histamine and bradykinin, which cause unrestricted passage of proteins and fluid through the vascular epithelium. Direct cholinergic neurotransmitter release may cause stimulation of the bronchial smooth muscle.[68–70] The results is bronchoconstriction, which is a defining characteristic of asthma.

Chronicity of asthma

Asthma is a chronic disease of the lower airways that has 3 defining characteristics: (1) airway inflammation; (2) reversible airway obstruction, in most cases; and (3) increased airway responsiveness to extrinsic stimuli.[71] The inflammation that is the hallmark of asthma may be present for many years and is undetectable until the symptoms of asthma begin to appear. As described previously, in the prior two sections, the eosinophil appears to be the key inflammatory cell in the destructive process at the cellular level. The chronic inflammation that develops causes airway

remodeling. Remodeling involves tissue injury and subsequent repair. The pathophysiologic events included in this phenomenon are mucosa edema, vasodilation, cellular infiltration, epithelial injury, smooth muscle and mucous gland hypertrophy, angiogenesis, collagen deposition, basement membrane thickening, and subepithelial fibrosis in the lamina reticularis[50,60–62] (Table 1). Similar findings are seen in chronic rhinosinusitis although the reticular basement membrane thickening is not as pronounced in the nasal epithelium as it is in the bronchial epithelium.

It is important to note than even when symptoms appear to be under control, the inflammatory process in asthma can be ongoing and progressive.[72]

Conclusion

It is essential that otolaryngologists, head and neck surgeons, and allergists become familiar with the unified airway concept when managing our patients with AR. Asthma and AR are closely related epidemiologically and biologically.[1–12] Early and aggressive therapy to treat AR may prevent the progression of the disease to asthma. Healthcare providers who are aware of the close relationship of AR to asthma may be able to identify the early signs of asthma, enabling prompt treatment and preventing disease progression. Furthermore, appropriate management of AR has been shown to improve asthma control.

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