

# Clinical Practice Guideline (Update): Adult Sinusitis

Richard M. Rosenfeld, MD, MPH<sup>1</sup>, Jay F. Piccirillo, MD<sup>2</sup>,  
 Sujana S. Chandrasekhar, MD<sup>3</sup>, Itzhak Brook, MD, MSc<sup>4</sup>,  
 Kaparaboyana Ashok Kumar, MD, FRCS<sup>5</sup>, Maggie Kramper, RN, FNP<sup>6</sup>,  
 Richard R. Orlandi, MD<sup>7</sup>, James N. Palmer, MD<sup>8</sup>, Zara M. Patel, MD<sup>9</sup>,  
 Anju Peters, MD<sup>10</sup>, Sandra A. Walsh<sup>11</sup>, and Maureen D. Corrigan<sup>12</sup>

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## Abstract

**Objective.** This update of a 2007 guideline from the American Academy of Otolaryngology—Head and Neck Surgery Foundation provides evidence-based recommendations to manage adult rhinosinusitis, defined as symptomatic inflammation of the paranasal sinuses and nasal cavity. Changes from the prior guideline include a consumer added to the update group, evidence from 42 new systematic reviews, enhanced information on patient education and counseling, a new algorithm to clarify action statement relationships, expanded opportunities for watchful waiting (without antibiotic therapy) as initial therapy of acute bacterial rhinosinusitis (ABRS), and 3 new recommendations for managing chronic rhinosinusitis (CRS).

**Purpose.** The purpose of this multidisciplinary guideline is to identify quality improvement opportunities in managing adult rhinosinusitis and to create explicit and actionable recommendations to implement these opportunities in clinical practice. Specifically, the goals are to improve diagnostic accuracy for adult rhinosinusitis, promote appropriate use of ancillary tests to confirm diagnosis and guide management, and promote judicious use of systemic and topical therapy, which includes radiography, nasal endoscopy, computed tomography, and testing for allergy and immune function. Emphasis was also placed on identifying multiple chronic conditions that would modify management of rhinosinusitis, including asthma, cystic fibrosis, immunocompromised state, and ciliary dyskinesia.

**Action statements.** The update group made *strong recommendations* that clinicians (1) should distinguish presumed ABRS from acute rhinosinusitis (ARS) caused by viral upper respiratory infections and noninfectious conditions and (2) should confirm a clinical diagnosis of CRS with objective documentation of sinonasal inflammation, which may be accomplished using anterior rhinoscopy, nasal endoscopy, or computed tomography. The update group made *recommendations* that clinicians (1) should either offer watchful waiting (without antibiotics) or

prescribe initial antibiotic therapy for adults with uncomplicated ABRS; (2) should prescribe amoxicillin with or without clavulanate as first-line therapy for 5 to 10 days (if a decision is made to treat ABRS with an antibiotic); (3) should reassess the patient to confirm ABRS, exclude other causes of illness, and detect complications if the patient worsens or fails to improve with the initial management option by 7 days after diagnosis or worsens during the initial management; (4) should distinguish CRS and recurrent ARS from isolated episodes of ABRS and other causes of sinonasal symptoms; (5) should assess the patient with CRS or recurrent ARS for multiple chronic conditions that would modify management, such as asthma, cystic fibrosis, immunocompromised state, and ciliary dyskinesia; (6) should confirm the presence or absence of nasal polyps in a patient with CRS; and (7) should recommend saline nasal irrigation, topical intranasal corticosteroids, or both for symptom relief of CRS. The update group stated as *options* that clinicians may (1) recommend analgesics, topical intranasal steroids, and/or nasal saline irrigation for symptomatic relief of viral rhinosinusitis; (2) recommend analgesics, topical intranasal steroids, and/or nasal saline irrigation) for symptomatic relief of ABRS; and (3) obtain testing for allergy and immune function in evaluating a patient with CRS or recurrent ARS. The update group made *recommendations* that clinicians (1) should not obtain radiographic imaging for patients who meet diagnostic criteria for ARS, unless a complication or alternative diagnosis is suspected, and (2) should not prescribe topical or systemic antifungal therapy for patients with CRS.

## Keywords

adult sinusitis, rhinosinusitis

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## Differences from Prior Guideline

This clinical practice guideline is as an update, and replacement, for an earlier guideline published in 2007 by the American Academy of Otolaryngology—Head and Neck Surgery Foundation (AAO-HNS).<sup>1</sup> An update was planned

for 5 years after the initial publication date and was further necessitated by new primary studies and systematic reviews that might suggest a need for modifying clinically important recommendations.<sup>2</sup> Changes in content and methodology from the prior guideline include the following:

- Addition of a consumer advocate to the guideline development group
- New evidence from 5 clinical practice guidelines, 42 systematic reviews, and 70 randomized controlled trials
- Emphasis on patient education and counseling with new explanatory tables
- Expanded action statement profiles to explicitly state quality improvement opportunities, confidence in the evidence, intentional vagueness, and differences of opinion
- Enhanced external review process to include public comment and journal peer review
- New algorithm to clarify decision-making and action statement relationships
- Extension of watchful waiting (without antibiotic therapy) as an initial management strategy to all patients with uncomplicated acute bacterial rhinosinusitis (ABRS) regardless of severity, not just patients with “mild” illness (prior guideline)
- Change in recommendation from first-line antibiotic therapy for acute bacterial rhinosinusitis amoxicillin, with or without clavulanate, from amoxicillin alone (prior guideline)
- Addition of asthma as a chronic condition that modifies management of chronic rhinosinusitis (CRS)
- Three new key action statements on managing CRS that focus on polyps as a modifying factor, a recommendation in favor of topical intranasal therapy (saline irrigations, corticosteroids), and a recommendation against using topical or systemic antifungal agents

## Introduction

Sinusitis affects about 1 in 8 adults in the United States, resulting in over 30 million annual diagnoses.<sup>3,4</sup> The direct cost of managing acute and chronic sinusitis exceeds \$11 billion per year,<sup>4,5</sup> with additional expense from lost productivity, reduced

job effectiveness, and impaired quality of life.<sup>6–8</sup> More than 1 in 5 antibiotics prescribed in adults are for sinusitis, making it the fifth most common diagnosis responsible for antibiotic therapy.<sup>5</sup> Despite the high prevalence and economic impact of sinusitis, considerable practice variations exist across and within the multiple disciplines involved in managing the condition.<sup>9,10</sup>

The target patient for this guideline is age 18 years or older with a clinical diagnosis of uncomplicated rhinosinusitis:

- *Rhinosinusitis* is defined as symptomatic inflammation of the paranasal sinuses and nasal cavity. The term *rhinosinusitis* is preferred because sinusitis is almost always accompanied by inflammation of the contiguous nasal mucosa.<sup>11–13</sup> Therefore, *rhinosinusitis* is used in the remainder of the guideline.
- *Uncomplicated rhinosinusitis* is defined as rhinosinusitis without clinically evident extension of inflammation outside the paranasal sinuses and nasal cavity at the time of diagnosis (eg, no neurologic, ophthalmologic, or soft tissue involvement).

Rhinosinusitis may be classified by duration as *acute* rhinosinusitis (ARS) if less than 4 weeks' duration or as *chronic* rhinosinusitis (CRS) if lasting more than 12 weeks, with or without acute exacerbations. ARS may be classified further by presumed etiology, based on symptoms and time course (Key Action Statement 1), into acute *bacterial* rhinosinusitis (ABRS) or *viral* rhinosinusitis (VRS). Distinguishing presumed bacterial vs viral infection is important because antibiotic therapy is inappropriate for the latter. When patients have 4 or more annual episodes of rhinosinusitis, *without* persistent symptoms in between, the condition is termed *recurrent* ARS.

Nearly all authorities agree that CRS begins after 12 weeks' duration, but opinions about the duration of ARS vary, with some defining illness up to 12 weeks as ARS.<sup>14</sup> We agree with other guideline groups<sup>15,16</sup> that define ARS as up to 4 weeks' duration but recognize that this boundary is based more on consensus than research evidence. Moreover, very limited data are available on rhinosinusitis lasting 4 to 12 weeks, sometimes called *subacute* rhinosinusitis. We do not distinguish rhinosinusitis in this time frame as an explicit entity in the guideline, and decisions about whether such patients are more like ARS or CRS must therefore be individualized.

<sup>1</sup>Department of Otolaryngology, SUNY Downstate Medical Center, Brooklyn, New York, USA; <sup>2</sup>Department of Otolaryngology—Head and Neck Surgery, Washington University in St Louis, School of Medicine, St Louis, Missouri, USA; <sup>3</sup>New York Otolaryngology, New York Head and Neck Institute, New York, New York, USA; <sup>4</sup>Department of Pediatrics, Georgetown University, Washington, DC, USA; <sup>5</sup>Department of Family Medicine, University of Texas Health Sciences Center at San Antonio, San Antonio, Texas, USA; <sup>6</sup>Department of Otolaryngology, Washington University in St Louis School of Medicine, St Louis, Missouri, USA; <sup>7</sup>Division of Otolaryngology, University of Utah School of Medicine, Salt Lake City, Utah, USA; <sup>8</sup>Department Otolaryngology, University of Pennsylvania Hospital, Philadelphia, Pennsylvania, USA; <sup>9</sup>Department of Otolaryngology Head & Neck Surgery, Emory University, Atlanta, Georgia, USA; <sup>10</sup>Department of Internal Medicine, Northwestern University Allergy Division, Chicago, Illinois, USA; <sup>11</sup>Consumers United for Evidence-Based Healthcare, Davis, California, USA; <sup>12</sup>AAO-HNS, Alexandria, Virginia, USA

### Corresponding Author:

Richard M. Rosenfeld, MD, MPH, Chairman and Professor of Otolaryngology, SUNY Downstate Medical Center, Long Island College Hospital, Brooklyn, NY 11201, USA.

Email: richrosenfeld@msn.com

## Guideline Purpose

The purpose of this multidisciplinary guideline is to identify quality improvement opportunities in managing adult rhinosinusitis and to create explicit and actionable recommendations to implement these opportunities in clinical practice. Specifically, the goals are to improve diagnostic accuracy for adult rhinosinusitis, promote judicious use of systemic and topical therapy, and promote appropriate use of ancillary tests to confirm diagnosis and guide management, which include radiography, nasal endoscopy, computed tomography, and testing for allergy and immune function. Emphasis was also placed on identifying multiple chronic conditions that would modify management of rhinosinusitis, including asthma, cystic fibrosis, immunocompromised state, and ciliary dyskinesia.

The guideline is intended for all clinicians who are likely to diagnose and manage adults with rhinosinusitis and applies to any setting in which an adult with rhinosinusitis would be identified, monitored, or managed. This guideline, however, does not apply to patients younger than 18 years or to patients of any age with complicated rhinosinusitis.

The guideline will not consider management of the following clinical presentations, although differential diagnosis for these conditions and bacterial rhinosinusitis will be discussed: allergic rhinitis, eosinophilic nonallergic rhinitis, vasomotor rhinitis, invasive fungal rhinosinusitis, allergic fungal rhinosinusitis, vascular headaches, and migraines. Similarly, the guideline will not consider management of rhinosinusitis in patients with the following modifying factors but will discuss the importance of assessing patients with recurrent ARS or CRS for their presence: cystic fibrosis, immotile cilia disorders, ciliary dyskinesia, immune deficiency, prior history of sinus surgery, and anatomic abnormalities (eg, deviated nasal septum).

Surgical management of CRS is not discussed in this guideline because of insufficient evidence (eg, randomized controlled trials) for evidence-based recommendations.

## Burden of Rhinosinusitis

Twelve percent of the US population (nearly 1 in 8 adults) reported being diagnosed with rhinosinusitis in the prior 12 months in a 2012 national health survey.<sup>4</sup> Rhinosinusitis was diagnosed more frequently than hay fever (7%), bronchitis (4%), or chronic obstructive pulmonary disease (4%), and the individuals surveyed were almost as likely to receive a diagnosis of rhinosinusitis as they were of asthma (13%).

The broad category of rhinosinusitis in the preceding paragraph includes ARS and CRS. Most ARS begins when a viral upper respiratory infection (URI) extends into the paranasal sinuses, which may be followed by bacterial infection. About 20 million cases of presumed bacterial ARS (ABRS) occur annually in the United States,<sup>5</sup> rendering it one of the most common conditions encountered by clinicians. The importance of ABRS relates not only to prevalence but also to the potential for uncommon, but serious, complications that include meningitis, brain abscess, orbital cellulitis, and orbital abscess.<sup>17,18</sup>

National ambulatory care data from 2006 to 2010 revealed that rhinosinusitis accounted for more outpatient antibiotic

prescriptions than any other diagnosis. Despite guidelines that encourage judicious antibiotic use for ARS,<sup>16,19</sup> they are prescribed in about 82% of visits.<sup>20</sup> From 2006 to 2010, rhinosinusitis accounted for 11% of all primary care antibiotic-related visits, with ARS accounting for 3.9% and CRS accounting for 7.1%.<sup>20</sup> ARS and CRS combined accounted for more primary ambulatory care visits with antibiotic prescriptions than any other diagnosis or commonly grouped diagnoses.

ARS has significant economic implications. The cost of antibiotic treatment failure, including additional prescriptions, outpatient visits, tests, and procedures,<sup>21</sup> contributes to a substantial total ARS-related health care expenditure of more than \$3 billion per year in the United States.<sup>5</sup> The average patient with recurrent ARS incurs about \$1100 per year in total direct health costs.<sup>22</sup> Aside from the direct treatment costs, decreased productivity and lost work days contribute to an even greater indirect health care cost associated with ABRS and recurrent ARS.

CRS also has significant socioeconomic implications. In 2001, there were 18.3 million office visits for CRS, most of which resulted in prescription medications.<sup>23</sup> Patients with CRS visit primary care clinicians twice as often as those without the disorder and have 5 times as many prescriptions filled.<sup>24</sup> A survey in 2007 found that approximately \$8.3 billion is spent annually on CRS, primarily on prescription drugs and office-based care.<sup>25</sup> Surgery for CRS, which is performed nearly 250,000 times annually in the United States, averages a cost of \$7700 per patient. Average annual per-patient spending is \$770, which increases to \$2450 in the year prior to surgery.<sup>26</sup>

The indirect cost of CRS is substantial, making it potentially more important than the direct cost. CRS accounts for, on average, 1 to 2 lost workdays per patient per year and 73 million days of restricted activity.<sup>24,27</sup> In contrast, those with medically refractory CRS miss 18 annual workdays.<sup>6</sup> Patients with CRS are absent from work because of sinusitis 6.5% of the time, have a 36% reduction in on-the-job effectiveness, and suffer a 38% loss of productivity.<sup>7</sup> Compared with patients without CRS, patients with CRS have greater activity limitations, work limitations, and social limitations.<sup>22</sup> The overall annual productivity cost for refractory CRS is estimated at \$10,077 per patient.<sup>6</sup>

CRS can also have a substantial impact on health-related quality of life. Patients with CRS referred to otolaryngologists score significantly lower on measures of bodily pain and social functioning than do those with angina, back pain, congestive heart failure, and chronic obstructive pulmonary disease.<sup>8</sup> Similarly, patients with CRS have health utility scores that are worse than many chronic diseases, including congestive heart failure, coronary artery disease, and chronic obstructive pulmonary disease.<sup>28</sup> Moreover, treatment of CRS can improve health state utility values and substantially reduce fatigue and bodily pain.<sup>28-31</sup>

## Methods

### General Methods and Literature Search

In developing this update of the evidence-based clinical practice guideline, the methods outlined in the AAO-HNSF

Guideline Development Manual, third edition, were followed explicitly.<sup>32</sup>

An executive summary of the original adult sinusitis guideline<sup>1</sup> was first sent to a panel of expert reviewers who were asked to assess the key action statements and decide if they should be revised, be kept as stands, or removed based on relevancy, omissions, or controversies that the guideline spurred and to identify any new literature or treatments that might affect the guideline recommendations. The reviewers concluded that the original guideline action statements remained valid but should be updated with minor modifications. Suggestions were also made for new key action statements.

A systematic literature search was performed by an information specialist to identify systematic reviews, clinical practice guidelines, and randomized controlled trials published since the prior guideline (2007). The original MEDLINE search was updated from December 2006 to March 2014 to include Medline, National Guidelines Clearinghouse, Cochrane Database of Systematic Reviews, Excerpta Medica database (EMBASE), Cumulative Index to Nursing and Allied Health (CINAHL), and Web of Science using the search string “(sinusit\* OR rhinosinusit\*).” The initial English-language search identified 54 potential clinical practice guidelines, 166 systematic reviews, and 352 randomized controlled trials (RCTs). Systematic reviews were emphasized and included if they met quality criteria of (a) clear objective and methods, (b) an explicit search strategy, and (c) valid data extraction. Additional evidence was identified, as needed, with targeted searches to support needs of the guideline development group in updating sections of the guideline text. After assessing quality and relevance of the initial search results, we retained 5 guidelines, 42 systematic reviews, and 70 RCTs.

The AAO-HNSF assembled a guideline update group (GUG) representing the disciplines of otolaryngology—head and neck surgery, infectious disease, family medicine, allergy and immunology, advanced practice nursing, and a consumer advocate. The GUG also included a staff liaison from AAO-HNSF, but this individual was not a voting member of the GUG and served only in an editorial capacity in writing the guideline. Although radiology was represented on the original guideline development group, they were excluded from the update since the AAO-HNSF had recently published a clinical consensus statement on imaging for sinusitis.<sup>33</sup> We did, however, solicit radiology feedback about pertinent statements to ensure they remained valid and current.

The GUG had several conference calls and one in-person meeting, during which comments from the expert panel review and the literature search were reviewed for each key action statement. The GUG then decided to leave the statement unaltered, change slightly, or rewrite the statement based on the impact of the literature search and the reviewer comments. The supporting text was then edited to explain any changes from the original key action statement, and the recommendation level was modified accordingly.

The evidence profile for each statement was then converted into an action statement profile, which was moved up in the

text to immediately follow the action statement. Statements about the quality improvement opportunity, level of confidence in the evidence, differences of opinion, intentional vagueness, and any exclusion to which the action statement does not apply were added to the action statement profiles. These additions reflect the current methodology for guideline development by the AAO-HNSF and conform to the Institute of Medicine’s standards for developing trustworthy guidelines.<sup>2,32</sup> The updated guideline then underwent Guideline Implementability Appraisal (GLIA) to appraise adherence to methodologic standards, to improve clarity of recommendations, and to predict potential obstacles to implementation.<sup>34</sup> The GUG received summary appraisals in June and modified an advanced draft of the guideline based on the appraisal.

The final draft of the updated clinical practice guideline was revised based on comments received during multidisciplinary peer review, open public comment, and journal editorial peer review. The recommendations contained in the guideline are based on the best available published data through March 2014. Where data were lacking, a combination of clinical experience and expert consensus was used. A scheduled review process will occur at 5 years from publication or sooner if new, compelling evidence warrants earlier consideration.

### Classification of Evidence-Based Statements

Guidelines are intended to reduce inappropriate variations in clinical care, to produce optimal health outcomes for patients, and to minimize harm. The evidence-based approach to guideline development requires that the evidence supporting a policy be identified, appraised, and summarized and that an explicit link between evidence and statements be defined. Evidence-based statements reflect both the *quality of evidence* and the *balance of benefit and harm* that are anticipated when the statement is followed. The definitions for evidence-based statements<sup>35</sup> are listed in **Tables 1** and **2**.

Guidelines are never intended to supersede professional judgment; rather, they may be viewed as a relative constraint on individual clinician discretion in a particular clinical circumstance. Less frequent variation in practice is expected for a strong recommendation than might be expected with a recommendation. Options offer the most opportunity for practice variability.<sup>36</sup> Clinicians should always act and decide in a way that they believe will best serve their individual patients’ interests and needs, regardless of guideline recommendations. Guidelines represent the best judgment of a team of experienced clinicians and methodologists addressing the scientific evidence for a particular topic.<sup>35</sup>

Making recommendations about health practices involves value judgments on the desirability of various outcomes associated with management options. Values applied by the GUG sought to minimize harm, diminish unnecessary and inappropriate therapy, and reduce the unnecessary use of systemic antibiotics. A major goal of the panel was to be transparent and explicit about how values were applied and to document the process.

**Table 1.** Strength of Action Terms in Guideline Statements and Implied Levels of Obligation.

Strength	Definition	Implied Obligation
Strong Recommendation	A strong recommendation means the benefits of the recommended approach clearly exceed the harms (or, in the case of a strong negative recommendation, that the harms clearly exceed the benefits) and that the quality of the supporting evidence is high (Grade A or B). <sup>a</sup> In some clearly identified circumstances, strong recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Recommendation	A recommendation means the benefits exceed the harms (or, in the case of a negative recommendation, that the harms exceed the benefits), but the quality of evidence is not as high (Grade B or C). <sup>a</sup> In some clearly identified circumstances, recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms.	Clinicians should also generally follow a recommendation but should remain alert to new information and sensitive to patient preferences.
Option	An option means that either the quality of evidence is suspect (Grade D) <sup>a</sup> or that well-done studies (Grade A, B, or C) <sup>a</sup> show little clear advantage to one approach vs another.	Clinicians should be flexible in their decision making regarding appropriate practice, although they may set bounds on alternatives; patient preference should have a substantial influencing role.

<sup>a</sup>See **Table 2** for definitions of evidence grades.

### Financial Disclosure and Conflicts of Interest

The cost of developing this guideline, including travel expenses of all panel members, was covered in full by the AAO-HNSF. Potential conflicts of interest for all panel members in the past 5 years were compiled and distributed before the first conference call. After review and discussion of these disclosures,<sup>37</sup> the panel concluded that individuals with potential conflicts could remain on the panel if they (1) reminded the panel of potential conflicts before any related discussion, (2) recused themselves from a related discussion if asked by the panel, and (3) agreed not to discuss any aspect of the guideline with industry before publication. Last, panelists were reminded that conflicts of interest extend beyond financial relationships and may include personal experiences, how a participant earns a living, and the participant's previously established "stake" in an issue.<sup>38</sup>

### Rhinosinusitis Guideline Evidence-Based Statements

Each evidence-based statement is organized in a similar fashion: an evidence-based key action statement in bold, followed by the strength of the recommendation in italics. Each key action statement is followed by an "action statement profile," which explicitly states the quality improvement opportunity, aggregate evidence quality, level of confidence in evidence (high, medium, low), benefit, harms, risks, costs, and a benefits-harm assessment. In addition, there are statements of any value judgments, the role of patient (caregiver) preferences, clarification of any intentional vagueness by the panel, exceptions to the statement, any differences of opinion, and a

repeat statement of the strength of the recommendation. Several paragraphs subsequently discuss the evidence base supporting the statement. An overview of each evidence-based statement in this guideline can be found in **Table 3**, and the relationship between statements is illustrated in **Figure 1**.

The role of patient preference in decision making deserves further clarification. For some statements, where the evidence base demonstrates clear benefit, although the role of patient preference for a range of treatments may not be relevant, clinicians should provide patients with clear and comprehensible information on the benefits to facilitate patient understanding and shared decision making, which leads to better patient adherence and outcomes. In cases where evidence is weak or benefits are unclear, the practice of shared decision making, again where the management decision is made by a collaborative effort between the clinician and an informed patient, is extremely useful. Factors related to patient preference include (but are not limited to) absolute benefits (numbers needed to treat), adverse effects (number needed to harm), cost of drugs or procedures, and frequency and duration of treatment.

**STATEMENT 1A. DIFFERENTIAL DIAGNOSIS OF ACUTE RHINOSINUSITIS: Clinicians should distinguish presumed acute bacterial rhinosinusitis (ABRS) from acute rhinosinusitis caused by viral upper respiratory infections and noninfectious conditions. A clinician should diagnose ABRS when (a) symptoms or signs of acute rhinosinusitis (purulent nasal drainage accompanied by nasal obstruction, facial pain-pressure-fullness, or both) persist without**

**Table 2.** Aggregate Grades of Evidence by Question Type.<sup>a</sup>

Grade	Treatment	Diagnosis	Prognosis
A	Systematic review <sup>b</sup> of randomized trials	Systematic review <sup>b</sup> of cross-sectional studies with consistently applied reference standard and blinding	Systematic review <sup>b</sup> of inception cohort studies <sup>c</sup>
B	Randomized trials or observational studies with dramatic effects or highly consistent evidence	Cross-sectional studies with consistently applied reference standard and blinding	Inception cohort studies <sup>c</sup>
C	Nonrandomized or historically controlled studies, including case-control and observational studies	Nonconsecutive studies, case-control studies, or studies with poor, nonindependent, or inconsistently applied reference standards	Cohort study, control arm of a randomized trial, case series, or case-control studies; poor quality prognostic cohort study
D	Case reports, mechanism-based reasoning, or reasoning from first principles		
X	Exceptional situations where validating studies cannot be performed and there is a clear preponderance of benefit over harm		

<sup>a</sup>American Academy of Otolaryngology—Head and Neck Surgery Foundation guideline development manual.<sup>32</sup>

<sup>b</sup>A systematic review may be downgraded to level B because of study limitations, heterogeneity, or imprecision.

<sup>c</sup>A group of individuals identified for subsequent study at an early, uniform point in the course of the specified health condition or before the condition develops.

**evidence of improvement for at least 10 days beyond the onset of upper respiratory symptoms, or (b) symptoms or signs of acute rhinosinusitis worsen within 10 days after an initial improvement (double worsening).** *Strong recommendation based on diagnostic studies with minor limitations and a preponderance of benefit over harm.*

### Action Statement Profile

- **Quality improvement opportunity:** Avoid inappropriate use of antibiotics for presumed viral infections
- **Aggregate evidence quality:** Grade B, systematic reviews, diagnostic studies with minor limitations regarding signs and symptoms associated with acute bacterial rhinosinusitis (ABRS)
- **Level of confidence in evidence:** Medium
- **Benefit:** Decrease inappropriate use of antibiotics for nonbacterial illness; distinguish noninfectious conditions from rhinosinusitis
- **Harms, risks, costs:** Risk of misclassifying acute bacterial rhinosinusitis as viral or vice versa
- **Benefits-harm assessment:** Preponderance of benefit over harm
- **Value judgments:** Importance of avoiding inappropriate antibiotic treatment of viral or nonbacterial illness; emphasis on clinical signs and symptoms for initial diagnosis; importance of avoiding unnecessary diagnostic tests
- **Intentional vagueness:** None
- **Role of patient preferences:** None
- **Exceptions:** None
- **Policy level:** Strong recommendation
- **Differences of opinion:** None regarding the persistent and double-worsening presentations of ABRS; minor regarding whether to include a severe pattern of ABRS presentation (1 group member was in favor; 9 against)

### Supporting Text

The purpose of this statement is to emphasize the importance of differentiating acute bacterial rhinosinusitis (ABRS) from acute rhinosinusitis (ARS) caused by viral upper respiratory infections to prevent unnecessary treatment with antibiotics. This also helps the clinician avoid ordering unnecessary diagnostic tests, thus controlling costs and improving quality of care. In contrast to the version of this statement in the original sinusitis guideline,<sup>1</sup> we changed the diagnostic criteria to include not just the *persistence* of signs and symptoms beyond 10 days but *failure to improve* in 10 days, for greater specificity in distinguishing presumed bacterial infection for persistent, but resolving, viral illness.

This key action statement is also in line with the *Choosing Wisely* initiative of the American Board of Internal Medicine Foundation.<sup>39</sup> This initiative was launched to help physicians and patients engage in conversations about the overuse of tests and procedures and support physician efforts to help patients make smart and effective care choices. Having clear, actionable criteria for distinguishing presumed bacterial ARS from viral infection is a prerequisite for judicious antibiotic therapy. Without such criteria, antibiotics are more likely to be inappropriately prescribed for viral illness, adding to the global problem of rising bacterial resistance that is directly correlated with community antibiotic use.<sup>40-44</sup>

### Cardinal Symptoms of Acute Rhinosinusitis

*Acute rhinosinusitis* is diagnosed when a patient presents with up to 4 weeks of purulent (not clear) nasal drainage accompanied by nasal obstruction, facial pain-pressure-fullness, or both (**Table 4**). Nasal obstruction without purulent nasal drainage is not consistent with ARS and is beyond the scope of this guideline. Similarly, facial pain without purulent nasal drainage is not consistent with ARS, even though many patients present with a history of self-reported or physician-diagnosed “sinus”

**Table 3.** Summary of Evidence-Based Statements.

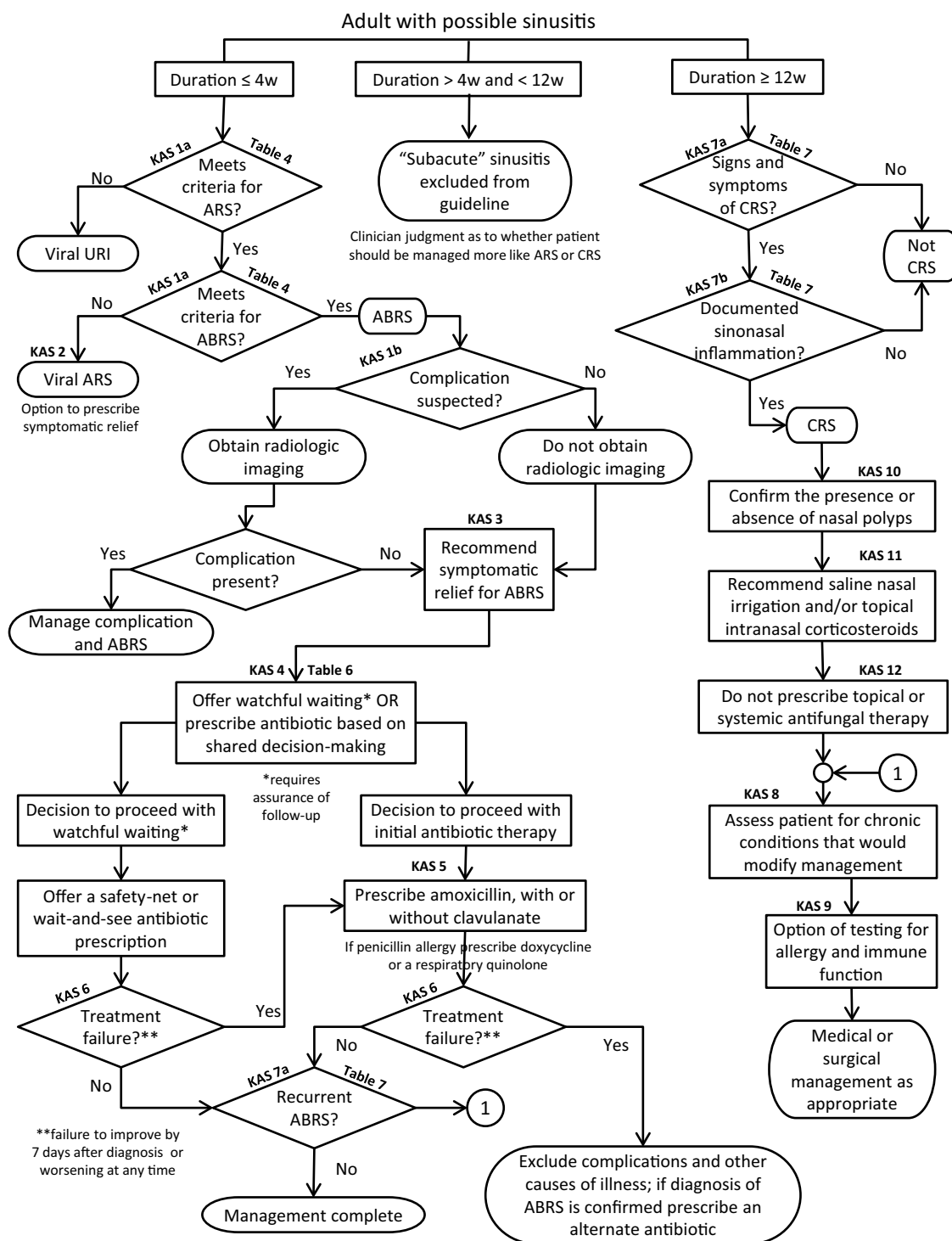
Statement	Action	Strength
1A. Differential diagnosis	Clinicians should distinguish presumed ABRS from ARS caused by viral upper respiratory infections and noninfectious conditions. A clinician should diagnose ABRS when (a) symptoms or signs of ARS (purulent nasal drainage accompanied by nasal obstruction, facial pain-pressure-fullness, or both) <i>persist without evidence of improvement for at least 10 days</i> beyond the onset of upper respiratory symptoms, or (b) symptoms or signs of ARS worsen within 10 days after an initial improvement (double worsening).	Strong recommendation
1B. Radiographic imaging and ARS	Clinicians should not obtain radiographic imaging for patients who meet diagnostic criteria for ARS, unless a complication or alternative diagnosis is suspected.	Recommendation (against imaging)
2. Symptomatic relief of VRS	Clinicians may recommend analgesics, topical intranasal steroids, and/or nasal saline irrigation for symptomatic relief of VRS.	Option
3. Symptomatic relief of ABRS	Clinicians may recommend analgesics, topical intranasal steroids, and/or nasal saline irrigation for symptomatic relief of ABRS.	Option
4. Initial management of ABRS	Clinicians should either offer watchful waiting (without antibiotics) or prescribe initial antibiotic therapy for adults with uncomplicated ABRS. Watchful waiting should be offered only when there is assurance of follow-up, such that antibiotic therapy is started if the patient's condition fails to improve by 7 days after ABRS diagnosis or if it worsens at any time.	Recommendation
5. Choice of antibiotic for ABRS	If a decision is made to treat ABRS with an antibiotic agent, the clinician should prescribe amoxicillin with or without clavulanate as first-line therapy for 5 to 10 days for most adults.	Recommendation
6. Treatment failure for ABRS	If the patient worsens or fails to improve with the initial management option by 7 days after diagnosis or worsens during the initial management, the clinician should reassess the patient to confirm ABRS, exclude other causes of illness, and detect complications. If ABRS is confirmed in the patient initially managed with observation, the clinician should begin antibiotic therapy. If the patient was initially managed with an antibiotic, the clinician should change the antibiotic.	Recommendation
7A. Diagnosis of CRS or recurrent ARS	Clinicians should distinguish CRS and recurrent ARS from isolated episodes of ABRS and other causes of sinonasal symptoms.	Recommendation
7B. Objective confirmation of a diagnosis of CRS	The clinician should confirm a clinical diagnosis of CRS with objective documentation of sinonasal inflammation, which may be accomplished using anterior rhinoscopy, nasal endoscopy, or computed tomography.	Strong recommendation
8. Modifying factors	Clinicians should assess the patient with CRS or recurrent ARS for multiple chronic conditions that would modify management, such as asthma, cystic fibrosis, immunocompromised state, and ciliary dyskinesia.	Recommendation
9. Testing for allergy and immune function	The clinician may obtain testing for allergy and immune function in evaluating a patient with CRS or recurrent ARS.	Option
10. CRS with polyps	The clinician should confirm the presence or absence of nasal polyps in a patient with CRS.	Recommendation
11. Topical intranasal therapy for CRS	Clinicians should recommend saline nasal irrigation, topical intranasal corticosteroids, or both for symptom relief of CRS.	Recommendation
12. Antifungal therapy for CRS	Clinicians should not prescribe topical or systemic antifungal therapy for patients with CRS.	Recommendation (against therapy)

Abbreviations: ABRS, acute bacterial rhinosinusitis; ARS, acute rhinosinusitis; CRS, chronic rhinosinusitis; VRS, viral rhinosinusitis.

headache, which is often related to migraines and is responsive to migraine therapy.<sup>45,46</sup>

When a patient meets the criteria for ARS in **Table 4**, the clinician should distinguish between viral rhinosinusitis (VRS) and presumed ABRS.<sup>5,13,47,48</sup> This distinction is based on illness pattern and duration (**Table 4**), because purulent nasal drainage as a sole criterion cannot distinguish between

viral and bacterial infection.<sup>49</sup> Although there is no high-level evidence showing that symptom duration and purulent discharge can reliably distinguish presumed bacterial vs viral ARS,<sup>50</sup> the GUG considered the criteria in **Table 4** to be best for this purpose based on first principles, subsidiary evidence, and expert consensus, as explained in the remainder of this section.



ARS, acute RS; AB, acute bacterial RS; CRS, chronic RS; KAS, key action statement; RS, rhinosinusitis; URI, upper respiratory infection

**Figure 1.** Algorithm showing the interrelationship of guideline key action statements. ABRS, acute bacterial rhinosinusitis; ARS, acute rhinosinusitis; CRS, chronic rhinosinusitis; KAS, key action statement; URI, upper respiratory infection.

The rationale for selecting 3 cardinal symptoms is based on their high sensitivity and their relatively high specificity for ABRS, especially when considering the time interval of persistence for 10 days or longer.<sup>51-53</sup> Purulent (infected, colored, or oozing) nasal drainage predicts presence of bacteria on

antral aspiration when reported as purulent rhinorrhea by the patient, when manifest as postnasal drip or purulent discharge in the posterior pharynx, or when observed in the nasal cavity or near the sinus ostium.<sup>54,55</sup> Purulent rhinorrhea also predicts radiographic evidence of ABRS.<sup>56,57</sup> Facial or dental pain also



**Table 4.** Acute Rhinosinusitis Definitions.

Term	Definition
Acute rhinosinusitis (ARS)	Up to 4 weeks of <i>purulent nasal drainage</i> (anterior, posterior, or both) accompanied by <i>nasal obstruction, facial pain-pressure-fullness, or both</i> . <sup>a</sup> <i>Purulent nasal discharge</i> is cloudy or colored, in contrast to the clear secretions that typically accompany viral upper respiratory infection, and may be reported by the patient or observed on physical examination. <i>Nasal obstruction</i> may be reported by the patient as nasal obstruction, congestion, blockage, or stuffiness, or may be diagnosed by physical examination. <i>Facial pain-pressure-fullness</i> may involve the anterior face, periorbital region, or manifest with headache that is localized or diffuse.
Viral rhinosinusitis (VRS)	Acute rhinosinusitis that is caused by, or is presumed to be caused by, viral infection. A clinician should diagnose VRS when: a. symptoms or signs of acute rhinosinusitis are present less than 10 days and the symptoms are not worsening
Acute bacterial rhinosinusitis (ABRS)	Acute rhinosinusitis that is caused by, or is presumed to be caused by, bacterial infection. A clinician should diagnose ABRS when: a. symptoms or signs of acute rhinosinusitis fail to improve within 10 days or more beyond the onset of upper respiratory symptoms, or b. symptoms or signs of acute rhinosinusitis worsen within 10 days after an initial improvement (double worsening)

<sup>a</sup>Facial pain-pressure-fullness in the absence of purulent nasal discharge is insufficient to establish a diagnosis of ARS.

predicts ABRS,<sup>53,55</sup> but the location correlates poorly with the specific sinuses involved.<sup>58</sup> Last, patient complaints of nasal obstruction correlate with objective measures, such as rhinomanometry or nasal peak flow rate.<sup>59</sup>

Since the usual clinical dilemma is to differentiate ABRS from VRS, the specificity of ABRS symptoms has typically been studied in this context. The antecedent history of viral URI likely contributes to the specificity of these symptoms for ABRS, but the extent to which this is true has not been quantified. Similarly, although the differential diagnosis of isolated nasal obstruction or facial pain is broad (and beyond the scope of this guideline), the specificity for ABRS increases when coupled with concurrent purulent nasal discharge (**Table 4**). For example, migraine headaches, tension headaches, and dental abscess can mimic rhinosinusitis pain, but the absence of purulent nasal discharge excludes this diagnosis based on our definition.

Additional signs and symptoms of ABRS include fever, cough, fatigue (malaise), reduced sense of smell (hyposmia), lack of the sense of smell (anosmia), maxillary dental pain, and ear fullness or pressure.<sup>60</sup> Although combinations of major and minor symptoms were used to define ARS in early consensus reports,<sup>60</sup> more recent reports<sup>13,61</sup> abandoned this system and instead focus on the 3 cardinal features outlined above.

The initial diagnostic evaluation for ARS should include measurement of vital signs (temperature, pulse, blood pressure, respiratory rate) and a physical examination of the head and neck. Particular attention should be paid to the presence or absence of the following: altered (hyponasal) speech indicating nasal obstruction, swelling, redness of the skin due to congestion of the capillaries (erythema) or abnormally large fluid volume (edema) localized over the involved cheek bone or

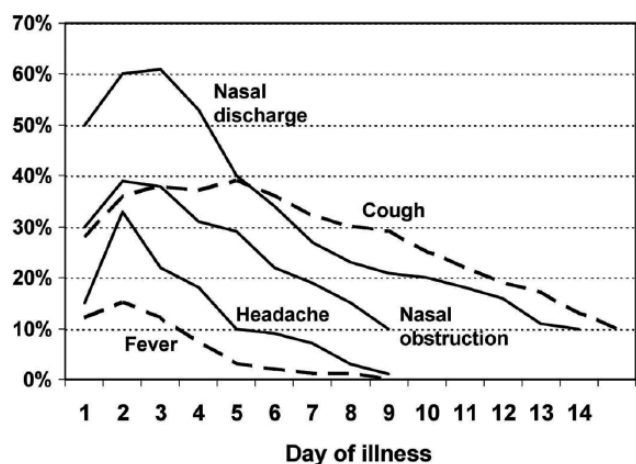
periorbital area; palpable cheek tenderness or percussion tenderness of the upper teeth; purulent drainage in the nose or posterior pharynx; and signs of extra-sinus involvement (orbital or facial cellulitis, orbital protrusion, abnormalities of eye movement, neck stiffness). However, of these physical findings, the only finding shown to have diagnostic value is that of purulence in the nasal cavity or posterior pharynx as discussed above.

Culture of secretions from the nasal cavity or nasopharynx does not differentiate ABRS from VRS, because nasal cultures correlate poorly with maxillary sinus cultures obtained by direct aspiration.<sup>62</sup> A culture of secretions from the middle meatus guided by endoscopy has better correlation, but its role in routine management of uncomplicated ABRS has not been established.<sup>63</sup>

### Transition from Viral to Bacterial Infection

Only about 0.5 to 2.0% of VRS episodes are complicated by bacterial infection.<sup>64</sup> Antecedent viral infection can promote ABRS by obstructing sinus drainage during the nasal cycle,<sup>65</sup> promoting growth of bacterial pathogens that colonize the nose and nasopharynx,<sup>64</sup> and depositing nasal bacteria into the sinuses during nose-blowing. Although ABRS is often considered a transition from a preceding viral URI,<sup>51</sup> bacterial infection can develop at any time during the course of the illness. The concept of a transition, however, is useful for management decisions,<sup>53</sup> especially when considering the time course of VRS and which disease patterns are most likely to be associated with bacterial infection.

In the first 3 to 4 days of illness VRS cannot be differentiated from an early-onset ABRS; therefore, only patients with unusually severe presentations or extra-sinus manifestations of infection are presumed to have a bacterial illness. Similarly,



**Figure 2.** Symptom prevalence by day for rhinovirus illness (data from Gwaltney 1967).<sup>67</sup>

between 5 and 10 days of persistent symptoms are consistent with VRS or may represent the beginning stages of ABRS. In this time period, however, a pattern of initial improvement followed by worsening (“double worsening”) is consistent with ABRS.<sup>13,56,57</sup> Beyond 10 days, residual sinus mucosal thickness induced by the virus may persist, usually in the absence of active viral infection, but the probability of confirming a bacterial infection by sinus aspiration is about 60%.<sup>66</sup>

Gwaltney and colleagues<sup>67</sup> studied the time course of signs and symptoms of spontaneous rhinovirus infections (**Figure 2**). Typical symptoms peak at days 2 to 3 and wane thereafter but may persist 14 days or longer. Symptoms of VRS may persist for longer than 10 days, but they gradually decrease in severity. Therefore, the GUG decided to change the statement from “A clinician should diagnose ABRS when (a) symptoms or signs of acute rhinosinusitis are present 10 days or more beyond the onset of upper respiratory symptoms” to “A clinician should diagnose ABRS when (a) symptoms or signs of acute rhinosinusitis persist without evidence of improvement for at least 10 days beyond the onset of upper respiratory symptoms.”

Fever is present in some patients with VRS in the first few days of illness (**Figure 2**) but does not predict bacterial infection as an isolated diagnostic criterion. Fever has a sensitivity and specificity of only about 50% for ABRS,<sup>52,53</sup> and a systematic review concluded that evidence was lacking regarding the ability of fever and facial/dental pain to distinguish ABRS from VRS.<sup>68</sup> For this reason, we did not include fever as a cardinal sign/symptom in diagnosing ABRS.

Although our GUG concluded that evidence was insufficient to support a “severe” presentation of ABRS, others have explicitly highlighted this subgroup of patients with ABRS. Meltzer and coworkers<sup>13</sup> defined a special circumstance of ABRS when purulent nasal discharge for 3 to 4 days was accompanied by high fever. “High fever” was not defined, but the criterion only applied to severe disease with a shorter duration of illness. A guideline on sinusitis in children from the American Academy of Pediatrics<sup>69</sup> considered 3 or more days of concurrent high fever and purulent nasal discharge as

a “severe” presentation of ABRS that warrants antibiotic therapy. Similarly, the Infectious Disease Society of America guideline on ABRS<sup>15</sup> recommended that the clinician consider a diagnosis of ABRS if the patient presented with severe symptoms at the onset or has high fever (>39°C or 102°F) and purulent discharge or facial pain lasting at least 3 to 4 consecutive days at the beginning of illness.

We recommend that patients be engaged in understanding what causes ARS and why it is important to distinguish presumed viral ARS from ABRS. The patient information sheet in **Table 5** could be used as a teaching aid to conveniently communicate this information.

**STATEMENT 1B. RADIOGRAPHIC IMAGING AND ACUTE RHINOSINUSITIS: Clinicians should not obtain radiographic imaging for patients who meet diagnostic criteria for acute rhinosinusitis, unless a complication or alternative diagnosis is suspected.** *Recommendation (against imaging)* based on diagnostic studies with minor limitations and a preponderance of benefit over harm for not obtaining imaging.

#### Action Statement Profile

- Quality improvement opportunity: Avoid costly diagnostic tests that do not improve diagnostic accuracy yet expose the patient to unnecessary radiation
- Aggregate evidence quality: Grade B, diagnostic studies with minor limitations
- Level of confidence in evidence: High
- Benefit: Avoid unnecessary radiation exposure; avoid delays in diagnosis from obtaining and interpreting imaging studies; incur financial savings by not performing routine radiologic imaging; avoid incidental findings that may cause undue patient concern or result in additional imaging studies
- Risks, harms, costs: Delayed diagnosis of serious underlying condition
- Benefits-harm assessment: Preponderance of benefit over harm
- Value judgments: Importance of avoiding unnecessary radiation and cost in diagnosing acute rhinosinusitis
- Intentional vagueness: None
- Role of patient preferences: None
- Exceptions: Suspicion of complicated acute rhinosinusitis or alternative diagnosis based on severe headache, proptosis, cranial nerve palsies, facial swelling, or other clinical findings
- Policy level: Recommendation
- Differences of opinion: None

#### Supporting Text

The purpose of this statement is to emphasize that clinicians should not obtain radiographic imaging for patients presenting with uncomplicated acute rhinosinusitis (ARS) to distinguish ABRS from VRS, unless a complication or alternative diagnosis is suspected.

**Table 5.** Patient Information Sheet on Diagnosis of Acute Sinusitis.

Question	Answer
What are the sinuses?	Sinuses are hollow spaces in the bones around the nose that connect to the nose through small, narrow channels. The sinuses stay healthy when the channels are open, which allows air from the nose to enter the sinuses and mucus made in the sinuses to drain into the nose.
What is sinusitis?	Sinusitis, also called rhinosinusitis, affects about 1 in 8 adults annually and generally occurs when viruses or bacteria infect the sinuses (often during a cold) and begin to multiply. Part of the body's reaction to the infection causes the sinus lining to swell, blocking the channels that drain the sinuses. This causes mucus and pus to fill up the nose and sinus cavities.
How can I tell if I have acute sinusitis?	You have acute sinusitis when there has been up to 4 weeks of cloudy or colored (not clear) drainage from the nose plus one or both of the following: (a) a stuffy, congested, or blocked nose or (b) pain, pressure or fullness in the face, head, or around the eyes.
How can I tell if my sinusitis is caused by viruses or bacteria?	Acute <i>viral</i> sinusitis is likely if you have been sick less than 10 days and are not getting worse. Acute <i>bacterial</i> sinusitis is likely when you do not improve at all within 10 days of getting sick or when you get worse within 10 days after beginning to get better.
Why is it important to tell if my sinusitis is caused by bacteria?	Because sinusitis is treated differently based on cause: acute viral sinusitis does <i>not</i> benefit from antibiotics, but some patients with acute bacterial sinusitis may get better faster with an antibiotic.

Radiographic imaging of the paranasal sinuses is unnecessary for diagnosis in patients who already meet clinical diagnostic criteria (**Table 4**) for ABRS.<sup>33,70-72</sup> Imaging modalities for the paranasal sinuses include computed tomography (CT) and magnetic resonance (MR) imaging. The American College of Radiology (ACR) has stated that plain films of the sinuses are inaccurate in a high percentage of patients and should be supplanted by CT imaging.<sup>70</sup> A meta-analysis of 6 studies showed that sinus radiography has moderate sensitivity (76%) and specificity (79%) compared with sinus puncture in diagnosing ABRS.<sup>73</sup> Sinus involvement is common in documented viral URIs,<sup>74</sup> making it impossible to distinguish ABRS from VRS based solely on imaging studies. Moreover, clinical criteria may have a comparable diagnostic accuracy to sinus radiography, and radiography is not cost-effective regardless of baseline sinusitis prevalence.<sup>73</sup>

When a complication of ABRS or an alternative diagnosis is suspected, imaging studies may be obtained.<sup>33</sup> Complications of ABRS include orbital, intracranial, or soft tissue involvement. Alternative diagnoses include malignancy and other noninfectious causes of facial pain. Radiographic imaging may also be obtained when the patient has modifying factors or comorbidities that predispose to complications, including diabetes, immune-compromised state, or a history of facial trauma or surgery.

CT imaging of the sinuses is appropriate when a complication of ABRS is suspected based on severe headache, facial swelling, cranial nerve palsies, or forward displacement or bulging of the eye (proptosis); CT findings that correlate with ABRS include opacification, air-fluid level, and moderate to severe mucosal thickening. Complications of ABRS are best assessed using iodine contrast-enhanced CT or gadolinium-based MR imaging to identify extra-sinus extension or involvement.<sup>33,75-77</sup> Suspected complications are the only indication for MR imaging of the paranasal sinuses in the setting of ABRS.

Limitations of CT imaging include increased cost and radiation dosage. Radiation dose is related to technique and, if appropriate technique is not used, may deliver over 10 times the dosage compared with plain film radiography. With careful choice of technical factors, however, CT dosage can be lowered to 2 times the dose of plain film radiography. Other limitations of CT include lack of specificity for bacterial infection, a relative lack of correlation between localizing symptoms and sinus disease on CT, and the high frequency of incidental abnormal findings in asymptomatic persons.<sup>74,78-80</sup>

An alternative to traditional CT imaging is in-office cone-beam CT scanning, which offers advantages of point-of-care testing and possible decreased radiation dosage. The indications for office-based CT imaging are the same as for traditional scanners, and they should not be used for diagnosing or managing uncomplicated ABRS.

**STATEMENT 2. SYMPTOMATIC RELIEF OF VIRAL RHINOSINUSITIS (VRS): Clinicians may recommend analgesics, topical intranasal steroids, and/or nasal saline irrigation for symptomatic relief of VRS.** *Option based on randomized controlled trials with limitations and cohort studies with an unclear balance of benefit and harm that varies by patient.*

#### Action Statement Profile

- **Quality improvement opportunity:** To encourage consideration of supportive therapies that may improve quality of life for individuals with VRS and furthermore support the avoidance of unnecessary antibiotics in viral disease
- **Aggregate evidence quality:** Grade B and C, randomized controlled trials with limitations and cohort studies
- **Level of confidence in evidence:** Medium
- **Benefit:** Reduction of symptoms; avoidance of unnecessary antibiotics

- **Risks, harms, costs:** Adverse effects of decongestants, antihistamines, topical steroid sprays; cost of medications
- **Benefits-harm assessment:** Balance of benefit and harm
- **Value judgments:** A desire to call attention to VRS as a subset of the “common cold,” yet distinct from ABRS, that may benefit from explicit diagnosis and discussion of management options for symptomatic relief
- **Intentional vagueness:** The specific “symptomatic relief” is at the discretion of the clinician and patient but should not include antibiotics
- **Role of patient preferences:** Large role in selection and use of therapies for symptomatic relief based on shared decision making
- **Exceptions:** None
- **Policy level:** Option
- **Differences of opinion:** Minor regarding the need to explicitly discuss VRS in a distinct key action statement

### Supporting Text

The purpose of this statement is to encourage consideration of supportive therapies that may improve quality of life for individuals with viral rhinosinusitis (VRS) and to avoid unnecessary prescribing of antibiotics for viral disease.

VRS is a self-limited disease characterized by cough, sneezing, rhinorrhea, sore throat, and nasal congestion.<sup>67</sup> The incidence of acute VRS is high, estimated to occur from 2 to 5 times per year in the average adult. In contrast, secondary bacterial infection is believed to complicate only 0.5% to 2.0% of these events.<sup>19</sup> While the presentation of viral vs bacterial infection can be very similar, clinical emphasis on duration, illness pattern, and severity of symptoms can help to differentiate between viral vs bacterial infection (**Table 4**). Symptoms in acute VRS typically peak within 3 days then gradually decline and resolve within 10 to 14 days.

Nasal purulence alone does not indicate a bacterial infection; discolored nasal discharge is a sign of inflammation and is not specific for infection. Coloration of nasal discharge is related to the presence of neutrophils not bacteria.<sup>49,81-83</sup> Normal transport of mucus requires robust ciliary action. VRS promotes a vigorous inflammatory response, causing epithelial disruption, edema, and excessive mucus production, which further impairs normal ciliary function.<sup>84</sup>

Management of VRS is primarily directed toward relief of symptoms. Antibiotics are not recommended for treating VRS since antibiotics are ineffective for viral illness and do not provide direct symptom relief.<sup>85</sup> Therefore, palliative medications—such as analgesics, anti-inflammatory agents, nasal saline, decongestants, antihistamines, mucolytics, cough suppressants, and topical or oral corticosteroids—may be used alone or in varying combinations for symptom relief.<sup>16</sup>

Analgesics or antipyretic drugs (acetaminophen, ibuprofen, or other nonsteroidal anti-inflammatory agents) may be given for pain or fever. Nasal saline may be palliative and cleansing with low risk of adverse reactions.<sup>15</sup> A Cochrane

review<sup>86</sup> reported minor improvements in nasal symptom scores with the use of nasal saline in both physiologic and hypertonic concentrations.

Oral decongestants may provide symptomatic relief and should be considered barring any medical contraindications, such as hypertension or anxiety. The use of topical decongestant is likely to be palliative, but continuous duration of use should not exceed 3 to 5 days, as recommended by the manufacturers, to avoid rebound congestion and rhinitis medicamentosa.<sup>87</sup> Clinical experience suggests oral antihistamines may provide symptomatic relief of excessive secretions and sneezing, although there are no clinical studies supporting the use of antihistamines in acute VRS. Guaifenesin (an expectorant) and dextromethorphan (a cough suppressant) are often used for symptomatic relief of VRS symptoms, but evidence of clinical efficacy is lacking and decisions regarding their use are largely related to patient and provider preference.

Topical intranasal steroids may have a role in managing VRS, even though they do not have a Food and Drug Administration (FDA) indication for this purpose. A systematic review<sup>88</sup> found that topical nasal steroids relieved facial pain and nasal congestion in patients with rhinitis and acute sinusitis, even though many patients likely had viral illness. The magnitude of effect, however, was small: 66% of patients improved with placebo at 14 to 21 days, rising to 73% with steroid therapy. Adverse events, however, were rare, so the choice of whether or not the modest clinical benefit of therapy justifies the cost is a decision that should be based largely on patient preference.

**STATEMENT 3. SYMPTOMATIC RELIEF OF ACUTE BACTERIAL RHINOSINUSITIS (ABRS): Clinicians may recommend analgesics, topical intranasal steroids, and/or nasal saline irrigation for symptomatic relief of ABRS. *Option* based on randomized controlled trials with heterogeneous populations, diagnostic criteria, and outcome measures with a balance of benefit and harm.**

### Action Statement Profile

- **Quality improvement opportunity:** Promote interventions that may relieve ABRS symptoms (analgesics, saline irrigation, topical intranasal steroids) and discourage interventions with questionable or unproven efficacy (antihistamines, systemic steroids, guaifenesin)
- **Aggregate evidence quality:** Grade A, systematic review of RCTs for topical nasal steroids; Grade B, randomized controlled trials with heterogeneous populations, diagnostic criteria, and outcomes measures for saline irrigation and systemic steroids; grade D, first principles, for analgesics, decongestants, antihistamines (in non-atopic patients) and guaifenesin.
- **Level of confidence in evidence:** Medium
- **Benefit:** Relief of facial pain with analgesics, modest increase in symptom relief from topical nasal steroids (number needed to treat 14), and possible

symptom relief from saline irrigations; avoidance of adverse events from ineffective therapies

- **Risks, harms, costs:** Side effects of medications, which include local and systemic adverse reactions; cost of medications
- **Benefits-harm assessment:** Balance of benefit and harm
- **Value judgments:** Provide symptomatic relief while minimizing adverse events and costs
- **Intentional vagueness:** We use the broad term *symptomatic relief* to acknowledge there are several interventions available for this purpose and to encourage a conversation between clinicians and patients about which specific intervention(s) may be best for their specific ABRS symptoms
- **Role of patient preferences:** Large role for shared decision making regarding use of analgesics, topical nasal steroids, and saline irrigation
- **Exceptions:** None
- **Policy level:** Option
- **Differences of opinion:** None

### Supporting Text

The purpose of this statement is to raise awareness of interventions that may be used to provide symptomatic relief of ABRS (analgesics, saline irrigation, topical nasal steroids), to discourage use of interventions with questionable or unproven efficacy (antihistamines, systemic steroids), and to provide information on commonly used interventions (decongestants, guaifenesin) with unknown effects on ABRS symptoms.

Adjunctive treatments for rhinosinusitis that may aid in symptomatic relief include analgesics, decongestants ( $\alpha$ -adrenergic), corticosteroids, saline irrigation, and mucolytics. None of these products has been specifically approved by the FDA for use in acute rhinosinusitis (as of March 2014), and only some have data from controlled clinical studies supporting this use. Moreover, existing trials often include cointerventions and a heterogeneous population of patients with viral, recurrent bacterial, chronic, and allergic rhinosinusitis. Nonetheless, clinicians may wish to consider adjuvant therapy for ABRS on an individualized basis, and we therefore provide a brief overview of evidence in the remainder of this section.

### Analgesic Therapy

Pain relief is a major goal in managing ABRS and often a reason that patients with this condition seek health care.<sup>52,53</sup> Facial pain is a cardinal symptom for diagnosing ABRS (**Table 4**) and may involve the anterior face, periorbital region, or manifest with diffuse or localized headache. Over-the-counter analgesics, such as nonsteroidal anti-inflammatory drugs or acetaminophen, are usually sufficient to relieve facial pain associated with ABRS. Narcotics are rarely necessary and should be discouraged because of potential adverse events.

### Topical and Oral Steroids

Topical nasal steroids have been used alone or in combination with oral antibiotics for symptomatic relief of ABRS.

Prescription drugs studied in these trials include mometasone,<sup>89-91</sup> fluticasone,<sup>92</sup> flunisolide,<sup>93</sup> and budesonide.<sup>94</sup> An over-the-counter intranasal steroid, triamcinolone acetonide, is also available but has not been studied explicitly for ABRS.

A Cochrane review,<sup>95</sup> which included 4 RCTs of topical intranasal steroid vs placebo or no intervention as monotherapy for ABRS, found that steroids increased the rate of symptom improvement from 66% to 73% after 15 to 21 days (risk ratio, 1.10; 95% CI, 1.02-1.18). The studies had low risk of bias, and only minor adverse events were reported, which included epistaxis, headache, and nasal itching. The authors concluded that clinicians should weigh the modest (number needed to treat of 14) but clinically important benefits of intranasal steroid therapy against the associated cost and minor adverse events.

Although intranasal steroid therapy has been used as an adjunct to oral antibiotic therapy for managing ABRS, the results may not apply to patients with sporadic ABRS as defined in this guideline. Dolor and colleagues<sup>92</sup> increased the rate of treatment success for ABRS at 3 weeks from 74% to 93% when adding fluticasone nasal spray to oral cefuroxime, but all the patients studied had a history of CRS or recurrent ARS. Conversely, Williamson and colleagues<sup>94</sup> studied patients with nonrecurrent ARS and found no benefits for amoxicillin alone, or with topical budesonide, over placebo. This study, however, may have included many patients with VRS, because most patients had symptoms for less than 10 days (median of 7 days) and would not meet our diagnostic criteria for ABRS (**Table 4**).

A Cochrane review<sup>96</sup> of *systemic* steroids for ABRS found no benefit over placebo when oral steroids were used as monotherapy. Limited data from 5 trials were found to suggest that oral steroids used in combination with antibiotics may have a modest short-term beneficial effect for symptom relief (number needed to treat of 7), but confidence in results was limited by a significant risk of attrition bias caused by missing outcomes. Adverse events were mild (nausea, vomiting, gastric complaints), but the authors conclude that additional research is needed for adequate confidence in the true effect of systemic steroids.

### Saline Irrigation, Decongestants, Antihistamines, and Guaifenesin

Nasal saline irrigation, alone or in conjunction with other adjunctive measures, may improve quality of life, decrease symptoms, and decrease medication use for ABRS, particularly in patients with frequent sinusitis. Buffered hypertonic (3%-5%) saline irrigation showed a modest benefit for ARS in 2 clinical trials.<sup>97,98</sup> Compared with isotonic saline, hypertonic saline may have a superior anti-inflammatory effect and better ability to thin mucous and transiently improve mucociliary clearance.<sup>99-101</sup> One randomized controlled trial of patients with the common cold and ARS, however, found no difference in outcomes for hypertonic saline, normal saline, or observation.<sup>102</sup> There are no systematic reviews assessing the use of nasal saline irrigation in ABRS in adults.

Topical and systemic decongestants (sympathomimetics) have been used to treat nasal congestion associated with the common cold for many years.<sup>103-107</sup> There are no RCTs that specifically study the efficacy of decongestants for ABRS, but 2 small studies have shown that xylometazoline nasal spray reduces congestion of sinus and nasal mucosa on imaging studies<sup>65,108</sup> and is superior to a single orally administered dose of pseudoephedrine.<sup>108</sup> Another small, nonrandomized study showed improved outcomes when xylometazoline spray was added to antibiotics for ABRS.<sup>97</sup> Topical decongestants should not be used more than 3 to 5 consecutive days without a prolonged intervening drug-free period due to their propensity to cause rebound congestion and rhinitis medicamentosa.<sup>87</sup>

Antihistamines have no role in the symptomatic relief of ABRS in nonatopic patients.<sup>47,59,109</sup> No studies support their use in an infectious setting, and antihistamines may worsen congestion by drying the nasal mucosa. Conversely, 1 randomized controlled trial in allergic patients with ABRS showed reduced sneezing and nasal congestion for loratadine vs placebo when used as an adjunct to antibiotics and oral corticosteroids.<sup>110</sup> Antihistamine therapy, therefore, can be considered for patients with ABRS whose symptoms support a significant allergic component. In this regard, second-generation H1-antagonists cause less sedation and anticholinergic side effects than do older first-generation H1-antagonists.<sup>111</sup>

Guaifenesin is a water- and alcohol-soluble agent that is used as an expectorant to loosen phlegm and bronchial secretions. The product is available over the counter and is sometimes recommended to “loosen” nasal discharge, but there is no evidence regarding the effect, if any, on symptomatic relief of ABRS.

**STATEMENT 4. INITIAL MANAGEMENT OF ACUTE BACTERIAL RHINOSINUSITIS (ABRS): Clinicians should either offer watchful waiting (without antibiotics) or prescribe initial antibiotic therapy for adults with uncomplicated ABRS. Watchful waiting should be offered only when there is assurance of follow-up, such that antibiotic therapy is started if the patient’s condition fails to improve by 7 days after ABRS diagnosis or if it worsens at any time.**

*Recommendation based on systematic reviews of double-blind randomized controlled trials with some heterogeneity in diagnostic criteria and illness severity and a relative balance of benefit and risk.*

#### Action Statement Profile

- **Quality improvement opportunity:** Make explicit to clinicians and patients that not prescribing antibiotics for clinically diagnosed ABRS is an appropriate initial management strategy, because many patients will improve spontaneously and antibiotics could be started later if follow-up was assured.
- **Level of confidence in evidence:** Medium
- **Aggregate evidence quality:** Grade A, multiple systematic reviews of randomized controlled trials with some heterogeneity in diagnostic criteria and illness severity

- **Benefit:** Promote more informed, shared decision making regarding whether or not to prescribe initial antibiotics for ABRS given the favorable natural history in placebo groups, the small to modest benefits of antibiotic therapy, and the higher rates of adverse events when antibiotics are prescribed; more selective initial use of antibiotics will reduce adverse events and the risk of bacterial resistance
- **Risks, harms, costs:** Antibiotics could be withheld from patients who would have derived benefit from their use; antibiotics could be prescribed to patients who would have improved equally on their own.
- **Benefits-harm assessment:** Preponderance of benefit over harm (regarding the decision for initial management)
- **Value judgments:** Perception by the GUG that watchful waiting, without antibiotics, is an underused strategy for initial management of uncomplicated ABRS, despite existing guidelines and systematic reviews that support this approach.
- **Intentional vagueness:** No restrictions have been stated for illness severity (eg, mild, moderate, or severe), which was done in the prior guideline, because insufficient evidence to determine that severity would affect outcomes of antibiotic therapy, including the potential for complications.
- **Role of patient preferences:** Large role for shared decision making
- **Exceptions:** Complicated sinusitis, immune deficiency, or coexisting bacterial illness; the clinician should also consider the patient’s age, general health, cardiopulmonary status, and comorbid conditions when assessing suitability for watchful waiting.
- **Policy level:** Recommendation
- **Differences of opinion:** No difference of opinion regarding the choice to initially observe or prescribe antibiotics (one abstention); minor difference of opinion (1 against, 9 in favor) regarding the decision to remove severity (eg, mild illness) as a criterion for watchful waiting

#### Supporting Text

The purpose of this statement is to emphasize that both watchful waiting and antibiotic therapy are appropriate, evidence-based strategies for the initial management of uncomplicated ABRS. The precursor to this guideline<sup>1</sup> endorsed watchful waiting without an antibiotic as an option for initial management, even when ABRS signs and symptoms had persisted for 10 days or longer. More recent evidence, however, allows elevating watchful waiting to the status of a recommendation (not just an option). Moreover, whereas the prior guideline restricted watchful waiting to patients with only “mild” ABRS, current evidence supports offering this to patients regardless of illness severity.

Watchful waiting for ABRS refers to deferring antibiotic treatment of selected patients for up to 7 days after diagnosis of ABRS and limiting management to symptomatic relief.

Patients are candidates for watchful waiting when follow-up is ensured and a system is in place that permits reevaluation if the illness persists or worsens. Antibiotics are started if the patient's condition fails to improve by 7 days following ABRS diagnosis or worsens at any time.

### Outcomes of Placebo vs Antibiotic Therapy

Four systematic reviews of RCTs, all published since the prior version of this guideline,<sup>1</sup> have addressed the performance of antibiotics compared with placebo for the management of ABRS.<sup>112-115</sup> All of the analyses included RCTs that diagnosed patients on clinical signs and symptoms only. Some of the included RCTs also used radiology, serology, or microbiology studies to confirm the diagnosis. Collectively, the systematic review findings can be summarized as follows:

- Cure or improvement rates at 7 to 15 days favored antibiotics but the clinical benefit was small: 91% for antibiotic therapy vs 86% for patients who received placebo. The number needed to treat for benefit ranged from 11 to 15 patients and odds ratios for overall treatment effect ranged from 1.25 to 1.87.
- Duration of pain or illness associated with ABRS did not show any consistent relationship to initial management.<sup>113</sup>
- Adverse events were more common in the antibiotic-treated patients (odds ratio, 1.87 to 2.10; number needed to harm, 8.1), but the rate of dropout due to adverse events was small (1%-1.5%) and similar between both groups.
- Complications were similar regardless of initial management.

While the RCTs that comprised these meta-analyses typically excluded from randomization patients with "severe" disease, they did not specifically or consistently define what was meant by this term. As a result, there is no evidence supporting or refuting the stance that patients with more severe ABRS should always be treated with initial antibiotics. One study found ARS patients with pharyngeal purulence to be more likely to benefit from antibiotics.<sup>114</sup> Unfortunately, the literature is otherwise lacking on which patients may benefit more or less from antibiotic therapy. Further, there is no conclusive evidence that increased age or allergic rhinitis predicts a prolonged or chronic course of ABRS<sup>116,117</sup> or any evidence that older patients benefit more from antibiotic therapy.<sup>114</sup>

This guideline differs from its previous version<sup>1</sup> in no longer restricting watchful waiting to patients with mild to moderate ABRS because evidence is lacking to support additional benefits of antibiotic therapy for more severe presentations. This approach also differs from other guidelines and consensus statements that recommend antibiotics for patients with severe ABRS, manifesting as high fever and severe or worsening facial pain.<sup>15,19,69</sup>

### Shared Decision Making with Patients

Clinicians deciding whether or not to treat ABRS with antibiotics should also solicit and consider patient preference and

determine the relevance of existing evidence to their specific practice setting and patient population. Some patients may place great value on avoiding antibiotic therapy, whenever possible, but others may request initial antibiotics because they value the small but significant increase in clinical improvement they provide. Regardless of which initial strategy is used, clinicians should provide patients with clear information on management options, including symptomatic relief (**Table 6**). Clinicians may also find it helpful to evaluate the patient's preexisting knowledge and attitudes about antibiotic therapy and ABRS, because they could affect treatment preference.

Some patients will fail a period of watchful waiting and will benefit from antibiotics. To avoid the expense and inconvenience of another office visit in these patients, the clinician may wish to use a WASP (wait-and-see antibiotic prescription) or a SNAP (safety net antibiotic prescription). Such a prescription, with instructions on when to fill, can provide a sense of security for the patient who agrees to initial watchful waiting and is concerned about accessing the clinician to obtain an antibiotic prescription, if necessary. Patients are informed that they should fill the prescription and begin antibiotic therapy if they fail to improve within 7 days or if they worsen at any time. They should also call the physician's office and let them know they have begun antibiotic therapy.

**STATEMENT 5. CHOICE OF ANTIBIOTIC FOR ACUTE BACTERIAL RHINOSINUSITIS (ABRS):** If a decision is made to treat ABRS with an antibiotic agent, the clinician should prescribe amoxicillin with or without clavulanate as first-line therapy for 5 to 10 days for most adults. *Recommendation based on randomized controlled trials with heterogeneity and noninferiority design with a preponderance of benefit over harm.*

### Action Statement Profile

- Quality improvement opportunity: Discourage initial prescribing of antibiotics other than amoxicillin, with or without clavulanate, that may have lower efficacy or have comparable efficacy but more adverse events.
- Aggregate evidence quality: Grade A, systematic reviews of randomized controlled trials with heterogeneity and noninferiority design
- Level of confidence in evidence: Moderate regarding choice of antibiotic but lower regarding the optimal duration of antibiotic therapy because of limited supporting evidence and statistical power
- Benefit: Clinical outcomes that are comparable to broader spectrum antibiotics for initial therapy; potential reduced bacterial resistance by using a narrow-spectrum antibiotic as first-line therapy; cost-effectiveness of amoxicillin vs other antibiotic choices
- Risks, harms, costs: Potential increased gastrointestinal adverse effects with amoxicillin-clavulanate compared with other antibiotics; adverse effects from penicillin allergy

**Table 6.** Patient Information Sheet on Treating Acute Bacterial Rhinosinusitis (ABRS).

Question	Answer
How long will it take before I feel better?	Most patients with ABRS feel better within 7 days, and by 15 days, about 90% are cured or improved.
Is there anything I can do for symptomatic relief?	There are several ways to relieve sinusitis symptoms that should be discussed with your doctor to decide which are best for you: <ol style="list-style-type: none"> <li>1. <i>Acetaminophen</i> or <i>ibuprofen</i> can relieve pain and fever.</li> <li>2. <i>Saline irrigations</i>, or washing out the nose with salt water, can relieve symptoms and remove mucus that is hard to blow out.</li> <li>3. <i>Nasal steroid sprays</i> can reduce symptoms after 15 days of use, but the benefit is small (about 14 people must use them to get 1 person better), and side effects include headache, nasal itching, and nosebleeds.</li> </ol> <i>Decongestants</i> may help you breathe easier and can be taken as a nasal spray (for no more than 3 days in a row to avoid worsening congestion) or by mouth.
Is there anything I should not do?	<i>Antihistamines</i> and <i>oral steroid medicines</i> should not be used routinely because they have side effects and do not relieve symptoms.
If I have ABRS, do I have to take an antibiotic?	No, both <i>watchful waiting</i> and <i>antibiotic therapy</i> are proven ways to treat ABRS. Most people get better naturally, and antibiotics only slightly increase symptom relief (about 10 to 15 people must use antibiotics to get 1 more person better after 7-15 days).
Is there any downside to using antibiotic?	Antibiotics have side effects that include rash, upset stomach, nausea, vomiting, allergic reactions, and causing resistant germs.
What is “watchful waiting” for ABRS?	Watchful waiting means delaying antibiotic treatment of ABRS for up to 7 days after diagnosis to see if you get better on your own.
How is watchful waiting done?	Your doctor can give you an antibiotic prescription, but you should only fill the prescription and take the antibiotic if you do not get better after 7 days or if you get worse at any time. If you do use the antibiotic, contact your doctor’s office and let them know.
If I use an antibiotic, for how many days should I take it?	Antibiotics are usually given for 10 days to treat ABRS, but shorter courses may be equally effective. Ask your doctor about a 5- to 7-day course of antibiotics since side effects are less common.

- Benefits-harm assessment: Preponderance of benefit over harm
- Value judgments: Promote safe and cost-effective initial therapy
- Intentional vagueness: Whether to prescribe amoxicillin or amoxicillin-clavulanate is at the discretion of the clinician, as is the duration of therapy because systematic review has not shown consistent benefits for 10 days of therapy compared with shorter courses. A longer course of therapy may be appropriate for more severe illness or when symptoms persist despite a shorter course.
- Role of patient preferences: Moderate role for shared decision making; large role in determining duration of antibiotic therapy since adverse events are reduced with shorter duration of therapy.
- Exceptions: Patients with penicillin allergy for whom amoxicillin is contraindicated
- Policy level: Recommendation
- Differences of opinion: None

### Supporting Text

The purpose of this statement is to promote prescribing of antibiotics with known efficacy and safety for ABRS and to reduce prescribing of antibiotics with potentially inferior efficacy because of more limited coverage of the usual pathogens

that cause ABRS in adults. A secondary goal is to promote cost-effective antibiotic therapy of ABRS.

The rationale for antibiotic therapy of ABRS is to eradicate bacterial infection from the sinuses, hasten resolution of symptoms, and enhance disease-specific quality of life. Antibiotic therapy should be efficacious, cost-effective, and result in minimal side effects. Dozens of RCTs have assessed the comparative clinical efficacy of antibiotics for ABRS in adults,<sup>112</sup> with many trials either funded by pharmaceutical companies or conducted by authors associated with the pharmaceutical industry.<sup>48</sup>

### Choice of Initial Antibiotic for ABRS

No significant differences have been found in clinical outcomes for ABRS among different antibiotic agents. A systematic review<sup>112</sup> and 2 RCTs<sup>118,119</sup> of sinusitis patients with radiologic or bacteriologic confirmation found no significant difference in rates of clinical resolution for patients treated with amoxicillin or amoxicillin-clavulanate compared with cephalosporins or macrolides. Another review<sup>48</sup> found no differences in 11 comparative meta-analyses but did find a small decrease in failure rates for amoxicillin-clavulanate vs cephalosporins (number needed to treat of 30).

The justification for amoxicillin as first-line therapy for most patients with ABRS relates to its safety, efficacy, low cost, and narrow microbiologic spectrum.<sup>5,11,112,120-122</sup> Consideration to



**Table 7.** Factors That Would Prompt Clinicians to Consider Prescribing Amoxicillin-Clavulanate Instead of Amoxicillin Alone for Initial Management of Acute Bacterial Rhinosinusitis (ABRS).

Factor	Comment
Situations in which bacterial resistance is likely	Antibiotic use in the past month Close contact with treated individuals, health care providers, or a health care environment Failure of prior antibiotic therapy Breakthrough infection despite prophylaxis Close contact with a child in a daycare facility Smoker or smoker in the family High prevalence of resistant bacteria in community
Presence of moderate to severe infection	Moderate to severe symptoms of ABRS Protracted symptoms of ABRS Frontal or sphenoidal sinusitis History of recurrent ABRS
Presence of comorbidity or extremes of life	Comorbid conditions, including diabetes and chronic cardiac, hepatic, or renal disease Immunocompromised patient Age older than 65 years

prescribing amoxicillin-clavulanate for adults with ABRS is given to those at a high risk of being infected by an organism resistant to amoxicillin. Factors that would prompt clinicians to consider prescribing amoxicillin-clavulanate instead of amoxicillin are listed in **Table 7**.<sup>123,124</sup>

The use of high-dose amoxicillin with clavulanate (2 g orally twice daily or 90 mg/kg/d orally twice daily) is recommended<sup>15</sup> for adults with ABRS who are at a high risk of being infected with an amoxicillin-resistant organism. High-dose amoxicillin is preferred over standard-dose amoxicillin primarily to cover penicillin nonsusceptible (PNS) *Streptococcus pneumoniae*. This risk exists in those from geographic regions with high endemic rates (>10%) of invasive PNS *S pneumoniae*, those with severe infection (eg, evidence of systemic toxicity with temperature of 39°C [102°F] or higher, and threat of suppurative complications), age >65 years, recent hospitalization, antibiotic use within the past month, or those who are immunocompromised.<sup>125</sup>

### Penicillin-Allergic Patients

For penicillin-allergic patients, either doxycycline or a respiratory fluoroquinolone (levofloxacin or moxifloxacin) is recommended as an alternative agent for empiric antimicrobial therapy. Fluoroquinolones, however, are not recommended for first-line therapy of ABRS in patients without penicillin allergy because outcomes are comparable to amoxicillin-clavulanate, and adverse events are higher in some trials.<sup>126</sup> Combination therapy with clindamycin plus a third-generation oral cephalosporin (cefixime or cefpodoxime) is recommended in adults with a history of non-type I hypersensitivity to penicillin.

Macrolide antibiotics and trimethoprim-sulfamethoxazole are not recommended for initial therapy of ABRS. The high prevalence of macrolide-resistant *S pneumoniae* in the United States (>40%)<sup>124</sup> and the high rates of resistance to trimethoprim-sulfamethoxazole among both *S pneumoniae* (50%) and

*Haemophilus influenzae* (27%) may result in treatment failures,<sup>127</sup> but this concern has not been substantiated by comparisons in RCTs.

### Duration of Therapy and Adverse Events

Most trials of ABRS administer antibiotic for 10 days. A systematic review of 12 randomized controlled trials with radiologically confirmed ABRS found no difference in clinical success for antibiotics given for 3 to 7 days vs a 6- to 10-day course of therapy.<sup>128</sup> Similar findings have been noted in other trials, with similar resolution rates up to 3 weeks after treatment regardless of therapy duration.<sup>48,129-131</sup> When 5 days of antibiotic therapy is compared with 10 days, similar success rates are again observed.<sup>128</sup> Adverse events are common with antibiotic therapy, but the diverse reporting among studies precludes meaningful comparisons of rates across different antibiotic classes.<sup>48</sup> An average event rate of 15% to 40% is observed, with the most frequent complaints being nausea, vomiting, diarrhea, abdominal pain, headache, skin rash, photosensitivity, and vaginal moniliasis. Adverse events rarely are of sufficient severity to cause a change in therapy, but the impact of antibiotics on bacterial resistance must also be considered.

Adverse events are more common with antibiotic therapy compared with watchful waiting and are more common with 10 days of therapy compared to shorter courses. Antibiotic therapy increases adverse event rate by, on average, 10% to 12% over placebo,<sup>112,113</sup> with an odds ratio of 1.8 to 2.1.<sup>113,115</sup> Conversely, the incidence of adverse events is lower when antibiotics are given for 5 days instead of 10 days (odds ratio, 0.79),<sup>128</sup> so short courses should be considered for patients with less severe illness.

### Bacteriology of ABRS

The most common bacterial species isolated from the maxillary sinuses of patients with initial episodes of ABRS are

*S pneumoniae*, *H influenzae*, and *Moraxella catarrhalis*,<sup>5,132</sup> the latter being more common in children. A review of sinus aspiration studies performed in adults with ABRS suggests that *S pneumoniae* is isolated in approximately 20% to 43% of aspirates, *H influenzae* in 22% to 35%, *M catarrhalis* in 2% to 10%, and *Staphylococcus aureus* in 10%.<sup>66,133-136</sup>

Resistance patterns must be considered when prescribing antibiotics for ABRS to avoid using an antibiotic that may be rendered ineffective by bacterial resistance. For example,  $\beta$ -lactamase producing *H influenzae* has a prevalence of 27% to 43% in the United States<sup>137</sup> and would not be expected to respond to amoxicillin unless clavulanate was added. Similarly, the prevalence of penicillin-resistant *S pneumoniae* varies geographically, being highest in the Southeast (about 25%) and lowest in the Northwest (about 9%). Last, *S aureus*, which is found in up to 10% of cases of ABRS, nearly always produces  $\beta$ -lactamase,<sup>136,138</sup> making it resistant to amoxicillin but not amoxicillin-clavulanate.

The bacteriology of ABRS has changed since immunization of children with pneumococcal conjugate vaccine (PCV) was introduced in 2000. When patients with ABRS underwent middle meatal culture, the recovery of *S pneumoniae* decreased (35% postvaccination vs 46% prevaccination), but recovery of *H influenzae* increased (36% prevaccination vs 43% postvaccination).<sup>123</sup> In addition to a shift in organism prevalence, PCV has decreased the prevalence of invasive *S pneumoniae* isolates that are penicillin resistant to about 8% to 11%.<sup>127,138,139</sup> The introduction of the 13-valent PCV in 2010 may further decrease the prevalence of invasive pneumococcal infections,<sup>140</sup> making it easier to manage pneumococcus as an ABRS pathogen.

**STATEMENT 6. TREATMENT FAILURE FOR ACUTE BACTERIAL RHINOSINUSITIS (ABRS):** If the patient fails to improve with the initial management option by 7 days after diagnosis or worsens during the initial management, the clinician should reassess the patient to confirm ABRS, exclude other causes of illness, and detect complications. If ABRS is confirmed in the patient initially managed with observation, the clinician should begin antibiotic therapy. If the patient was initially managed with an antibiotic, the clinician should change the antibiotic. *Recommendation based on randomized controlled trials with limitations supporting a cut-point of 7 days for lack of improvement and expert opinion and first principles for changing therapy with a preponderance of benefit over harm.*

#### Action Statement Profile

- Quality improvement opportunity: Define realistic expectations regarding clinical response to initial management and to articulate clearly when reassessment of the patient is warranted
- Aggregate evidence quality: Grade B, randomized controlled trials with limitations supporting a cut-point of 7 days for lack of improvement; Grade D, expert opinion and first principles for changing therapy, including the use of rescue antibiotic in randomized controlled trials

- Level of confidence in evidence: High
- Benefit: Prevent complications, detect misdiagnosis, institute effective therapy
- Risks, harms, costs: Delay of up to 7 days in changing therapy if patient fails to improve; medication cost
- Benefits-harm assessment: Preponderance of benefit over harm
- Value judgments: Avoid excessive classification as treatment failures because of a premature time point for assessing outcomes; emphasize importance of worsening illness in definition of treatment failure
- Intentional vagueness: How to define *worsening* is left to the judgment of the clinician and patient, but there was group consensus that fluctuations in signs and symptoms within the first 48 to 72 hours of initial therapy were not uncommon and not necessarily indicative of failure.
- Role of patient preferences: None (unless the patient declines reassessment)
- Exceptions: Include but are not limited to severe illness, complicated sinusitis, immune deficiency, prior sinus surgery, or coexisting bacterial illness; the clinician should also consider the patient's age, general health, cardiopulmonary status, and comorbid conditions in determining an appropriate cut-point for assessing treatment failure; changing antibiotic therapy before failure would be appropriate in the face of adverse treatment effects.
- Policy level: Recommendation
- Differences of opinion: None

#### Supporting Text

The purpose of this statement is to emphasize that signs and symptoms of ABRS should generally improve within 7 days of diagnosis, but if they do not improve, or if they worsen at any time, the clinician should reassess the patient. A cut-point of 7 days to define treatment failure can help avoid unnecessary drugs or diagnostic tests caused by prematurely concluding the patient has failed treatment after only a few days, when randomized controlled trials show that improvement may take up to 7 days even when antibiotics are initially prescribed.<sup>1</sup>

#### Initial Treatment Failure of Presumed ABRS

Initial treatment failure of ABRS occurs when the patient worsens or fails to improve with the initial management option by 7 days after diagnosis. Assessing patients who fail initial treatment is important to reaffirm the diagnosis (**Table 4**), detect complications, exclude other causes of illness, and change management, if necessary. *Worsening* is defined as progression of presenting signs or symptoms of ABRS or onset of new signs or symptoms. *Failure to improve* is lack of reduction in presenting signs or symptoms of ABRS by 7 days after diagnosis, which would not apply if the patient had persistent, yet gradually improving, symptoms.

The rationale for using a cut-point of 7 days after initial diagnosis to assess treatment failure for ABRS is based on clinical outcomes in RCTs. A systematic review of ABRS by Rosenfeld and colleagues<sup>1</sup> found that between 7 and 12 days after trial enrollment, 73% of patients randomized to placebo have clinical improvement, rising to 85% when antibiotics are administered. A subsequent Cochrane review<sup>112</sup> had similar findings, with 86% cure or improvement at 7 to 15 days after receiving placebo and 91% after antibiotic therapy.

Defining treatment failure as a lack of clinical improvement within 7 days would result in an acceptable percentage of poor outcomes. Rates of improvement at 3 to 5 days are only 30% for placebo with a nonsignificant rise to 41% for antibiotic.<sup>1</sup> A cut-point of 5 days, therefore, would overdiagnose treatment failure since about two-thirds of patients would not have improved by that time, regardless of initial therapy. Using a stricter criterion of clinical cure (instead of improvement) would result in a failure rate of over 50% at 7 to 12 days. Clinicians and patients must therefore understand that ABRS may take up to 7 days to improve, persistence or minor worsening prior to 7 days does not necessarily indicate treatment failure, and complete cure (absence of all signs and symptoms) may take 14 days or longer.

Patients included in RCTs may not have identical risk factors or illness severity compared with patients not included in (or excluded from) RCTs. Therefore, a 7-day cut-point for improvement may not apply to patients with severe illness, complicated sinusitis, immune deficiency, prior sinus surgery, or coexisting bacterial illness; the clinician should also consider the patient's age, general health, cardiopulmonary status, and comorbid conditions in determining an appropriate cut-point for assessing treatment failure.

### Assessing the Patient with ABRS Who Fails Initial Treatment

Clinicians should confirm the diagnosis of ABRS by applying the diagnostic criteria in **Table 4**. If the patient does not have the symptom cluster of “up to 4 weeks purulent nasal drainage . . . accompanied by nasal obstruction, facial pain-pressure-fullness, or both” but instead has individual symptoms, alternate diagnoses should be explored. Migraines, tension headaches, cluster headaches, and temporomandibular joint disorder are common causes of facial pain that can be mistaken for ABRS. Similarly, nasal discharge or congestion can arise from common noninfectious causes that include allergic rhinitis, vasomotor rhinitis, deviated nasal septum, and nasal valve collapse. Imaging studies are not indicated for uncomplicated ABRS but may be appropriate to “rule out” ABRS (eg, a misdiagnosis) if the patient does not respond to therapy.

Patients with a reconfirmed diagnosis of ABRS who fail treatment, especially those with a worsening pattern of illness, should be examined for complications that include orbital or intracranial spread of infection. Suggestive findings on physical examination include proptosis, visual changes, severe headache, abnormal extraocular movements, changes in mental status, and periorbital inflammation, edema, or erythema. Acute

frontal sinusitis typically causes severe headache localized to the forehead over the orbits, with tenderness produced by pressure on the floor of the frontal sinus. Sphenoidal sinusitis typically causes a dull ache in the back of head, specifically over the occiput with radiation to the frontal and retro-orbital regions.

Culture of nasal secretions may help guide subsequent antibiotic therapy and is best performed by direct sinus aspiration rather than by nasopharyngeal swab. Endoscopically guided cultures of the middle meatus are an alternative in adults. A systematic review by Benninger and colleagues<sup>63</sup> showed that endoscopically directed cultures of the middle meatus had a sensitivity of 81%, specificity of 91%, positive predictive value of 83%, negative predictive value of 89%, and overall accuracy of 87% (95% CI, 81%-93%) compared with direct sinus aspiration.

### Antibiotic Therapy for ABRS Initial Treatment Failures

If the diagnosis of ABRS is confirmed and the treatment failure involves a patient managed initially with observation, the clinician should begin treatment with amoxicillin with or without clavulanate as discussed in the preceding section. For penicillin-allergic patients, either doxycycline or a respiratory fluoroquinolone (levofloxacin or moxifloxacin) is recommended. Combination therapy with clindamycin plus a third-generation oral cephalosporin (cefixime or cefpodoxime) is recommended in adults with a history of non-type I hypersensitivity to penicillin.

Patients who were initially treated with amoxicillin without clavulanate can be treated with high-dose amoxicillin plus clavulanate, doxycycline, a respiratory fluoroquinolone (levofloxacin or moxifloxacin), or the combination of clindamycin plus a third-generation oral cephalosporin (cefixime or cefpodoxime).

If, while on antibiotic therapy, the patient worsens or fails to improve after 7 days, infection with drug-resistant bacteria should be considered and should prompt a switch to alternate antibiotic therapy and reevaluation of the patient. When a change in antibiotic therapy is made, the clinician should consider the limitations in coverage of the initial agent.<sup>5</sup> For example, in patients receiving amoxicillin, it is common to identify a  $\beta$ -lactamase producing *H influenzae* or *M catarrhalis*. Recovery of *S pneumoniae* with reduced susceptibility to  $\beta$ -lactams, macrolides, tetracyclines, and trimethoprim-sulfamethoxazole is also common and has been strongly correlated with previous antibiotic therapy.

Very few studies have investigated the microbiology of treatment failure in ABRS; however, those that cultured sinus material identified a large percentage of bacteria with reduced susceptibility to the original antibiotic.<sup>125,141-145</sup> Brook and Gober<sup>125</sup> performed consecutive nasopharyngeal cultures of 20 children with ABRS who failed initial empiric antimicrobial therapy. Enhanced levels of resistance as demonstrated by a minimum inhibitory concentration (MIC) at least 2-fold higher than for the pretreatment isolate was observed in 49% of patients.

The choice of antibiotic for ABRS treatment failure is based on adequate coverage of anticipated bacteria or on antimicrobial sensitivity results if a culture was obtained. Antibiotic exposure increases the likelihood of resistant organisms, such as  $\beta$ -lactam and doxycycline-resistant *S pneumoniae* and  $\beta$ -lactamase producing *H influenzae* and *M catarrhalis*.<sup>141,146-148</sup> Predicting the likelihood of adequate antibiotic coverage for resistant organisms is addressed by studies of pharmacokinetics, in vitro susceptibility testing, and minimum inhibitory concentration.<sup>149-154</sup> Experimental and clinical studies suggest a relationship between treatment outcomes and pharmacodynamic concepts but involve extrapolations from acute otitis media and community-acquired pneumonia.

Optimal therapy of multi-drug-resistant *S pneumoniae* and  $\beta$ -lactamase producing *H influenzae* and *M catarrhalis* would include high-dose amoxicillin-clavulanate (4 g/d amoxicillin equivalent) or a respiratory fluoroquinolone (levofloxacin, moxifloxacin). These agents would also cover less common pathogens, such as *S aureus* and anaerobic bacteria. Conversely, oral cephalosporins and macrolides are predicted to offer inadequate coverage for *S pneumoniae* or *H influenzae*.

**STATEMENT 7A. DIAGNOSIS OF CHRONIC RHINOSINUSITIS (CRS) OR ACUTE RHINOSINUSITIS (ARS): Clinicians should distinguish CRS and recurrent ARS from isolated episodes of acute bacterial rhinosinusitis and other causes of sinonasal symptoms. Recommendation based on cohort and observational studies with a preponderance of benefit over harm.**

#### Action Statement Profile

- **Quality improvement opportunity:** Raise awareness of the distinct clinical entities of CRS and recurrent ARS so that appropriate management strategies may be implemented
- **Aggregate evidence quality:** Grade C, cohort and observational studies
- **Level of confidence in evidence:** High
- **Benefit:** Distinguish conditions that might benefit from additional management strategies than isolated cases of ABRS
- **Risks, harms, costs:** Potential misclassification of illness because of overlapping symptomatology with other illnesses; no cost
- **Benefits-harm assessment:** Preponderance of benefit over harm
- **Value judgments:** Importance of accurate diagnosis
- **Intentional vagueness:** None
- **Role of patient preferences:** Not applicable
- **Exceptions:** None
- **Policy level:** Recommendation
- **Differences of opinion:** None

#### Supporting Text

The purpose of this statement is to improve awareness of the distinct clinical entities of CRS, with and without polyps, and

recurrent ARS so that appropriate management strategies may be implemented. These strategies may include additional diagnostic tests, medical therapy, and surgical interventions.

CRS, with and without polyps, and recurrent ARS are temporal- and frequency-based patterns of illness (**Table 8**) that are distinct from isolated episodes of ABRS.<sup>13,60,155</sup> In both diagnoses, the clinical presentation, disease impact, subsequent diagnostic evaluation, and therapy differ significantly from ABRS. Furthermore, because of the chronicity and variety of symptoms that accompany CRS with or without polyps and recurrent ARS, these should be distinguished from other causes of symptoms that are commonly associated with sinonasal disorders.

#### CRS with and without Polyps

Symptoms of CRS vary in severity and prevalence. Nasal obstruction is most common (81%-95%) followed by facial congestion-pressure-fullness (70%-85%), discolored nasal discharge (51%-83%) and hyposmia (61%-69%). The presence of 2 or more signs or symptoms persisting beyond 12 weeks is highly sensitive for diagnosing CRS, but symptom-based criteria alone are relatively nonspecific.<sup>78,156-158</sup>

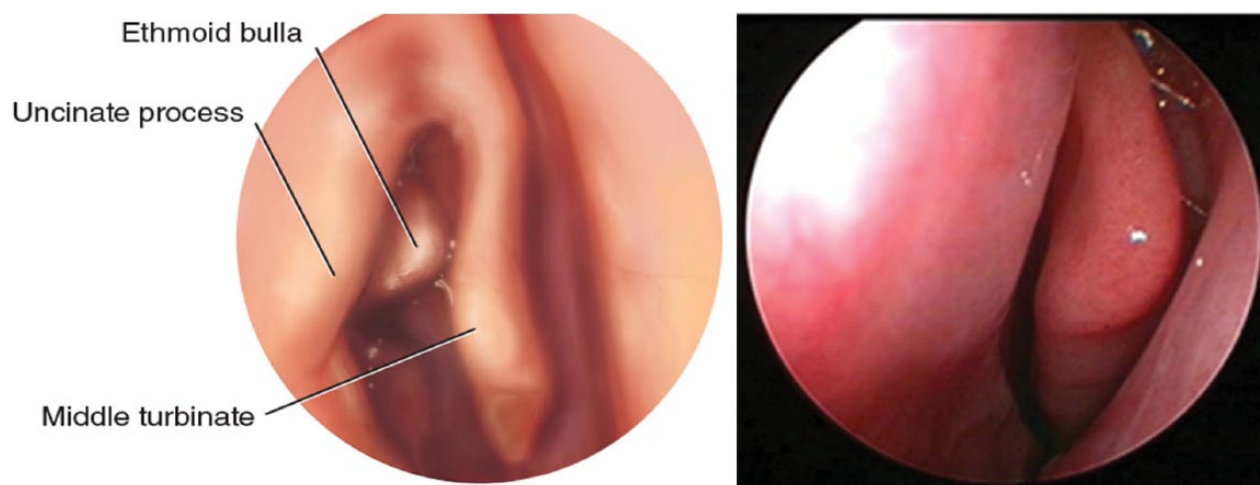
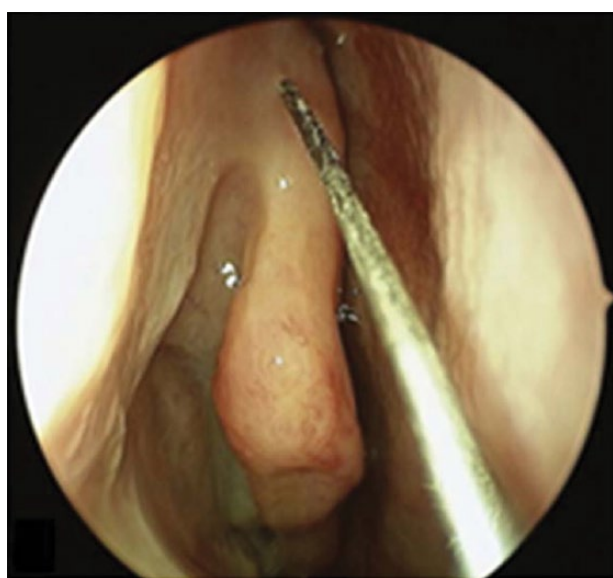
Diagnosing CRS requires that inflammation be documented (polyps, edema, or purulent mucus) in addition to persistent symptoms.<sup>155,156,159</sup> Examination of the nasal cavity can be performed using an endoscope or a headlight and nasal speculum, with specific attention to the middle turbinate and middle meatus (**Figure 3**); an otoscope may also be used but is suboptimal. Edema is often characterized by a boggy or swollen appearance to the mucosa as well as a lighter shade of pink or white mucosa (**Figure 4**). Inflammation could also manifest with polyps in the nasal cavity or middle meatus (**Figure 5**). Rarely, CRS may be suspected based primarily on objective findings (eg, nasal polyps or CT imaging) when other conditions have been excluded.

Distinguishing CRS from conditions with similar symptoms can be difficult. Using CT imaging as the criterion standard, the true prevalence of CRS in patients referred for evaluation of potential CRS based on patients' reported symptoms ranges from 65% to 80%. This prevalence may be lower in primary care settings. CRS may be accompanied by headache, fever, cough, halitosis, fatigue, dental pain, and other nonspecific signs or symptoms. Therefore, the differential diagnosis of CRS includes allergic rhinitis, nonallergic rhinitis, vasomotor rhinitis, eosinophilic nonallergic rhinitis, nasal septal deformity, and nonrhinogenic causes of facial pain. The latter include neurologic disorders, such as vascular headaches, migraine, cluster headache, trigeminal neuralgia, and other facial pain syndromes.<sup>45,161,162</sup>

CRS is primarily an inflammatory disease, with occasional exacerbations (ABRS) associated with infection. Treating the episodic infections alone leaves the underlying condition untreated, likely contributing to an increased frequency of exacerbations. In this way, CRS is very similar to chronic bronchitis. CRS is associated with sinus edema and impaired mucociliary clearance. With edema-related obstruction and retained mucus, bacterial infection can more easily set up

**Table 8.** Definitions of Chronic Rhinosinusitis and Recurrent Acute Rhinosinusitis.

Term	Definition
Chronic rhinosinusitis	<p>Twelve weeks or longer of two or more of the following signs and symptoms:</p> <ul style="list-style-type: none"> <li>• mucopurulent drainage (anterior, posterior, or both),</li> <li>• nasal obstruction (congestion),</li> <li>• facial pain-pressure-fullness, or</li> <li>• decreased sense of smell.</li> </ul> <p>AND inflammation is documented by one or more of the following findings:</p> <ul style="list-style-type: none"> <li>• purulent (not clear) mucus or edema in the middle meatus or anterior ethmoid region,</li> <li>• polyps in nasal cavity or the middle meatus, and/or</li> <li>• radiographic imaging showing inflammation of the paranasal sinuses.</li> </ul>
Recurrent acute rhinosinusitis	<p>Four or more episodes per year of acute bacterial rhinosinusitis (ABRS) without signs or symptoms of rhinosinusitis between episodes:</p> <ul style="list-style-type: none"> <li>• each episode of ABRS should meet diagnostic criteria in <b>Table 4</b></li> </ul>

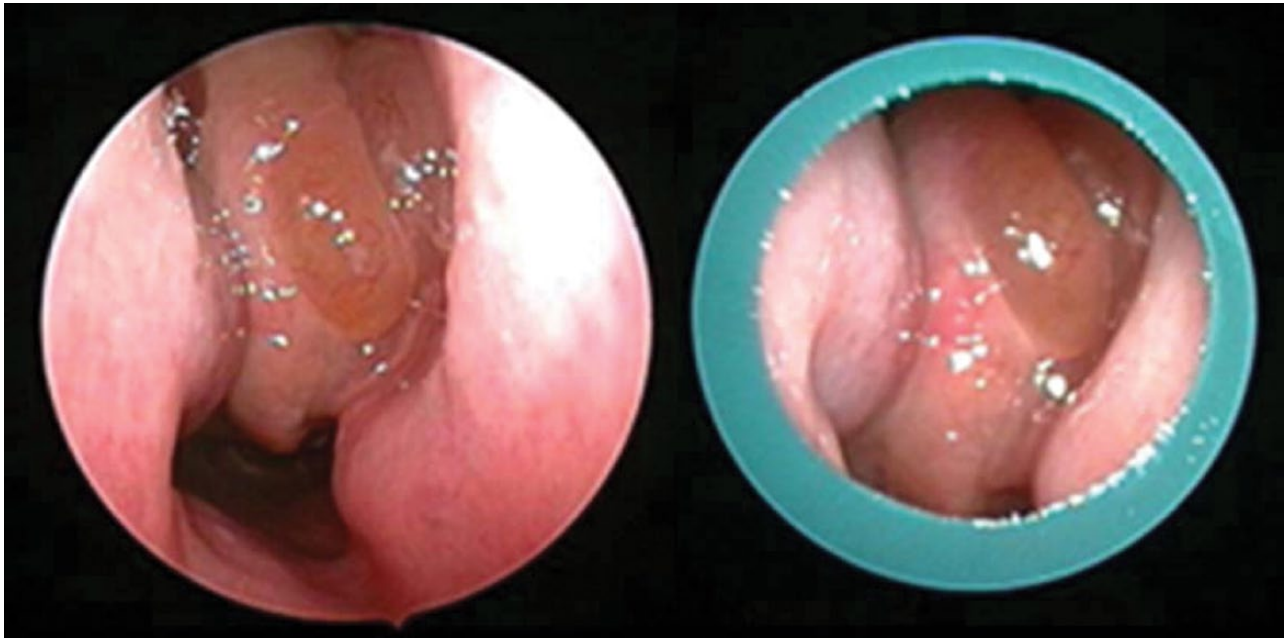
**Figure 3.** Paired images of the right middle meatus in an artist's view (left) and endoscopic view (right). Reproduced with permission from Palmer et al.<sup>160</sup>**Figure 4.** Endoscopic image of edema in the right middle meatus; needle tip points to the apex of the middle turbinate. Reproduced with permission from Palmer et al.<sup>160</sup>

within the sinuses. Therefore, when CRS is present, it should be treated with medications and other therapies that will target the underlying inflammatory disorder.

### Recurrent Acute Rhinosinusitis

Recurrent acute rhinosinusitis is diagnosed when 4 or more episodes of ABRS occur in the past 12 months without signs or symptoms of rhinosinusitis between episodes.<sup>60</sup> Although recognized as a distinct form of rhinosinusitis, only a few cohort studies have documented the characteristics and clinical impact of recurrent acute rhinosinusitis. The frequency cutoff for a minimum number of episodes to be considered for the diagnosis of recurrent acute rhinosinusitis from a multidisciplinary panel has reaffirmed a minimum cutoff of 4 or more episodes per year of ABRS.<sup>155</sup>

The proper diagnosis of recurrent ARS requires that each episode meets the criteria for ABRS (**Table 4**). Confirming a true bacterial episode of rhinosinusitis is desirable, but not essential, for substantiating an underlying diagnosis of recurrent ARS. In such cases, examination of the patient during an episode of ABRS (among the 4 episodes occurring per year) is necessary to



**Figure 5.** Paired images through an endoscope and a nasal speculum (circled image) showing polyps from the right middle meatus, filling the space in the nasal cavity between the inferior turbinate (on the left side of the image) and nasal septum (on the right). Reproduced with permission from Palmer et al.<sup>160</sup>

corroborate the diagnosis.<sup>163</sup> Examination of the middle meatus for purulence in the decongested state may strongly suggest ABRS and allows endoscopically guided culture.<sup>164</sup>

ARS should be distinguished from isolated ABRS because of a greater disease burden, diagnostic approach, and approach to management. The symptom burden of recurrent ARS is similar to CRS, but antibiotic utilization is higher.<sup>163</sup> Patients with both conditions may benefit from nasal culture or imaging studies. Neither chronic antibiotic therapy<sup>165</sup> nor nasal steroids<sup>166</sup> have demonstrated benefit in reducing episodes of recurrent acute sinusitis. An allergy-immunology evaluation may be considered to detect coexisting allergic rhinitis or an underlying immunologic deficiency. Sinus surgery may be considered in patients with recurrent ARS.<sup>167</sup>

**STATEMENT 7B. OBJECTIVE CONFIRMATION OF A DIAGNOSIS OF CHRONIC RHINOSINUSITIS (CRS):** The clinician should confirm a clinical diagnosis of CRS with objective documentation of sinonasal inflammation, which may be accomplished using anterior rhinoscopy, nasal endoscopy, or computed tomography. *Strong recommendation based on cross-sectional studies with a preponderance of benefit over harm.*

#### Action Statement Profile

- **Quality improvement opportunity:** Reduce overdiagnosis of CRS based on self-reported symptoms
- **Aggregate evidence quality:** B, cross-sectional studies
- **Level of confidence in evidence:** High
- **Benefit:** Improved diagnostic certainty for CRS and fewer false-positive diagnoses, which allows patients with CRS to be managed more promptly and those

without CRS to seek additional evaluation of their sinusitis-like symptoms and institute effective therapy

- **Risks, harms, costs:** None associated with improved diagnostic certainty, but diagnostic modalities have their own risk and direct cost profiles
- **Benefits-harm assessment:** Preponderance of benefit over harm
- **Value judgments:** Strong consensus by the GUG that the need for objective documentation of sinonasal inflammation is likely underappreciated and underperformed, despite its critical role in substantiating a diagnosis of CRS
- **Intentional vagueness:** Which of the three listed diagnostic modalities to use is not stated
- **Role of patient preferences:** Large role for shared decision making with clinicians regarding choice of the confirmatory diagnostic modality
- **Exceptions:** None
- **Policy level:** Strong recommendation
- **Differences of opinion:** None

#### Supporting Text

The purpose of this statement is to strongly emphasize that a diagnosis of CRS cannot be based on signs and symptoms alone but also requires objective evidence of sinonasal inflammation (**Table 8**). Requiring objective signs of inflammation increases diagnostic accuracy for CRS and serves to limit overdiagnosis. Moreover, objective confirmation of inflammation will prevent unnecessary tests and interventions for individuals with self-reported sinonasal symptoms that can be readily mistaken for CRS, such as those caused by perennial allergic rhinitis.

**Table 9.** Comparison of Modalities for Objective Confirmation of Sinonasal Inflammation.

Modality	Method	Cost	Discomfort	Risk	Sensitivity <sup>a</sup>
Nasal endoscopy	Direct visualization	Moderate	Minimal to moderate	Minimal	Good
Anterior rhinoscopy	Direct visualization	Minimal	Minimal	Minimal	Fair
Computed tomography	Radiographic	High	Minimal	Radiation exposure	Excellent

<sup>a</sup>Ability to detect signs of inflammation if present in the nasal cavity or sinuses.

Objective confirmation of sinonasal inflammation may be made by direct visualization or by CT scanning. Direct visualization is best accomplished with nasal endoscopy, but in some patients, anterior rhinoscopy using an otoscope or nasal speculum may suffice. An important part of direct visualization is identification of nasal polyps, as that will lead the clinician to rule out neoplasm in unilateral polyps, as well as suggest slightly different treatment stratagems for bilateral polyps.

Patient preference does influence in the choice of confirmatory modality. Anterior rhinoscopy has the least cost and procedural risk but is less sensitive than endoscopy and increases the chance of misdiagnosis. Nasal endoscopy and CT scanning both have a much higher diagnostic accuracy, but CT scanning includes the small associated risk of radiation exposure, while nasal endoscopy includes an added cost. These differences are summarized in **Table 9** and discussed further below.

### Direct Visualization by Endoscopy or Anterior Rhinoscopy

Direct visualization of the sinonasal mucosa at its most refined state is performed by nasal endoscopy.<sup>168</sup> Endoscopic evaluation is generally an office procedure used to evaluate the inflammatory status of the sinonasal mucosa and to assess nasal masses or lesions that are noted on physical examination.<sup>169</sup> Nasal endoscopy can be performed with a flexible or rigid endoscope, typically after a topical decongestant and anesthetic are applied to the nasal mucosa. Areas visualized during endoscopy include the nasal cavity, inferior turbinate, inferior meatus, middle meatus, uncinate process, hiatus semilunaris, maxillary ostia, anterior ethmoidal bulla, nasofrontal recess, sphenoidal recess, sphenoidal ostium, and the nasopharynx.

Findings on nasal endoscopy that support a diagnosis of CRS include purulent mucus or edema in the middle meatus or ethmoid region, or polyps in the nasal cavity or middle meatus.<sup>13,61,155</sup> Examples include abnormalities directly related to CRS or recurrent acute rhinosinusitis, such as nasal polyps, purulent nasal discharge, and septal deviation. Alternative findings that may suggest a more complicated or different disease process include neoplasms, soft tissue masses, foreign objects, tissue necrosis, and findings consistent with autoimmune or granulomatous disease.

A systematic review<sup>168</sup> assessed the diagnostic value of nasal endoscopy for adults with suspected CRS, using CT imaging as the gold standard for diagnostic certainty. Compared with baseline risk for CRS, a positive nasal endoscopy (pus or polyps) had an added value for confirming CRS of 25% to 28%, and a negative nasal endoscopy had an added

value of ruling out CRS of 5% to 30%. The authors concluded that nasal endoscopy should be a first-line confirmatory test for CRS, reserving CT scanning for patients with a prolonged or complicated clinical course.

Anterior rhinoscopy allows visualization of the anterior one-third of the nasal cavity with direct illumination and a speculum or other instrument to dilate the nasal vestibule. In the primary care setting, an otoscope is often used to examine the nasal cavity. In cases of large polyps or gross purulence, anterior rhinoscopy is sufficient; however, nasal endoscopy is superior in that it also allows visualization of the posterior nasal cavity, nasopharynx, and often the sinus drainage pathways in the middle meatus and superior meatus. Advantages of nasal endoscopy over anterior rhinoscopy are the ability to identify posterior septal deviation, polyps or secretions in the posterior nasal cavity, and polyps or secretions within the middle meatus or in the sphenoidal recess. Furthermore, nasal endoscopy allows directed aspiration of abnormal secretions for analysis and culture.

### CT Imaging

A diagnosis may also be confirmed by CT scanning or magnetic resonance imaging (MRI). MRI for confirmation of diagnosis is discouraged because of increased cost and hypersensitivity (overdiagnosis) in comparison to CT without contrast.

CT scanning can help quantify the extent of inflammatory disease based on opacification of the paranasal sinuses<sup>169</sup> and improves diagnostic accuracy because CT imaging findings correlate with the presence or absence of CRS in patients with suggestive clinical symptoms.<sup>163,170</sup> Although CT findings do not necessarily correlate with symptom severity, they offer an objective method for monitoring recurrent or chronic disease.<sup>78,171</sup> Mucosal abnormalities, sinus ostial obstruction, anatomic variants, and sinonasal polyposis are best displayed on CT. The appearance of the mucosa, however, is nonspecific, and mucosal thickening should be interpreted in the context of clinical examination, nasal endoscopy, or both.<sup>172</sup>

An important role of CT imaging in CRS with or without polyps is to exclude aggressive infections or neoplastic disease that might mimic CRS or ARS. Osseous destruction, extra-sinus extension of the disease process, and local invasion suggest neoplasia. If any such findings are noted, MRI should be performed to differentiate benign obstructed secretions from tumor and to assess for spread outside the nasal cavity and sinuses.<sup>76</sup>

CT of the paranasal sinuses should be obtained when endoscopic sinus surgery is considered or planned in patients with

CRS or recurrent ARS.<sup>173</sup> In addition to demonstrating abnormal mucosa and opacified sinuses, the study will provide the anatomic detail necessary to guide the surgery.<sup>76,174</sup> CT imaging of the paranasal sinuses has traditionally involved direct axial and coronal images to adequately visualize the ostiomeatal complex. Multidetector CT is a newer technology that offers advantages over single-detector imaging of the paranasal sinuses, because the patient is scanned once and all other planes (eg, coronal, sagittal) are reconstructed from the original data set. Multidetector CT imaging may reduce total radiation dose to the patient, and in the setting of nonneoplastic evaluation, it is acceptable to use not only for diagnosis but also for surgical intervention.

**STATEMENT 8. MODIFYING FACTORS: Clinicians should assess the patient with chronic rhinosinusitis or recurrent acute rhinosinusitis for multiple chronic conditions that would modify management such as asthma, cystic fibrosis, immunocompromised state, and ciliary dyskinesia.** *Recommendation based on one systematic review and multiple observational studies with a preponderance of benefit over harm.*

#### Action Statement Profile

- Quality improvement opportunity: Identify comorbid conditions that are known to accompany CRS and recurrent ARS, the knowledge of which would improve management of the sinusitis, and conversely, management of sinusitis may improve the associated chronic condition (asthma)
- Aggregate evidence quality: Grade B, one systematic review and multiple observational studies
- Level of confidence in evidence: Medium
- Benefit: Identify modifying factors that would alter management of CRS or recurrent acute rhinosinusitis; identify conditions that require therapy independent of rhinosinusitis
- Risks, harms, costs: Identifying and treating incidental findings or subclinical conditions that might not require independent therapy; morbidity related to specific tests; variable costs based on testing ordered
- Benefits-harm assessment: Preponderance of benefit over harm
- Value judgments: Consensus that identifying and managing modifying factors will improve outcomes
- Intentional vagueness: The method of assessing for these conditions is at the discretion of the clinician and may include history, physical examination, or diagnostic tests.
- Role of patient preferences: Small
- Exceptions: None
- Policy level: Recommendation
- Differences of opinion: None

#### Supporting Text

The purpose of this statement is to make clinicians aware of the benefit of diagnosing and treating underlying conditions

associated with CRS, so as to improve clinical outcomes. In contrast to ABRS, CRS and recurrent ARS have potential predisposing factors that may contribute to illness persistence, recurrence, or both.<sup>60</sup> Asthma,<sup>175,176</sup> cystic fibrosis,<sup>177</sup> immunocompromised state,<sup>178</sup> ciliary dyskinesia,<sup>179</sup> and anatomic variation<sup>180</sup> are some factors that have been investigated in this regard. Ideally, early identification of factors contributing to the recurrence or persistence of rhinosinusitis could play a crucial role in selecting the most appropriate treatment for individual patients.

The obligation to “assess” the patient for asthma, cystic fibrosis, immunocompromised state, and ciliary dyskinesia is fulfilled by documenting in the medical record that these conditions were considered in the differential diagnosis of CRS or recurrent ARS. Further assessment may include history, physical examination, or diagnostic tests at the discretion of the clinician. The guideline development group recognizes that except for asthma, these conditions are rare, and does not recommend a “shotgun” approach to extensive, nontargeted testing for all patients. Rather, testing should be individualized based on the patient’s history and physical examination.

#### Asthma and Rhinosinusitis

The association between rhinosinusitis and asthma is supported by the high prevalence of CRS and recurrent ARS in asthmatics<sup>181,182</sup> and is most noticeable when the asthma is severe.<sup>176,183</sup> Asthma severity has a direct correlation with the severity of radiographic sinus disease,<sup>183</sup> and 84% to 100% of patients with severe asthma have abnormal sinus CT scan findings.<sup>175</sup> Moreover, when CRS is treated (medically or surgically), asthma symptoms improve and the need for asthma-related medications decreases.<sup>184-186</sup>

A systematic review<sup>187</sup> found that endoscopic sinus surgery improves asthma control while decreasing asthma exacerbations, hospitalizations, and use of systemic and inhaled corticosteroids; pulmonary function, however, is unchanged.<sup>187</sup> These findings suggest a benefit of prompt therapy for CRS in asthmatics if rhinosinusitis is considered a reason for poor asthma control. Similarly, asthmatics with difficult to control illness should be assessed for unsuspected rhinosinusitis, with CT scanning or nasal endoscopy, since the signs and symptoms of CRS may be subtle and overlooked if not specifically sought.

#### Cystic Fibrosis and Rhinosinusitis

The association between cystic fibrosis (CF) and CRS has long been recognized, with CRS reported in 30% to 67% of patients with CF over all age groups.<sup>188-191</sup> Symptoms of CRS are reported by 36% of obligate carriers of a cystic fibrosis gene mutation,<sup>157</sup> compared with an estimated background prevalence of CRS between 13% and 14%.<sup>192,193</sup>

The association of CF mutation and CRS has been assessed in different fashions and within different populations, sometimes yielding conflicting results. In Finland, where the reported incidence of mutation carriage is about 1:80, only 1:127 patients with CRS screened for  $\Delta F508$  and 394delTT revealed the presence of a cystic fibrosis mutation.<sup>194</sup> It is well



documented, however, that concordance exists between microorganisms isolated in the upper and lower airways of CF patients with CRS, and upper airway colonization may precede spread of these bacteria to the lower airways.<sup>195-198</sup>

Multiple observational studies show that using a more aggressive treatment paradigm for CF patients with CRS, with regard to both maximizing surgery as well as postoperative medical therapy, can have a beneficial effect on the course of the sinus disease.<sup>199-202</sup> Since CRS or recurrent ARS, especially if associated with nasal polyps, can be the first manifestation of CF, patients with polyps who present before age 18 years or have refractory rhinosinusitis should be screened for underlying CF.

### **Immunodeficiency and Rhinosinusitis**

Several immunodeficient states have been documented in patients with CRS or recurrent acute rhinosinusitis,<sup>203-205</sup> supporting the role of immunological testing when evaluating patients with refractory or recurrent disease.<sup>203</sup> Common immunodeficiencies identified include decreases in serum IgA and IgG and abnormalities in IgG functional response to polysaccharide vaccines.<sup>203-206</sup> See Key Action Statement 9 in this clinical practice guideline for more details on appropriate testing to evaluate for this small, yet important, group of patients.

### **Ciliary Dyskinesia and Rhinosinusitis**

Ciliary dyskinesia accounts for a small percentage of patients with CRS demonstrating decreased mucociliary clearance.<sup>207-210</sup> Even in patients without an underlying genetic disorder causing ciliary dyskinesia, the normal mucociliary transit time (MTT) of 10 to 14 minutes is prolonged significantly when CRS is present.<sup>209</sup> Increased MTT has been identified in a growing number of patients with human immunodeficiency virus and has been implicated in this population's increased risk of recurrent rhinosinusitis.<sup>210</sup>

Not all studies, however, support the role of decreased mucociliary function in the pathogenesis of CRS. Ciliary beat frequency in mucosa from the nose and paranasal sinuses of patients with CRS showed no difference compared with normal controls, and frequency was increased in specimens recovered from patients with nasal polyposis.<sup>208</sup> Similar to CF and immunologic testing, ciliary dyskinesia testing may be indicated when patients have intractable rhinosinusitis, especially when accompanied by frequent or prolonged lower respiratory infections. Patients with CF and CRS may benefit from endoscopic sinus surgery, especially when obstructing nasal polyps are present, but relapse is common and revision surgery is often required.

### **Other Considerations**

Early research on the pathogenesis of CRS and recurrent ARS focused on anatomic abnormalities,<sup>211-214</sup> which could obstruct the paranasal sinuses and trigger infection.<sup>215,216</sup> Based on this assumption, descriptions of anatomic relationships, variances, associations with adjacent anatomic regions, and the importance of accurate radiographic data on surgical planning and intervention have populated the early endoscopic literature.<sup>174,217-221</sup> Nonetheless, evidence is lacking regarding a causal relationship between anatomic abnormalities and

chronic disease. One study<sup>180</sup> has correlated recurrent ARS with anatomic abnormalities in the anterior ethmoid sinus.

The relationship between gastroesophageal reflux disease (GERD) and rhinosinusitis is unclear, although there is an increasing body of literature suggesting a direct or indirect link. High-level evidence, however, to support this relationship is lacking. Most of the studies that suggest an association are small case series.<sup>222-224</sup> For example, in one small study,<sup>225</sup> 95% of patients with medically and surgically refractory rhinosinusitis had a positive pharyngeal pH probe, but nasopharyngeal pH did not correlate with pH in the pharynx. One mechanism by which GERD may cause sinonasal symptoms is through a nasal-esophageal reflex. Wong and colleagues<sup>226</sup> instilled hydrochloric acid and saline at the gastroesophageal junction and described a vagal reflex causing increased nasal mucus production and symptom scores.

Vaezi and colleagues<sup>227</sup> found that proton pump inhibitors significantly reduced symptoms of postnasal discharge in patients with rhinitis compared with placebo. Although there are no placebo-controlled studies that show a direct benefit of treating GERD on rhinosinusitis, these 2 conditions often coexist and share similar symptoms. Patients with clinically significant GERD should be managed accordingly, but whether treating mild or subclinical GERD can affect rhinosinusitis is unknown.

**STATEMENT 9. TESTING FOR ALLERGY AND IMMUNE FUNCTION: The clinician may obtain testing for allergy and immune function in evaluating a patient with chronic rhinosinusitis or recurrent acute rhinosinusitis.** *Option based on observational studies with an unclear balance of benefit vs harm.*

### **Action Statement Profile**

- **Quality improvement opportunity:** Improve patient quality of life by identifying, and managing, allergies that often coexist with CRS and recurrent ARS and have overlapping symptoms that may make diagnosis difficult using strictly clinical criteria without testing
- **Aggregate evidence quality:** Grade C, systematic review of observational studies
- **Level of confidence in evidence:** Medium
- **Benefit:** Identify allergies or immunodeficient states that are potential modifying factors for CRS or recurrent acute rhinosinusitis and improve management strategies
- **Risks, harms, costs:** Procedural discomfort; instituting therapy based on test results with limited evidence of efficacy for CRS or recurrent acute rhinosinusitis; very rare chance of anaphylactic reactions during allergy testing; procedural and laboratory cost
- **Benefits-harm assessment:** Balance of benefit and harm
- **Value judgments:** Need to balance detecting allergy in a population with high prevalence vs limited evidence showing benefits of allergy management on rhinosinusitis outcomes

- Intentional vagueness: The methods and scope of testing for allergy and immune function are at the discretion of the clinician
- Role of patient preferences: Large for shared decision making
- Exceptions: None
- Policy level: Option
- Differences of opinion: None

### Supporting Text

The purpose of this statement is to describe the role of testing for allergy and immune function in patients with CRS or recurrent ARS, emphasizing that testing is optional because there is no substantive evidence to support a consistent beneficial effect of treatment despite the high prevalence of allergy in patients with rhinosinusitis.

### Testing for Allergy

The prevalence of allergic rhinitis (AR) is 40% to 84% in adults with CRS<sup>228-230</sup> and 25% to 31% in young adults with acute maxillary sinusitis.<sup>231,232</sup> About twice as many patients with allergic rhinitis, compared with normal subjects, have abnormal CT scans.<sup>233</sup> Extensive sinus disease, as quantified by sinus CT imaging, is associated with allergy in 78% of patients and asthma in 71%.<sup>234,235</sup> Patients with both allergy and CRS are more symptomatic than nonallergic patients with similar CT findings.<sup>236,237</sup> In one study of 200 patients with CRS, more than half had allergic rhinitis, which was considered the most important underlying cause of sinusitis.<sup>238</sup>

Edema caused by allergic rhinitis may obstruct the paranasal sinuses,<sup>212</sup> and this concept is supported by a higher prevalence of mucoperiosteal disease on CT imaging in patients with allergies compared to others without.<sup>235,236</sup> Furthermore, a hyperresponsive state associated with allergic rhinitis may increase susceptibility to inflammation within the nose and paranasal sinuses, thereby predisposing to rhinosinusitis.<sup>239</sup> A recent retrospective cohort study of CRS determined AR as a premorbid factor in newly diagnosed CRS.<sup>240</sup> Of note, most of the above studies are case series with heterogeneous inclusion criteria that suggest a link between these allergy and rhinosinusitis conditions but do not imply causality.

A systematic review by Wilson and colleagues<sup>241</sup> concluded that allergy testing is an option for patients with CRS or recurrent ARS. Allergy skin tests are the preferred method for detecting IgE-mediated sensitivity. For most allergens, in vitro allergen-specific immunoassays detect IgE-specific antibody in the serum of most, but not all, patients who respond clinically to those allergens. The sensitivity of immunoassay compared with prick or puncture skin tests ranges from 50% to 90%, with an average of 70-75% for most studies.<sup>242</sup> A direct correlation for clinical disease cannot be assumed by evidence provided from skin testing or in vitro allergen-specific immunoassays unless results are interpreted by a qualified clinician based on history and physical examination obtained on face-to-face contact with the patient.

If allergy testing is positive and appears clinically relevant based on individual assessment, management may include environmental control measures, pharmacologic therapy, or immunotherapy as an immunomodulating approach. There are, however, limited data to support that allergen avoidance and/or immunotherapy improves CRS or recurrent ARS,<sup>19,47</sup> and the level of evidence for existing research is poor.<sup>241</sup> Although allergic rhinitis can prolong the course of ABRS, the clinical impact is small (6%-8% increased risk) and does not support different management of ABRS patients with or without underlying allergy.<sup>117</sup>

### Testing for Immune Function

Immunodeficiency should be considered in patients with CRS or recurrent ARS when aggressive management has failed or when sinusitis is associated with otitis media, bronchiectasis, or pneumonia.<sup>203,205</sup> Sinusitis was one of the most frequent presenting infections in the French national study of primary hypogammaglobulinemia, and 36% of patients with common variable immunodeficiency (CVID) had sinusitis.<sup>243</sup> Another study of patients with radiographically diagnosed sinusitis refractory to medical and surgical therapy revealed 10% of patients to have CVID and 6% to have IgA deficiency.<sup>203</sup> Patients failing medical therapy and undergoing sinus surgery have been noted (11%) to have specific antibody deficiency.<sup>206</sup> CRS or recurrent ARS can affect 30% to 68% of patients with human immunodeficiency virus (HIV) infection.<sup>244</sup>

The most common primary immunodeficiency disorders associated with CRS or recurrent ARS are humoral immunodeficiencies, such as selective IgA deficiency, common variable immunodeficiency, and specific antibody deficiency, which features normal IgG levels but a defective response to polysaccharide vaccines.<sup>245</sup> Laboratory studies in patients with CRS or recurrent ARS may include quantitative immunoglobulin measurements (IgG, IgA, and IgM), preimmunization- and postimmunization-specific antibody responses to tetanus toxoid and pneumococcal polysaccharide vaccines, CH50, and measurement of T-cell number and function (delayed hypersensitivity skin tests and flow cytometric enumeration of T cells). IgG subclasses should not be checked routinely in immunodeficiency evaluation as the connection of IgG subclass deficiency to recurrent or CRS is controversial, and the clinical significance of abnormal IgG subclasses in patients with recurrent infections is unclear.<sup>246</sup>

**STATEMENT 10. CHRONIC RHINOSINUSITIS (CRS) WITH POLYPS: The clinician should confirm the presence or absence of nasal polyps in a patient with CRS.**  
*Recommendation based on observational studies with preponderance of benefit over harm.*

### Action Statement Profile

- Quality improvement opportunity: Improve awareness of the prevalence of polyps in patients with CRS and their role as a modifying factor for further diagnostic assessment and treatment.
- Aggregate evidence quality: High; Grade A, systematic review of multiple RCTs

- Level of confidence in evidence: Medium
- Benefit: Prioritize referral for specialty evaluation, identify patients likely to benefit most from topical (intranasal) or systemic corticosteroid therapy, identify patients for additional diagnostic tests to assess for conditions other than CRS that are associated with nasal polyposis and may require different management strategies
- Risks, harms, and costs: None related to identifying patients; specific costs and risks based on the choice of diagnostic procedure
- Benefits-harm assessment: Preponderance of benefit over harm
- Value judgments: Underappreciation of the importance of polyps as a modifying factor for CRS; perception of diagnostic uncertainty in the ability to detect or exclude the presence of polyps
- Intentional vagueness: The method of confirming the diagnosis is left to the discretion of the clinician, provided that a high degree of diagnostic certainty is achieved
- Role of patient preferences: None
- Exceptions: None
- Policy level: Recommendation
- Differences of opinion: None

### Supporting Text

The purpose of this statement is to encourage clinicians to assess for nasal polyps in a patient with CRS, because nasal polyps will likely affect the utility of additional diagnostic testing and treatment management.

The exact prevalence of nasal polyps in rhinosinusitis is unknown, but about 4% of patients with CRS have concurrent polyps.<sup>247</sup> An association between asthma, nasal polyps, and aspirin sensitivity was recognized many years ago,<sup>248,249</sup> but, conversely, nasal polyps do not seem to be related to allergic rhinitis.<sup>250-252</sup> The prevalence of nasal polyps likely varies by geography and environment, although large studies of the prevalence of polyps across different geographic areas are lacking.

Identifying nasal polyps requires careful examination of the nasal airway. Large polyps, which obstruct the nasal cavity, are easily visualized with a nasal speculum or handheld otoscope. Small nasal polyps in the middle meatus or in the posterior nasal cavity, however, may only be detected by nasal endoscopy.<sup>253</sup> A clinician who suspects nasal polyps in a patient with CRS and is unable to perform nasal endoscopy should refer the patient to a physician who can thoroughly examine the nasal cavity.

CT imaging of the sinuses is often useful in evaluating CRS with nasal polyps, especially for unilateral polyps, concern for polyps extending outside of the nasal cavity, or other atypical presentations.<sup>256</sup> CT examination defines the extent of involvement of nasal polyps throughout the nasal cavity, the status of bony landmarks (ie, lamina papyracea), and the integrity of the orbit and cranial vault. Patients with longstanding nasal polyps and a history of previous surgeries are

likely to have significant anatomical changes within the paranasal sinuses.

Unilateral nasal polyps may be a sign of CRS but are less common than bilateral polyps and should prompt investigation for other conditions that can mimic CRS, including carcinoma, inverting papilloma, antrochoanal polyp, or allergic fungal sinusitis. These conditions will require a more thorough diagnostic evaluation and treatment than suggested for bilateral nasal polyps associated with CRS. Tissue biopsy is required to make the diagnosis of nasal polyp and to rule out other pathologies; scraping of nasal polyps is not recommended. Testing for allergy or immune function in CRS is an option that is unaltered by the presence, or absence of polyps, and additional details can be found in the preceding key action statement (Key Action Statement 9).

Chronic topical or intravenous antibiotics for CRS with nasal polyps is not recommended, but select oral antibiotics, especially the macrolide class, may be beneficial because of their anti-inflammatory effects.<sup>19,255</sup> Conversely, topical nasal steroid sprays are indicated for long-term treatment of nasal polyps in the setting of CRS.<sup>256-258</sup> If no response is seen within 3 months, a short course of oral corticosteroids is reasonable to try.<sup>254,259-261</sup> Off-label topical corticosteroids in the nasal cavity, including budesonide, may also be beneficial.<sup>262,263</sup>

**STATEMENT 11. TOPICAL INTRANASAL THERAPY FOR CHRONIC RHINOSINUSITIS (CRS): Clinicians should recommend saline nasal irrigation, topical intranasal corticosteroids, or both for symptom relief of CRS.** *Recommendation based on a preponderance of benefit over harm.*

### Action Statement Profile

- Quality improvement opportunity: Address underutilization; promote awareness of efficacy; reduce confusion over delivery method, frequency, and duration; educate patients on optimal administration
- Aggregate evidence quality: Grade A, systematic reviews of RCTs
- Level of confidence in evidence: High
- Benefit: Symptomatic relief, promoting awareness of effective over-the-counter interventions, discouraging improper and ineffective usage, and avoiding adverse events from systemic therapies
- Risks, harms, costs: Intranasal discomfort, burning, stinging; epistaxis; direct costs of saline or steroid
- Benefits-harm assessment: Preponderance of benefit over harm
- Value judgments: None
- Intentional vagueness: The choice of saline, steroid, or both is a shared decision; it is not clear how long the treatment should last as the natural history is unknown
- Role of patient preferences: Large role for deciding which products to use and their duration
- Exceptions: None

**Table 10.** Patient Instructions for Optimal Use of Topical Nasal Steroid.<sup>a</sup>

1. Shake the bottle well.
2. Look down by bending your neck and looking toward the floor.
3. Put the nozzle just inside your nose using your right hand for the left nostril and your left hand for the right nostril.
4. Aim toward the outer wall and squirt once or twice as directed; do not aim toward the nasal septum (in the middle of the nose) to prevent irritation and bleeding.
5. Change hands and repeat for other side.
6. Do not sniff hard.

<sup>a</sup>Adapted from Scadding and colleagues.<sup>272</sup>

- Policy level: Recommendation
- Differences of opinion: None

### Supporting Text

The purpose of this statement is to highlight the importance of intranasal saline and intranasal corticosteroid therapy in providing symptomatic relief and improved quality of life for patients with CRS. Despite the benefits of these interventions seen in RCTs and systematic reviews, the GUG felt they were underused by clinicians managing patients with CRS.

### Saline Irrigation for CRS

The beneficial effects of saline in improving symptoms and quality of life include improvement in mucous clearance, enhanced ciliary activity, disruption and removal of antigens, biofilms and inflammatory mediators, and direct protection of the sinonasal mucosa. Nasal saline irrigation has been recommended by clinicians both as adjunctive therapy for chronic sinonasal symptoms and in the postoperative period to moisten and cleanse sinonasal clots and crust, as well as to promote mucosal healing.

A beneficial effect of nasal irrigation for symptomatic relief of CRS has been shown in a Cochrane review<sup>264</sup> and in other systematic reviews.<sup>258,265</sup> Nasal saline irrigation is effective as sole treatment for CRS or as an adjunct to topical nasal steroids, but compared directly with topical nasal steroids, the benefits of saline irrigation are less pronounced.<sup>264</sup> The safety and minimal side effects of saline irrigation, however, make it an attractive sole therapy for CRS. Common side effects of nasal irrigation include fluid dripping from the nose.

Clinicians should not confuse saline *spray* with saline *irrigation*, because irrigation is more effective in expelling secretions and improving quality of life.<sup>265,266</sup> Irrigation can be performed with isotonic or hypertonic nasal solution, but evidence is insufficient to support superiority of either approach.<sup>265</sup> In addition, the optimal frequency or method of irrigation is uncertain.<sup>264</sup> This uncertainty, combined with the time commitment required for regular saline irrigation, may explain underuse despite well-established efficacy in relieving CRS symptoms.

Availability of delivery devices and ready-made saline solutions over the counter may make it easier for the patients to perform nasal irrigation. Commercially available preparations, however, are expensive compared with homemade solutions. Costs of nasal irrigation vary but are generally low,

especially when patients are instructed to make their own solution.<sup>267</sup> Recipes for preparation of homemade solutions and delivery methods vary widely (pot, pulsatile irrigation, atomizer, bulb/syringe, squeeze bottle, and low-pressure irrigation [Neti pot]).

### Topical Intranasal Steroids

Inflammation is considered the pathological basis for CRS, and therefore corticosteroids are widely recommended.<sup>268</sup> Corticosteroids are effective as anti-inflammatory agents due to their actions on reducing proinflammatory and increasing anti-inflammatory gene transcription, reducing airway inflammatory cell infiltration, and suppressing proinflammatory mediators, cell chemotactic factors, and adhesion molecules.<sup>269</sup>

The efficacy of topical steroid therapy for reducing symptoms of CRS is supported by systematic reviews of randomized controlled trials from Cochrane authors<sup>270</sup> and others<sup>256-258,271</sup> that show benefits with excellent safety and minimal adverse events. In some reviews, however, subgroup analyses show benefits of topical steroids for CRS with polyps but absent or unknown efficacy for CRS without associated polyps.<sup>256,258</sup> Classes of topical steroids include first-generation intranasal steroids such as beclomethasone dipropionate, triamcinolone acetonide, flunisolide, and budesonide and newer preparations, such as fluticasone propionate, mometasone furoate, ciclesonide and fluticasone furoate.

Topical nasal steroids are most effective when properly administered. Since patients may not be familiar with the optimal method for using the medication, we recommend that clinicians describe or demonstrate how to properly administer a nasal steroid. Patient-friendly instructions are summarized in **Table 10** and may assist in this educational process.

Adverse events of topical nasal steroids are generally minor (epistaxis, headache, and nasal itching), but when steroids are used for long-term control of CRS, additional concerns arise regarding systemic absorption and ocular effects. Long-term use, however, has not been shown to affect systemic cortisol levels<sup>273</sup> or to increase the risk of lens opacity, elevated intraocular pressure, or any other ocular symptoms.<sup>274</sup> Patients on long-term topical nasal steroids should consult their physicians to determine if regular ophthalmic monitoring is appropriate.

The GUG agreed, based on expert consensus, that topical nasal steroids should be used for a least 8 to 12 weeks because of the time needed for symptomatic relief and to assess benefit to the patient. Moreover, there was strong agreement that

patients may not know how to best deliver steroid to the nasal cavity and should therefore be given simple instructions on how to use the medication. The GUG felt that no statement can be made regarding a specific length of treatment and that decisions should be individualized based on the degree of symptom relief, patient preference, and clinician experience.

**STATEMENT 12. ANTIFUNGAL THERAPY FOR CHRONIC RHINOSINUSITIS (CRS).** Clinicians should not prescribe topical or systemic antifungal therapy for patients with CRS. *Recommendation (against therapy) based on systematic review of RCTs with a preponderance of benefit over harm (for not treating).*

#### Action Statement Profile

- **Quality improvement opportunity:** Discourage use of antifungal therapy for CRS based on lack of efficacy and presence of significant cost and adverse effects
- **Aggregate evidence quality:** Grade A, systematic reviews of RCTs
- **Level of confidence in evidence:** High
- **Benefit:** Avoid cost of ineffective medications, avoid unnecessary adverse events, direct management away from ineffective therapy to beneficial therapy (opportunity cost), avoid selection of resistant fungi and alterations of sinonasal flora
- **Risks, harms, costs:** None (for avoiding ineffective therapy)
- **Benefits-harm assessment:** Preponderance of benefit over harm (for not treating)
- **Value judgments:** Antifungal therapy is frequently used, with regional variations, for treating CRS despite good evidence of no efficacy
- **Intentional vagueness:** None
- **Role of patient preferences:** None
- **Exceptions:** Patients with allergic fungal sinusitis or invasive fungal sinusitis
- **Policy level:** Recommendation
- **Differences of opinion:** None

#### Supporting Text

The purpose of this statement is to emphasize that clinicians should not prescribe systemic or topical antifungal therapy for patients with CRS because of potential adverse events that are not offset by consistent, significant benefits in systematic reviews from Cochrane<sup>275</sup> or other investigators.<sup>255,258,271,276</sup>

Despite a lack of efficacy, antifungal therapy for CRS is used widely by some clinicians with regional variations. Our main intent with this key action statement, therefore, is to educate patients and clinicians and to prevent antifungal therapy for CRS. This statement, however, does not apply to antifungals for invasive fungal sinusitis or to allergic fungal sinusitis, for which more evidence is needed to make any definitive conclusions.

#### Role of Fungi in CRS

Ponikau and colleagues<sup>277</sup> first described eosinophilic infiltrates within the mucosa in patients with CRS, suggesting a

possible role of fungus in these patients. This was bolstered by prior studies demonstrating fungi in the surgical specimens of patients with CRS,<sup>278-280</sup> leading to a hypothesis that patients with CRS have a distinctive immune response to ubiquitous fungi compared with normal control patients, involving a noninvasive, nonallergic interleukin 5–mediated response and eosinophilic inflammation.<sup>281,282</sup> This was the beginning of a continuing debate about how applicable this theory is to the general population of patients with CRS and how antifungal therapy might affect them.

Every systematic review that was limited to RCTs<sup>255,258,275</sup> concluded that there was no beneficial effect from either oral or topical antifungal therapy in CRS. The only potential benefits of oral antifungal therapies were found in a systematic review of observational studies with nonvalidated outcome measures,<sup>283</sup> which carry a risk of bias that makes conclusions impossible. In the Cochrane review,<sup>275</sup> which included both oral and topical antifungals and had strict inclusion criteria, there was no evidence of benefit for topical antifungals. Only 1 of 5 trials reported benefit for radiographic and endoscopic scores (not symptom scores) and no benefit of systemic antifungal therapy over placebo for the same outcomes.

Adverse effects of these therapies have been documented, including elevated liver function tests for oral antifungals, nasal irritation, decreased sinonasal-related quality of life, decreased ciliary function at increasing concentrations, and extremely high cost for topical antifungals.<sup>275,283,284</sup> There is also the potential for inducing fungal resistance due to the low concentrations used in topical formulations. Multiple trials used concentrations of amphotericin B at 100 µg/mL, a concentration that has been documented to not impede fungal growth in vitro compared with true inhibition at 200 and 300 µg/mL.<sup>285</sup> There is also the opportunity cost to patients, who may receive these treatments in the place of other management strategies with known benefit.

#### Implementation Considerations

The complete guideline is published as a supplement to *Otolaryngology–Head and Neck Surgery*, and an executive summary will be simultaneously published in the main journal. A full-text version of the guideline will also be accessible free of charge at the [www.entnet.org](http://www.entnet.org), the AAO-HNSF website. The guideline will be presented to AAO-HNSF members as a miniseminar at the annual meeting following publication. Existing brochures, publications, and patient information sheets from the AAO-HNSF will be updated to reflect the guideline recommendations.

An anticipated barrier to the diagnosis of rhinosinusitis is the differentiation of VRS from ABRS in a busy clinical setting. This is facilitated by the clear, unambiguous criteria in **Table 4** and in Key Action Statement 1a, which allow clinicians to identify illness that is likely bacterial based on the history and time course of illness, without invasive tests or imaging studies. Use of these criteria may be assisted by a teaching card or visual aid. Patient education (**Table 5**) may help address this barrier. When diagnosed with VRS, patients may pressure clinicians for antibiotics, in addition

to symptomatic therapy, especially when nasal discharge is colored or purulent. Existing educational material from the Centers for Disease Control and Prevention (CDC) Get Smart Campaign can be used by clinicians to help clarify misconceptions about viral illness and nasal discharge.<sup>286</sup>

Anticipated barriers to “watchful waiting” for ABRS are the reluctance of patients and clinicians to consider observing a presumed bacterial illness. Compared with the first version of this guideline,<sup>1</sup> however, there is now a more robust evidence base to substantiate watchful waiting as an initial management strategy, even when more severe symptoms are present. These barriers can be overcome with an educational handout (**Table 6**) of patient information of nonsevere ABRS, the moderate incremental benefit of antibiotics on clinical outcomes, and the potential adverse effects of orally administered antibiotics (including induced bacterial resistance).

A potential barrier to using “wait-and-see” or “safety net” prescriptions as part of a watchful waiting strategy for initial management of ABRS is that electronic health records may consider all antibiotic prescriptions, even if never filled by the patient, as “antibiotic prescribing,” which could adversely affect quality measures. One solution would be for companies that produce electronic health records to include a means of documenting delayed prescribing strategies (eg, wait-and-see) for antibiotic therapy.

Some patients and clinicians might object to amoxicillin, with or without clavulanate, as first-line therapy for ABRS, based on assumptions that newer, more expensive alternatives “must be” more effective. Most favorable clinical outcomes for nonsevere ABRS, however, result from natural history, not antibiotics, and randomized controlled trials of comparative efficacy do not support superiority of any single agent for initial empiric therapy. Pamphlets may help in dispelling myths about comparative efficacy.

Barriers may also be anticipated concerning guideline statements for CRS and recurrent acute rhinosinusitis. The diagnostic criteria for these entities are unfamiliar to many clinicians, who might benefit from a summary card or teaching aid that lists these criteria along with those for ABRS and VRS. Performance of nasal endoscopy, allergy evaluation, and immunologic assessment, when appropriate, may be hindered by access to equipment and by procedural cost.

## Research Needs

The guideline development group identified knowledge gaps based on existing practice patterns and the scope and quality of supporting literature. We present these gaps below to highlight areas for future research and investigation.

1. Define the natural history and management of sub-acute rhinosinusitis.
2. Determine the validity of diagnosing ABRS by patient history without confirmatory physical examination.
3. Refine and validate diagnostic criteria for VRS and ABRS
4. Determine whether a 7- or 10-day symptom duration is more likely to be associated with ABRS.
5. Assess the validity of diagnosing ABRS before 10 days based on persistent fever plus concurrent purulent nasal discharge.
6. Determine whether a diagnostic algorithm tool would change physician behavior in terms of antibiotic prescription practices.
7. Assess the impact of clinician beliefs about antibiotic prescribing for ABRS and how they might affect patient preferences and satisfaction.
8. Assess the value of viral screening methods in the routine management of patients with suspected ABRS.
9. Conduct randomized controlled trials (RCTs) to determine the efficacy of an “observation option” for nonsevere ABRS, by randomizing patients to immediate vs delayed antibiotics and assessing clinical outcomes.
10. Standardize the definition of “severe” illness in patients diagnosed with ABRS and determine whether it is a valid and useful distinction for diagnosis in adults. Establish the proper terminology and management of sinusitis symptoms lasting between 4 and 12 weeks.
11. Conduct RCTs with a superiority design that emphasize time to improvement/resolution, not just binary outcomes at fixed time points.
12. Perform RCTs of antibiotics vs placebo using strict diagnostic criteria and stratify by clinical severity (ie, mild, moderate, or severe).
13. Perform RCTs to assess the comparative efficacy of different antibiotics for initial management of uncomplicated ABRS.
14. Evaluate the role of analgesic therapy in managing rhinosinusitis and the comparative efficacy of different drug classes.
15. Assess the benefits of symptomatic therapy for VRS in properly conducted RCTs.
16. Assess the benefits of various symptomatic therapies for ABRS in properly conducted RCTs.
17. Determine optimum salinity, pH, and regimen for administering nasal saline irrigation.
18. Devise strategies or treatment regimens to avoid the rebound effect of topical nasal decongestants.
19. Determine the comparative clinical efficacy of antibiotics for culture-proven ABRS using RCTs with standardized, uniform definitions of clinical disease, severity, and clinical outcomes.
20. Conduct RCTs to determine the efficacy of adjuvant therapy (nasal steroids, antihistamines, decongestants) in combination with antibiotics.
21. Obtain greater evidence for which ABRS patients are most appropriate for short-course antibiotic regimens.
22. Perform RCTs examining antibiotic efficacy among patient subpopulations and efficacy of fluoroquinolones relative to other antibiotics.

23. Include quality-of-life and other patient-reported outcome measures as study outcomes in RCTs.
24. Further assess the diagnosis of CRS and recurrent acute rhinosinusitis in primary care settings, rather than specialty clinic settings, because of biased disease prevalence.
25. Conduct investigations to further characterize the role of fungi in the etiology of inflammation of the paranasal sinuses.
26. Conduct investigations to determine the underlying causes of the inflammation that characterizes CRS and to determine the value of individualizing therapy based on this information.
27. Determine the pathogenesis of CRS and the association of allergic rhinitis and CRS.
28. Establish the benefit of testing for allergy and immune function in subgroups of patients with CRS.
29. Perform RCTs to address outcomes of allergy management in patients with CRS or recurrent acute rhinosinusitis.
30. Perform RCTs to address outcomes of detecting and managing immunodeficient states in patients with CRS or recurrent acute rhinosinusitis.
31. Validate nasal endoscopy scoring systems.
32. Assess the impact of intravenous immunoglobulin (IVIG) on CRS or recurrent acute rhinosinusitis in patients with humoral immune deficiency.
33. Conduct longitudinal studies with comparable control groups to evaluate long-term benefits of adjunctive therapies in the secondary prevention of CRS and recurrent acute rhinosinusitis.
34. Perform quantitative studies evaluating the impact of healthy lifestyle changes, such as smoking cessation, dietary modification, and exercise on CRS.
35. Conduct RCTs of saline nasal irrigations as short-term vs long-term treatment for recurrent acute and CRS.
36. Determine whether there is a difference in efficacy between isotonic and hypertonic concentrations for intranasal saline irrigations.
37. Define what is maximal medical therapy, including the efficacy of certain medications over others and the amount of time required for treatment.
38. Identify the natural history of CRS and determine whether it is curable.
39. Determine if certain subtypes of CRS with nasal polyps may respond to antifungal therapy.
40. Further assess the cost-effectiveness of management strategies for CRS and their impact on resource utilization and patient quality of life.
41. Perform additional RCTs to clarify the impact of antibiotic therapy on CRS outcomes.

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David Andes, MD; Neil Bhattacharyya, MD; Dickson Cheung, MD, MBA; Steven Eisenberg, MD; Theodore G. Ganiats, MD; Andrea Gelzer, MD, MS; Daniel Hamilos, MD; Richard C. Haydon III, MD; Patricia A. Hudgins III, MD; Stacie Jones, MPH; Helene J. Krouse, PhD, APRN; Lawrence H. Lee, MD, MBA; Martin C. Mahoney, MD, PhD; Bradley F. Marple, MD; Col. John P. Mitchell, MC, MD; Robert Nathan, MD; Richard N. Shiffman, MD, MCIS; Timothy L. Smith, MD, MPH; and David L. Witsell, MD, MHS.

### Disclaimer

The clinical practice guideline is provided for information and educational purposes only. It is not intended as a sole source of guidance in managing adults with rhinosinusitis. Rather, it is designed to assist clinicians by providing an evidence-based framework for decision-making strategies. The guideline is not intended to replace clinical judgment or establish a protocol for all individuals with this condition and may not provide the only appropriate approach to diagnosing and managing this program of care. As medical knowledge expands and technology advances, clinical indicators and guidelines are promoted as conditional and provisional proposals of what is recommended under specific conditions but are not absolute. Guidelines are not mandates; these do not and should not purport to be a legal standard of care. The responsible physician, in light of all circumstances presented by the individual patient, must determine the appropriate treatment. Adherence to these guidelines will not ensure successful patient outcomes in every situation. The AAO-HNSF emphasizes that these clinical guidelines should not be deemed to include all proper treatment decisions or methods of care, or to exclude other treatment decisions or methods of care reasonably directed to obtaining the same results.

### Author Contributions

**Richard M. Rosenfeld**, writer, chair; **Jay F. Piccirillo**, writer, assistant chair; **Sujana S. Chandrasekhar**, writer, methodologist; **Itzhak Brook**, writer, panel member; **Kaparaboyana Ashok Kumar**, writer, panel member; **Maggie Kremper**, writer, panel member; **Richard R. Orlandi**, writer, panel member; **James N. Palmer**, writer, panel member; **Zara M. Patel**, writer, panel member; **Anju Peters**, writer, panel member; **Sandra A. Walsh**, writer, panel member; **Maureen D. Corrigan**, writer, AAO-HNSF staff liaison.

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### References

1. Rosenfeld RM, Andes D, Bhattacharyya N, et al. Clinical practice guideline: adult sinusitis. *Otolaryngol Head Neck Surg*. 2007;137(3)(suppl):S1-S31.

2. Institute of Medicine, Committee on Standards for Developing Trustworthy Guidelines. *Clinical Practice Guidelines We Can Trust*. Washington, DC: National Academies Press; 2011.
3. Lethbridge-Cejku M, Rose D, Vickerie J. Summary health statistics for US adults: National Health Interview Survey, 2004. *Vital Health Stat*. 2006;10:19-22.
4. Blackwell DL, Lucas JW, Clarke TC. Summary health statistics for U.S. adults: national health interview survey, 2012. *Vital Health Stat*. 2014;10:1-171.
5. Sinus and Allergy Health Partnership (SAHP). Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. *Otolaryngol Head Neck Surg*. 2004;130(suppl):1-45.
6. Rudmik L, Smith TL, Schlosser RJ, et al. Productivity costs in patients with refractory chronic rhinosinusitis. *Laryngoscope*. 2014;124:2007-2012.
7. Stankiewicz J, Tami T, Truitt T, et al. Impact of chronic rhinosinusitis on work productivity through one-year follow-up after balloon dilation of the ethmoid infundibulum. *Int Forum Allergy Rhinol*. 2011;1:38-45.
8. Gliklich RE, Metson R. The health impact of chronic sinusitis in patients seeking otolaryngologic care. *Otolaryngol Head Neck Surg*. 1995;113:104-109.
9. Kaszuba SM, Stewart MG. Medical management and diagnosis of chronic rhinosinusitis: a survey of treatment patterns by United States otolaryngologists. *Am J Rhinol*. 2006;20:186-190.
10. Winstead W. Rhinosinusitis. *Primary Care*. 2003;30:137-154.
11. Snow V, Mottur-Pilson C, Hickner JM, et al. Principles of appropriate antibiotic use for acute sinusitis in adults. *Ann Intern Med*. 2001;134:495-497.
12. Bhattacharyya N. Chronic rhinosinusitis: is the nose really involved? *Am J Rhinol*. 2001;15:169-173.
13. Meltzer EO, Hamilos DL, Hadley JA, et al. Rhinosinusitis: establishing definitions for clinical research and patient care. *Otolaryngol Head Neck Surg*. 2004;131(6)(suppl):S1-S62.
14. Scadding GK, Durham SR, Mirakian R. BSACI guidelines for the management of rhinosinusitis and nasal polyposis. *Clin Exp Allergy*. 2007;38:260-275.
15. Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *Clin Infect Dis*. 2012;54:e72-e112.
16. Desrosiers M, Evans GA, Keith PK, et al. Canadian clinical practice guidelines for acute and chronic rhinosinusitis. *Allergy Asthma Clin Immunol*. 2011;7:2.
17. Clayman GL, Adams GL, Paugh DR, et al. Intracranial complications of paranasal sinusitis: a combined institutional review. *Laryngoscope*. 1991;101:234-239.
18. Hytönen M, Atula T, Pitkäranta A. Complications of acute sinusitis in children. *Acta Otolaryngol*. 2000;543:154-157.
19. Fokkens WJ, Lund VJ, Mullol J. European position paper on rhinosinusitis and nasal polyps. *Rhinol Suppl*. 2012;50:1-298.
20. Smith SS, Evans CT, Tan BK, et al. National burden of antibiotic use for adult rhinosinusitis. *J Allergy Clin Immunol*. 2013;132:1230-1232.
21. Wu JH, Howard DH, McGowan JE, et al. Patterns of health care resource utilization after macrolide treatment failure: results from a large, population-based cohort with acute sinusitis, acute bronchitis, and community-acquired pneumonia. *Clin Ther*. 2004;26:2153-2162.
22. Bhattacharyya N, Grebner J, Martinson NG. Recurrent acute rhinosinusitis: epidemiology and health care cost burden. *Otolaryngol Head Neck Surg*. 2012;146:307-312.
23. Anand VK. Epidemiology and economic impact of rhinosinusitis. *Ann Oto Rhinol Laryngol*. 2004;193:3-5.
24. Ray NF, Baraniuk JN, Thamer M, et al. Healthcare expenditures for sinusitis in 1996: contributions of asthma, rhinitis, and other airway disorders. *J Allergy Clin Immunol*. 1999;103:408-414.
25. Bhattacharyya N. Incremental health care utilization and expenditures for chronic rhinosinusitis in the United States. *Ann Oto Rhinol Laryngol*. 2011;120:423-427.
26. Bhattacharyya N, Orlandi RR, Grebner J, et al. Cost burden of chronic rhinosinusitis: a claims-based study. *Otolaryngol Head Neck Surg*. 2011;144:440-445.
27. Bhattacharyya N. Assessing the additional disease burden of polyps in chronic rhinosinusitis. *Ann Oto Rhinol Laryngol*. 2009;118:185-189.
28. Soler ZM, Wittenberg E, Schlosser RJ, et al. Health state utility values in patients undergoing endoscopic sinus surgery. *Laryngoscope*. 2011;121:2672-2678.
29. Chester AC, Sindwani R, Smith TL, et al. Systematic review of change in bodily pain after sinus surgery. *Otolaryngol Head Neck Surg*. 2008;139:759-765.
30. Chester AC, Sindwani R, Smith TL, et al. Fatigue improvement following endoscopic sinus surgery: a systematic review and meta-analysis. *Laryngoscope*. 2008;118:730-739.
31. Rudmik L, Mace J, Soler ZM, et al. Long-term utility outcomes in patients undergoing endoscopic sinus surgery. *Laryngoscope*. 2014;124:19-23.
32. Rosenfeld RM, Shiffman RN, Robertson P, et al. Clinical Practice Guideline Development Manual, Third Edition: a quality-driven approach for translating evidence into action. *Otolaryngol Head Neck Surg*. 2013;148(1)(suppl):S1-S55.
33. Setzen G, Ferguson BJ, Han JK, et al. Clinical consensus statement: appropriate use of computed tomography for paranasal sinus disease. *Otolaryngol Head Neck Surg*. 2012;147:808-816.
34. Shiffman RN, Dixon J, Brandt C, et al. The GuideLine Implementability Appraisal (GLIA): development of an instrument to identify obstacles to guideline implementation. *BMC Med Inform Decis*. 2005;5:23.
35. AAP SCQIM (American Academy of Pediatrics Steering Committee on Quality Improvement and Management). Classifying recommendations for clinical practice guidelines. *Pediatrics*. 2004;114:874-877.
36. Eddy DM. Clinical decision making: from theory to practice: cost-effectiveness analysis. Will it be accepted? *JAMA*. 1992;268:132-136.
37. Choudhry NK, Stelfox HT, Detsky AS. Relationships between authors of clinical practice guidelines and the pharmaceutical industry. *JAMA*. 2002;287:612-617.
38. Detsky AS. Sources of bias for authors of clinical practice guidelines. *Can Med Assoc J*. 2006;175:1033, 1035.
39. Colla CH, Morden NE, Sequist TD, Schpero WL, Rosenthal MB. Choosing wisely: prevalence and correlates of low-value health



- care services in the United States [published online November 6, 2014]. *J Gen Intern Med*.
40. Albrich WC, Monnet DL, Harbarth S. Antibiotic selection pressure and resistance in *Streptococcus pneumoniae* and *Streptococcus pyogenes*. *Emerg Infect Dis*. 2004;10:514-517.
  41. Bronzwaer SL, Cars O, Buchholz U, et al. A European study on the relationship between antimicrobial use and antimicrobial resistance. *Emerg Infect Dis*. 2002;8:278-282.
  42. Seppala H, Klaukka T, Lehtonen R, et al. Outpatient use of erythromycin: link to increased erythromycin resistance in group A streptococci. *Clin Infect Dis*. 1995;21:1378-1385.
  43. Steinke D, Davey P. Association between antibiotic resistance and community prescribing: a critical review of bias and confounding in published studies. *Clin Infect Dis*. 2001;33(suppl 3):S193-S205.
  44. Goossens H, Ferech M, Vander Stichele R, et al. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet*. 2005;365:579-587.
  45. Schreiber CP, Hutchinson S, Webster CJ, et al. Prevalence of migraine in patients with a history of self-reported or physician-diagnosed "sinus" headache. *Arch Intern Med*. 2004;164:1769-1772.
  46. Kari E, DelGaudio JM. Treatment of sinus headache as migraine: the diagnostic utility of triptans. *Laryngoscope*. 2008;118:2235-2239.
  47. Slavin RG, Spector SL, Bernstein IL, et al. The diagnosis and management of sinusitis: a practice parameter update. *J Allergy Clin Immunol*. 2005;116(6)(suppl):S13-S47.
  48. Ip S, Fu L, Balk E, et al. *Update on Acute Bacterial Rhinosinusitis*. Evidence Report/Technology Assessment No. 124 (Prepared by Tufts-New England Medical Center Evidence-based Practice Center under Contract No. 290-02-0022). AHRQ Publication No. 05-E020-2. Rockville, MD: Agency for Healthcare Research and Quality; 2005.
  49. LaCroix JS, Ricchetti A, Lew D. Symptoms and clinical and radiological signs predicting the presence of pathogenic bacteria in acute rhinosinusitis. *Acta Otolaryngol*. 2002;122:192-196.
  50. van den Broek MF, Gudden C, Kluijfhout WP, et al. No evidence for distinguishing bacterial from viral acute rhinosinusitis using symptom duration and purulent rhinorrhea: a systematic review of the evidence base. *Otolaryngol Head Neck Surg*. 2014;150:533-537.
  51. Axelsson A, Runze U. Symptoms and signs of acute maxillary sinusitis. *ORL J Otorhinolaryngol Rel Spec*. 1976;38:298-308.
  52. Axelsson A, Runze U. Comparison of subjective and radiological findings during the course of acute maxillary sinusitis. *Ann Oto Rhinol Laryngol*. 1983;92:75-77.
  53. Williams J, Simel DL, Roberts L, et al. Clinical evaluation for sinusitis: making the diagnosis by history and physical examination. *Ann Intern Med*. 1992;117:705-710.
  54. Berg O, Carenfelt C, Rystedt G, et al. Occurrence of asymptomatic sinusitis in common cold and other acute ENT-infections. *Rhinology*. 1986;24:223-225.
  55. Berg O, Carenfelt C. Analysis of symptoms and clinical signs in the maxillary sinus empyema. *Acta Otolaryngol*. 1988;105:343-349.
  56. Lindbaek M, Hjortdahl P, Johnsen UL. Use of symptoms, signs, and blood tests to diagnose acute sinus infections in primary care: comparison with computed tomography. *Fam Med*. 1996;28:183-188.
  57. Lindbaek M, Hjortdahl P. The clinical diagnosis of acute purulent sinusitis in general practice—a review. *Br J Gen Pract*. 2002;52:491-495.
  58. Mudgil SP, Wise SW, Hopper KD, et al. Correlation between presumed sinusitis-induced pain and paranasal sinus computed tomographic findings. *Ann Allerg Asthma Im*. 2002;88:223-226.
  59. Fokkens WJ, Lund VJ, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps. *Rhinology Suppl*. 2012;23:1-298.
  60. Lanza DC, Kennedy DW. Adult rhinosinusitis defined. *Otolaryngol Head Neck Surg*. 1997;117:S1-S7.
  61. Fokkens W, Lund V, Bachert C, et al. EAACI position paper on rhinosinusitis and nasal polyps executive summary. *Allergy*. 2005;60:583-601.
  62. Benninger MS, Appelbaum PC, Denny JC, et al. Maxillary sinus puncture and culture in the diagnosis of acute rhinosinusitis: the case for pursuing alternative culture methods. *Otolaryngol Head Neck Surg*. 2002;127:7-12.
  63. Benninger MS, Payne SC, Ferguson BJ, et al. Endoscopically directed middle meatal cultures versus maxillary sinus taps in acute bacterial maxillary rhinosinusitis: a meta-analysis. *Otolaryngol Head Neck Surg*. 2006;134:3-9.
  64. Gwaltney MJ. Acute community acquired sinusitis. *Clin Infect Dis*. 1996;23:1209-1223.
  65. Stringer SP, Mancuso AA, Avino AJ. Effect of a topical vasoconstrictor on computed tomography of paranasal sinus disease. *Laryngoscope*. 1993;103:6-9.
  66. Gwaltney MJ, Scheld WM, Sande MA, et al. The microbial etiology and antimicrobial therapy of adults with acute community-acquired sinusitis: a fifteen-year experience at the University of Virginia and review of other selected studies. *Clin Immunol*. 1992;90:457-462.
  67. Gwaltney MJ, Hendley JO, Simon G. Rhinovirus infection in an industrial population, II: characteristics of illness and antibody response. *JAMA*. 1967;202:494-500.
  68. Hauer AJ, Luiten EL, van Erp NF, et al. No evidence for distinguishing bacterial from viral acute rhinosinusitis using fever and facial/dental pain: a systematic review of the evidence base. *Otolaryngol Head Neck Surg*. 2014;150:28-33.
  69. Wald ER, Applegate KE, Bordley C, et al. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. *Pediatrics*. 2013;132:e262-e280.
  70. Cornelius RS, Martin J, Wippold FJ, et al. ACR appropriateness criteria sinonasal disease. *JACR*. 2013;10:241-246.
  71. Balk EM, Zucker DR, Engels EA, et al. Strategies for diagnosing and treating suspected acute bacterial sinusitis: a cost-effectiveness analysis. *J Gen Intern Med*. 2001;16:701-711.
  72. Hickner JM, Bartlett JG, Besser RE, et al. Principles of appropriate antibiotic use for acute rhinosinusitis in adults: background. *Ann Intern Med*. 2001;134:498-505.
  73. Lau J, Zucker D, Engels EA, et al. *Diagnosis and Treatment of Acute Bacterial Rhinosinusitis*. Evidence Report/Technology Assessment No. 9 (Prepared by Tufts-New England Medical Center Evidence-based Practice Center under Contract No. 290-08-0019). Rockville, MD: Agency for Healthcare Research and Quality; 1999.

74. Gwaltney JM, Phillips CD, Miller RD, Riker DK. Computed tomographic study of the common cold. *N Engl J Med*. 1994;330:25-30.
75. Younis RT, Anand VK, Davidson B. The role of computed tomography and magnetic resonance imaging in patients with sinusitis with complications. *Laryngoscope*. 2002;112:224-229.
76. Mafee MF, Tran BH, Chapa AR. Imaging of rhinosinusitis and its complications: plain film, CT, and MRI. *Clin Rev Allergy Immunol*. 2006;30:165-186.
77. Hoxworth JM, Glastonbury CM. Orbital and intracranial complications of acute sinusitis. *Neuroimag Clin North Am*. 2010;20:511-526.
78. Bhattacharyya T, Piccirillo J, Wippold FJ. Relationship between patient-based descriptions of sinusitis and paranasal sinus computed tomographic findings. *Arch Otolaryngol*. 1997;123:1189-1192.
79. Havas TE, Motbey JA, Gullane PJ. Prevalence of incidental abnormalities on computed tomographic scans of the paranasal sinuses. *Arch Otolaryngol*. 1988;114:856-859.
80. Bolger WE, Butzin CA, Parsons DS. Paranasal sinus bony anatomic variations and mucosal abnormalities: CT analysis for endoscopic sinus surgery. *Laryngoscope*. 1991;101:56-64.
81. Hays GC, Mullard JE. Can nasal bacterial flora be predicted from clinical findings? *Pediatrics*. 1972;49:596-599.
82. Winther B. Effects on the nasal mucosa of upper respiratory viruses (common cold). *Dan Med Bull*. 1994;41:193-204.
83. Winther B, Brofeldt S, Grønberg H, et al. Study of bacteria in the nasal cavity and nasopharynx during naturally acquired common colds. *Acta Otolaryngol*. 1984;98:315-320.
84. Lund VJ. Therapeutic targets in rhinosinusitis: infection or inflammation? *Medscape J Med*. 2008;10:105.
85. Aroll B, Kenealy T. Antibiotics for the common cold and acute purulent rhinitis. *Cochrane Database Syst Rev*. 2005;(3):CD000247 1
86. Kassel JC, King D, Spurling GK. Saline nasal irrigation for acute upper respiratory tract infections. *Cochrane Database Syst Rev*. 2010;(3):CD006821.
87. Mortuaire G, de Gabory L, François M, et al. Rebound congestion and rhinitis medicamentosa: nasal decongestants in clinical practice. Critical review of the literature by a medical panel. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2013;130:137-144.
88. Hayward G, Heneghan C, Perera R, et al. Intranasal corticosteroids in management of acute sinusitis: a systematic review and meta-analysis. *Ann Fam Med*. 2012;10:241-249.
89. Barlan IB, Erkan E, Bakir M, et al. Intranasal budesonide spray as an adjunct to oral antibiotic therapy for acute sinusitis in children. *Ann Allergy Asthma Immunol*. 1997;78:598-601.
90. Meltzer EO, Charous BL, Busse WW, et al. Added relief in the treatment of acute recurrent sinusitis with adjunctive mometasone furoate nasal spray. The Nasonex Sinusitis Group. *J Allergy Clin Immunol*. 2000;106:630-637.
91. Meltzer EO, Bachert C, Staudinger H. Treating acute rhinosinusitis: comparing efficacy and safety of mometasone furoate nasal spray, amoxicillin, and placebo. *J Allergy Clin Immunol*. 2005;116:1289-1295.
92. Dolor RJ, Witsell DL, Hellkamp AS, et al. Comparison of cefuroxime with or without intranasal fluticasone for the treatment of rhinosinusitis. The CAFFS Trial: a randomized controlled trial. *JAMA*. 2001;286:3097-3105.
93. Meltzer EO, Orgel HA, Backhaus JW, et al. Intranasal flunisolide spray as an adjunct to oral antibiotic therapy for sinusitis. *Clin Immunol*. 2003;92:812-823.
94. Williamson IG, Rumsby K, Bengt S, et al. Antibiotics and topical nasal steroid for treatment of acute maxillary sinusitis: a randomized controlled trial. *JAMA*. 2007;298:2487-2496.
95. Zalmanovici A, Yaphe J. Intranasal steroids for acute sinusitis. *Cochrane Database Syst Rev*. 2013;2:CD005149.
96. Venekamp RP, Thompson MJ, Hayward G, et al. Systemic corticosteroids for acute sinusitis. *Cochrane Database Syst Rev*. 2014;3:CD008115.
97. Inanli S, Oztürk O, Korkmaz M, et al. The effects of topical agents of fluticasone propionate, oxymetazoline, and 3% and 0.9% sodium chloride solutions on mucociliary clearance in the therapy of acute bacterial rhinosinusitis in vivo. *Laryngoscope*. 2002;112:320-325.
98. Rabago D, Zgierska A, Mundt M, et al. Efficacy of daily hypertonic saline nasal irrigation among patients with sinusitis: a randomized controlled trial. *J Fam Pract*. 2002;51:1049-1055.
99. Keojampa BK, Nguyen MH, Ryan MW. Effects of buffered saline solution on nasal mucociliary clearance and nasal airway patency. *Otolaryngol Head Neck Surg*. 2004;131:679-682.
100. Talbott GA, Lynn AM, Levy FH, et al. Respiratory arrest precipitated by codeine in a child with chronic renal failure. *Clin Pediatr*. 1997;36:171-173.
101. Wabnitz DAM, Wormald P-J. A blinded, randomized, controlled study on the effect of buffered 0.9% and 3% sodium chloride intranasal sprays on ciliary beat frequency. *Laryngoscope*. 2005;115:803-805.
102. Adam P, Stiffman M, Blake RL. A clinical trial of hypertonic saline nasal spray in subjects with the common cold or rhinosinusitis. *Arch Fam Med*. 1998;7:39-43.
103. Eccles R, Jawad MSM, Jawad SSM, et al. Efficacy and safety of single and multiple doses of pseudoephedrine in the treatment of nasal congestion associated with common cold. *Am J Rhinol*. 2005;19:25-31.
104. Jawad SS, Eccles R. Effect of pseudoephedrine on nasal airflow in patients with nasal congestion associated with common cold. *Rhinology*. 1998;36:73-76.
105. Latte J, Taverner D, Slobodian P, et al. A randomized, double-blind, placebo-controlled trial of pseudoephedrine in coryza. *Clin Exp Pharmacol*. 2004;31:429-432.
106. Sperber SJ, Turner RB, Sorrentino JV, et al. Effectiveness of pseudoephedrine plus acetaminophen for treatment of symptoms attributed to the paranasal sinuses associated with the common cold. *Arch Fam Med*. 2000;9:979-985.
107. Taverner D, Danz C, Economos D. The effects of oral pseudoephedrine on nasal patency in the common cold: a double-blind single-dose placebo-controlled trial. *Clin Otolaryngol*. 1999;24:47-51.
108. Caenan M, Hamels K, Deron P, et al. Comparison of decongestive capacity of xylometazoline and pseudoephedrine with rhinomanometry and MRI. *Rhinology*. 2005;43:205-209.

109. Zeiger RS. Prospects for ancillary treatment of sinusitis in the 1990s. *J Allergy Clin Immunol.* 1992;90:478-495.
110. Braun JJ, Alabert JP, Michel FB, et al. Adjunct effect of loratadine in the treatment of acute sinusitis in patients with allergic rhinitis. *Allergy.* 1997;52:650-655.
111. Welch MJ, Meltzer EO, Simons FER. H1-antihistamines and the central nervous system. *Clin Allergy Immunol.* 2002;17:337-388.
112. Ahovuo-Saoranta A, Rautakorpi UM, Borisenko OV, et al. Antibiotics for acute maxillary sinusitis in adults. *Cochrane Database Syst Rev.* 2014;11;CD000243.
113. Lemiengre MB, van Driel ML, Merenstein D, et al. Antibiotics for clinically diagnosed acute rhinosinusitis in adults. *Cochrane Database Syst Rev.* 2012;10:CD006089.
114. Young J, De Sutter A, Merenstein D, et al. Antibiotics for adults with clinically diagnosed acute rhinosinusitis: a meta-analysis of individual patient data. *Lancet.* 2008;371:908-914.
115. Falagas ME, Giannopoulou KP, Vardakas KZ, et al. Comparison of antibiotics with placebo for treatment of acute sinusitis: a meta-analysis of randomised controlled trials. *Lancet.* 2008;8:543-552.
116. Broeder TP, Grooteman KV, Overdijk SB, et al. Inconclusive evidence that age predicts a prolonged or chronic course of acute rhinosinusitis in adults: a systematic review of the evidence base. *Otolaryngol Head Neck Surg.* 2014;150:365-370.
117. Frerichs KA, Nigten G, Romeijn K. Inconclusive evidence for allergic rhinitis to predict a prolonged or chronic course of acute rhinosinusitis. *Otolaryngol Head Neck Surg.* 2014;150:22-27.
118. Henry DC, Riffer E, Sokol WN, et al. Randomized double-blind study comparing 3- and 6-day regimens of azithromycin with a 10-day amoxicillin-clavulanate regimen for treatment of acute bacterial sinusitis. *Antimicrob Agents Chemother.* 2003;47:2770-2774.
119. Luterman M, Tellier G, Lasko B, et al. Efficacy and tolerability of telithromycin for 5 or 10 days vs amoxicillin/clavulanic acid for 10 days in acute maxillary sinusitis. *Ear Nose Throat J.* 2003;82:576-580, 582.
120. de Bock GH, Dekker FW, Stolk J, et al. Antimicrobial treatment in acute maxillary sinusitis: a meta-analysis. *J Clin Epidemiol.* 1997;50:881-890.
121. Lau J, Zucker D, Engels EA, et al. *Diagnosis and Treatment of Acute Bacterial Rhinosinusitis.* Evidence Report/Technology Assessment No. 9 (Prepared by Tufts-New England Medical Center Evidence-based Practice Center under Contract No. 290-08-0019). Rockville, MD: Agency for Healthcare Research and Quality; 1999.
122. Low DE, Desrosiers M, McSherry J. A practical guide for the diagnosis and treatment of acute sinusitis. *CMAJ.* 1997;156(suppl 6):1-14.
123. Brook I, Foote PA, Hausfeld JN. Frequency of recovery of pathogens causing acute maxillary sinusitis in adults before and after introduction of vaccination of children with the 7-valent pneumococcal vaccine. *J Med Microbiol.* 2006;55:943-946.
124. Jenkins SG, Farrell DJ, Patel M, et al. Trends in anti-bacterial resistance among *Streptococcus pneumoniae* isolated in the USA, 2000-2003: PROTEKT US years 1-3. *J Infect.* 2005;51:355-363.
125. Brook I, Gober AE. Resistance to antimicrobials used for therapy of otitis media and sinusitis: effect of previous antimicrobial therapy and smoking. *Ann Otol Rhinol Laryngol.* 1999;108:645-647.
126. Karageorgopoulos DE, Giannopoulou KP, Grammatikos AP, et al. Fluoroquinolones compared with beta-lactam antibiotics for the treatment of acute bacterial sinusitis: a meta-analysis of randomized controlled trials. *CMAJ.* 2008;178:845-854.
127. Harrison CJ, Woods C, Stout G, et al. Susceptibilities of *Haemophilus influenzae*, *Streptococcus pneumoniae*, including serotype 19A, and *Moraxella catarrhalis* paediatric isolates from 2005 to 2007 to commonly used antibiotics. *J Antimicrob Chemother.* 2009;63:511-519.
128. Falagas ME, Karageorgopoulos DE, Grammatikos AP, et al. Effectiveness and safety of short vs. long duration of antibiotic therapy for acute bacterial sinusitis: a meta-analysis of randomized trials. *Br J Clin Pharmacol.* 2009;67:161-171.
129. Contopoulos-Ioannidis DG, Ioannidis JP, Chew P, et al. Meta-analysis of randomized controlled trials on the comparative efficacy and safety of azithromycin against other antibiotics for lower respiratory tract infections. *J Antimicrob Chemother.* 2001;48:691-703.
130. Roos K, Tellier G, Baz M, et al. Clinical and bacteriological efficacy of 5-day telithromycin in acute maxillary sinusitis: a pooled analysis. *J Infect.* 2005;50:210-220.
131. Ah-see K. Sinusitis (acute). *Clin Evidence.* 2006;15:1-11.
132. Slavin RG. Sinusitis: viral, bacterial, or fungal and what is the role of Staph? *Allergy Asthma Proc.* 2006;27:447-450.
133. Gwaltney JM, Sydnor A, Sande MA. Etiology and antimicrobial treatment of acute sinusitis. *Ann Otol Rhinol Laryngol.* 1981;90:68-71.
134. Berg O, Carenfelt C, Kronvall G. Bacteriology of maxillary sinusitis in relation to character of inflammation and prior treatment. *Scand J Infect Dis.* 1988;20:511-516.
135. Brook I. Microbiology and management of sinusitis. *J Otolaryngol.* 1996;25:249-256.
136. Payne SC, Benninger MS. *Staphylococcus aureus* is a major pathogen in acute bacterial rhinosinusitis: a meta-analysis. *Clin Infect Dis.* 2007;45:e121-e127.
137. Sahm DF, Brown NP, Draghi DC, et al. Tracking resistance among bacterial respiratory tract pathogens: summary of findings of the TRUST Surveillance Initiative, 2001-2005. *J Postgrad Med.* 2008;120(3)(suppl 1):8-15.
138. Critchley IA, Brown SD, Traczewski MM, et al. National and regional assessment of antimicrobial resistance among community-acquired respiratory tract pathogens identified in a 2005-2006 U.S. Faropenem surveillance study. *Antimicrob Agents Chemother.* 2007;51:4382-4389.
139. Sahm DF, Jones ME, Hickey ML, et al. Resistance surveillance of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* isolated in Asia and Europe, 1997-1998. *J Antimicrob Chemother.* 2000;45:457-466.
140. Miller E, Andrews NJ, Waight PA, et al. Effectiveness of the new serotypes in the 13-valent pneumococcal conjugate vaccine. *Vaccine.* 2011;29:9127-9131.
141. Brook I, Gober AE. Antimicrobial resistance in the nasopharyngeal flora of children with acute maxillary sinusitis and

- maxillary sinusitis recurring after amoxicillin therapy. *J Antimicrob Chemother.* 2004;53:399-402.
142. Nava JM, Bella F, Garau J, et al. Predictive factors for invasive disease due to penicillin-resistant *Streptococcus pneumoniae*: a population-based study. *Clinical Infect Dis.* 1994;19:884-890.
143. Doone JL, Klespies SL, Sabella C. Risk factors for penicillin-resistant systemic pneumococcal infections in children. *Clin Pediatr.* 1997;36:187-191.
144. Brook I, Gober AE. Resistance to antibiotics used for therapy of otitis media and sinusitis: effect of previous antimicrobial therapy and smoking. *Ann Otol Rhinol Laryngol.* 1999;108:645-647.
145. Nuorti JP, Butler JC, Crutcher JM, et al. An outbreak of multidrug-resistant pneumococcal pneumonia and bacteremia among unvaccinated nursing home residents. *N Engl J Med.* 1998;338:1861-1868.
146. Jacobs MR, Bajaksouzian S. Evaluation of *Haemophilus influenzae* isolates with elevated MICs to amoxicillin/clavulanic acid. *Diagn Microbiol Infect Dis.* 1997;28:105-112.
147. Jacobs MR, Felmingham D, Appelbaum PC, et al. The Alexander Project 1998-2000: susceptibility of pathogens isolated from community-acquired respiratory tract infection to commonly used antimicrobial agents. *J Antimicrob Chemother.* 2003;52:229-246.
148. Dohar J, Cantón R, Cohen R, et al. Activity of telithromycin and comparators against bacterial pathogens isolated from 1,336 patients with clinically diagnosed acute sinusitis. *Ann Clin Microb Antimicrob.* 2004;3:15.
149. Craig WA, Andes D. Pharmacokinetics and pharmacodynamics of antibiotics in otitis media. *Pediatr Infect Dis J.* 1996;15:255-259.
150. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis.* 1998;26:1-11.
151. Ambrose PG, Quintiliani R, Nightingdale CH. Continuous vs intermittent infusion of cefuroxime for the treatment of community-acquired pneumonia. *Infect Dis Clin Pract.* 1997;7:463-470.
152. Ambrose PG, Grasela DM, Grasela TH, et al. Pharmacodynamics of fluoroquinolones against *Streptococcus pneumoniae* in patients with community-acquired respiratory tract infections. *Antimicrob Agents Chemother.* 2001;45:2793-2797.
153. Preston SL, Drusano GL, Berman AL, et al. Levofloxacin population pharmacokinetics and creation of a demographic model for prediction of individual drug clearance in patients with serious community-acquired infection. *Antimicrob Agents Chemother.* 1998;42:1098-1104.
154. Forrest A, Nix DE, Ballow CH, et al. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. *Antimicrob Agents Chemother.* 1993;37:1073-1081.
155. Benninger MS, Ferguson BJ, Hadley JA, et al. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. *Otolaryngol Head Neck Surg.* 2003;129(3)(suppl):S1-S32.
156. Bhattacharyya N. Clinical and symptom criteria for the accurate diagnosis of chronic rhinosinusitis. *Laryngoscope.* 2006;116(7, pt 2)(suppl 110):1-22.
157. Hwang PH, Irwin SB, Griest SE, et al. Radiologic correlates of symptom-based diagnostic criteria for chronic rhinosinusitis. *Otolaryngol Head Neck Surg.* 2003;128:489-496.
158. Stankiewicz JA, Chow JM. Nasal endoscopy and the definition and diagnosis of chronic rhinosinusitis. *Otolaryngol Head Neck Surg.* 2002;126:623-627.
159. Arango P, Kountakis SE. Significance of computed tomography pathology in chronic rhinosinusitis. *Laryngoscope.* 2001;111:1779-1782.
160. Palmer JN, Chiu AG. *Atlas of Endoscopic Sinus and Skull Base Surgery.* Philadelphia, PA: Saunders; 2013.
161. Bhattacharyya N. Symptom and disease severity differences between nasal septal deviation and chronic rhinosinusitis. *Otolaryngol Head Neck Surg.* 2005;133:173-177.
162. Cady RK, Dodick DW, Levine HL, et al. Sinus headache: a neurology, otolaryngology, allergy, and primary care consensus on diagnosis and treatment. *Mayo Clin Proc.* 2005;80:908-916.
163. Bhattacharyya N. A comparison of symptom scores and radiographic staging systems in chronic rhinosinusitis. *Am J Rhinol.* 2005;19:175-179.
164. Dubin MG, Ebert CS, Coffey CS, et al. Concordance of middle meatal swab and maxillary sinus aspirate in acute and chronic sinusitis: a meta-analysis. *Am J Rhinol.* 2005;19:462-470.
165. Kaper NM, Breukel L, Venekamp RP, et al. Absence of evidence for enhanced benefit of antibiotic therapy on recurrent acute rhinosinusitis episodes: a systematic review of the evidence base. *Otolaryngol Head Neck Surg.* 2013;149:664-667.
166. Loon JW, van Harn RP, Venekamp RP, et al. Limited evidence for effects of intranasal corticosteroids on symptom relief for recurrent acute rhinosinusitis. *Otolaryngol Head Neck Surg.* 2013;149:668-673.
167. Leung R, Almassian S, Kern R, et al. Patient level decision making in recurrent acute rhinosinusitis: a cost-benefit threshold for surgery. *Laryngoscope.* 2013;123:11-16.
168. Wuister AM, Goto NA, Oostveen EJ, et al. Nasal endoscopy is recommended for diagnosing adults with chronic rhinosinusitis. *Otolaryngol Head Neck Surg.* 2014;150:359-364.
169. Meltzer EO, Hamilos DL, Hadley JA, et al. Rhinosinusitis: developing guidance for clinical trials. *Otolaryngol Head Neck Surg.* 2006;135(5)(suppl):S31-S80.
170. Bhattacharyya N, Fried MP. The accuracy of computed tomography in the diagnosis of chronic rhinosinusitis. *Laryngoscope.* 2003;113:125-129.
171. Kenny TJ, Duncavage J, Bracikowski J, et al. Prospective analysis of sinus symptoms and correlation with paranasal computed tomography scan. *Otolaryngol Head Neck Surg.* 2001;125:40-43.
172. Flinn J, Chapman ME, Wightman AJ, et al. A prospective analysis of incidental paranasal sinus abnormalities on CT head scans. *Clin Otolaryngol.* 1994;19:287-289.
173. East CA, Annis JA. Preoperative CT scanning for endoscopic sinus surgery: a rational approach. *Clin Otolaryngol.* 1992;17:60-66.
174. Melhem ER, Oliverio PJ, Benson ML, et al. Optimal CT evaluation for functional endoscopic sinus surgery. *Am J Neuroradiol.* 1996;17:181-188.

175. Brinke A, Grootendorst DC, Schmidt JT, et al. Chronic sinusitis in severe asthma is related to sputum eosinophilia. *Clin Immunol.* 2002;109:621-626.
176. Lin DC, Chandra RK, Tan BK, et al. Association between severity of asthma and degree of chronic rhinosinusitis. *Am J Rhinol Allergy.* 2011;25:205-208.
177. Wang L, Freedman SD. Laboratory tests for the diagnosis of cystic fibrosis. *Am J Clin Pathol.* 2002;117(suppl):S109-S115.
178. Cooper MA, Pommering TL, Korányi K. Primary immunodeficiencies. *Am Fam Physician.* 2003;68:2001-2008.
179. Cowan MJ, Gladwin MT, Shelhamer JH. Disorders of ciliary motility. *Am J Med Sci.* 2001;321:3-10.
180. Alkire BC, Bhattacharyya N. An assessment of sinonasal anatomic variants potentially associated with recurrent acute rhinosinusitis. *Laryngoscope.* 2010;120:631-634.
181. Jarvis D, Newson R, Lotvall J, et al. Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe. *Allergy.* 2012;67:91-98.
182. Matsuno O, Ono E, Takenaka R, et al. Asthma and sinusitis: association and implication. *Int Arch Allergy Immunol.* 2008;147:52-58.
183. Bresciani M, Paradis L, Des Roches A, et al. Rhinosinusitis in severe asthma. *J Allergy Clin Immunol.* 2001;107:73-80.
184. Palmer JN, Conley DB, Dong RG, et al. Efficacy of endoscopic sinus surgery in the management of patients with asthma and chronic sinusitis. *Am J Rhinol.* 2001;15:49-53.
185. Ikeda K, Tanno N, Tamura G, et al. Endoscopic sinus surgery improves pulmonary function in patients with asthma associated with chronic sinusitis. *Ann Otol Rhinol Laryngol.* 1999;108:355-359.
186. Ragab S, Scadding GK, Lund VJ, et al. Treatment of chronic rhinosinusitis and its effects on asthma. *Eur Respir J.* 2006;28:68-74.
187. Vashishta R, Soler ZM, Nguyen SA, et al. A systematic review and meta-analysis of asthma outcomes following endoscopic sinus surgery for chronic rhinosinusitis. *Int Forum Allergy Rhinol.* 2013;3:788-794.
188. Gysin C, Alothman GA, Papsin BC. Sinonasal disease in cystic fibrosis: clinical characteristics, diagnosis, and management. *Pediatr Pulmonol.* 2000;30:481-489.
189. Slavin RG. Resistant rhinosinusitis: what to do when usual measures fail. *Allergy Asthma Proc.* 2003;24:303-306.
190. Babinski D, Trawinska-Bartnicka M. Rhinosinusitis in cystic fibrosis: not a simple story. *Int J Pediatr Otorhinol.* 2008;72:619-624.
191. Marshak T, Rivlin Y, Bentur L, et al. Prevalence of rhinosinusitis among atypical cystic fibrosis patients. *Eur Arch Otorhinolaryngol.* 2011;268:519-524.
192. Benson V, Marano MA. *Current Estimates from the National Health Interview Survey, 1995.* Hyattsville, MD: National Center for Health Statistics; 1998:1-428.
193. Adams PF, Hendershot GE, Marano MA. Current estimates from the National Health Interview Survey, 1996. *Vital Health Stat.* 1996;10(200):1-203.
194. Hytönen M, Patjas M, Vento SI, et al. Cystic fibrosis gene mutations deltaF508 and 394delTT in patients with chronic sinusitis in Finland. *Acta Otolaryngol.* 2001;121:945-947.
195. Mainz JG, Naehrlich L, Schien M, et al. Concordant genotype of upper and lower airways *P aeruginosa* and *S aureus* isolates in cystic fibrosis. *Thorax.* 2009;64:535-540.
196. Bonestroo HJC, de Winter-de Groot KM, van der Ent CK, et al. Upper and lower airway cultures in children with cystic fibrosis: do not neglect the upper airways. *J Cyst Fibros.* 2010;9:130-134.
197. Godoy JM, Godoy AN, Ribalta G, et al. Bacterial pattern in chronic sinusitis and cystic fibrosis. *Otolaryngol Head Neck Surg.* 2011;145:673-676.
198. Berkhout MC, Rijntjes E, El Bouazzaoui LH, et al. Importance of bacteriology in upper airways of patients with cystic fibrosis. *J Cyst Fibros.* 2013;12:525-529.
199. Khalid AN, Mace J, Smith TL. Outcomes of sinus surgery in adults with cystic fibrosis. *Otolaryngol Head Neck Surg.* 2009;141:358-363.
200. Virgin FW, Rowe SM, Wade MB, et al. Extensive surgical and comprehensive postoperative medical management for cystic fibrosis chronic rhinosinusitis. *Am J Rhinol Allergy.* 2012;26:70-75.
201. Liang J, Higgins TS, Ishman SL, et al. Surgical management of chronic rhinosinusitis in cystic fibrosis: a systematic review. *Int Forum Allergy Rhinol.* 2013;3:814-822.
202. Aanaes K, von Buchwald C, Hjuler T, et al. The effect of sinus surgery with intensive follow-up on pathogenic sinus bacteria in patients with cystic fibrosis. *Am J Rhinol Allergy.* 2013;27:e1-e4.
203. Chee L, Graham SM, Carothers DG, et al. Immune dysfunction in refractory sinusitis in a tertiary care setting. *Laryngoscope.* 2001;111:233-235.
204. Tahkokallio O, Seppälä IJ, Sarvas H, et al. Concentrations of serum immunoglobulins and antibodies to pneumococcal capsular polysaccharides in patients with recurrent or chronic sinusitis. *Ann Otol Rhinol Laryngol.* 2001;110:675-681.
205. Cheng YK, Decker PA, O'Byrne MM, et al. Clinical and laboratory characteristics of 75 patients with specific polysaccharide antibody deficiency syndrome. *Ann Allerg Asthma Immunol.* 2006;97:306-311.
206. Carr TF, Koterba AP, Chandra R, et al. Characterization of specific antibody deficiency in adults with medically refractory chronic rhinosinusitis. *Am J Rhinol Allergy.* 2011;25:241-244.
207. Armengot M, Juan G, Carda C, et al. Young's syndrome: a further cause of chronic rhinosinusitis. *Rhinology.* 1996;34:35-37.
208. Braverman I, Wright ED, Wang CG, et al. Human nasal ciliary-beat frequency in normal and chronic sinusitis subjects. *J Otolaryngol.* 1998;27:145-152.
209. Mahakit P, Pumhirun P. A preliminary study of nasal mucociliary clearance in smokers, sinusitis and allergic rhinitis patients. *Asian Pac J Allergy.* 1995;13:119-121.
210. Milgrim LM, Rubin JS, Small CB. Mucociliary clearance abnormalities in the HIV-infected patient: a precursor to acute sinusitis. *Laryngoscope.* 1995;105:1202-1208.
211. Dastidar P, Heinonen T, Numminen J, et al. Semi-automatic segmentation of computed tomographic images in volumetric estimation of nasal airway. *Eur Arch Otol Rhinol Laryngol.* 1999;256:192-198.
212. Calhoun K. Diagnosis and management of sinusitis in the allergic patient. *Otolaryngol Head Neck Surg.* 1992;107:850-854.

213. Bingham B, Shankar L, Hawke M. Pitfalls in computed tomography of the paranasal sinuses. *J Otolaryngol*. 1991;20:414-418.
214. Kaliner M. Treatment of sinusitis in the next millennium. *Allergy Asthma Proc*. 1998;19:181-184.
215. Druce HM. Diagnosis of sinusitis in adults: history, physical examination, nasal cytology, echo, and rhinoscope. *J Allergy Clin Immunol*. 1992;90:436-441.
216. Nayak S, Kirtane MV, Ingle MV. Functional endoscopic sinus surgery—II (a preliminary study). *J Postgrad Med*. 1991;37:31-34.
217. Elahi M, Frenkiel S, Remy H, et al. Development of a standardized proforma for reporting computerized tomographic images of the paranasal sinuses. *J Otolaryngol*. 1996;25:113-120.
218. Goldstein JH, Phillips CD. Current indications and techniques in evaluating inflammatory disease and neoplasia of the sino-nasal cavities. *Curr Prob Diagn Radiol*. 1998;27:41-71.
219. Ide C, Trigaux JP, Eloy P. Chronic sinusitis: the role of imaging. *Acta Otorhinolaryngol*. 1997;51:247-258.
220. Nussenbaum B, Marple BF, Schwade ND. Characteristics of bony erosion in allergic fungal rhinosinusitis. *Otolaryngol Head Neck Surg*. 2001;124:150-154.
221. Zinreich SJ. Imaging for staging of rhinosinusitis. *Ann Otol Rhinol Laryngol*. 2004;193:19-23.
222. Ulualp SO, Toohill RJ, Shaker R. Pharyngeal acid reflux in patients with single and multiple otolaryngologic disorders. *Otolaryngol Head Neck Surg*. 1999;121:725-730.
223. Ozmen S, Yücel OT, Sinici I, et al. Nasal pepsin assay and pH monitoring in chronic rhinosinusitis. *Laryngoscope*. 2008;118:890-894.
224. DelGaudio JM. Direct nasopharyngeal reflux of gastric acid is a contributing factor in refractory chronic rhinosinusitis. *Laryngoscope*. 2005;115:946-957.
225. Loehrl TA, Samuels TL, Poetker DM, et al. The role of extra-esophageal reflux in medically and surgically refractory rhinosinusitis. *Laryngoscope*. 2012;122:1425-1430.
226. Wong IW, Rees G, Greiff L, et al. Gastroesophageal reflux disease and chronic sinusitis: in search of an esophageal-nasal reflex. *Am J Rhinol Allergy*. 2010;24:255-259.
227. Vaezi MF, Hagaman DD, Slaughter JC, et al. Proton pump inhibitor therapy improves symptoms in postnasal drainage. *Gastroenterology*. 2010;139:1887-1893.e1881, quiz e1811.
228. Dishoeck HAE, Franssen MGC. Van The incidence and correlation of allergy and chronic sinusitis. *Pract Otolaryngol*. 1957;19:502-506.
229. Emanuel IA, Shah SB. Chronic rhinosinusitis: allergy and sinus computed tomography relationships. *Otolaryngol Head Neck Surg*. 2000;123:687-691.
230. Tan BK, Zirkle W, Chandra RK, et al. Atopic profile of patients failing medical therapy for chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2011;1:88-94.
231. Savolainen S, Schlerter WW, Man WJ, et al. Allergy in patients with acute maxillary sinusitis. *Allergy*. 1989;44:1116-1122.
232. Van Dishoeck HAE. Allergy and infection of paranasal sinus. *Adv Otolaryngol*. 1961;10:1-29.
233. Berrettini S, Carabelli A, Sellari-Franceschini S, et al. Perennial allergic rhinitis and chronic sinusitis: correlation with rhinologic risk factors. *Allergy*. 1999;54:242-248.
234. Newman LJ, Platts-Mills TA, Phillips CD, et al. Chronic sinusitis: relationship of computed tomographic findings to allergy, asthma, and eosinophilia. *JAMA*. 1994;271:363-367.
235. Ramadan HH, Fornelli R, Ortiz AO, et al. Correlation of allergy and severity of sinus disease. *Am J Rhinol*. 1999;13:345-347.
236. Krouse JH. Computed tomography stage, allergy testing, and quality of life in patients with sinusitis. *Otolaryngol Head Neck Surg*. 2000;123:389-392.
237. Stewart MG, Donovan DT, Parke RB, et al. Does the severity of sinus computed tomography findings predict outcome in chronic sinusitis? *Otolaryngol Head Neck Surg*. 2000;123:81-84.
238. McNally PA, White MV, Kaliner MA. Sinusitis in an allergist's office: analysis of 200 consecutive cases. *Allergy Asthma Proc*. 1997;18:169-175.
239. Alho OP, Karttunen R, Karttunen TJ. Nasal mucosa in natural colds: effects of allergic rhinitis and susceptibility to recurrent sinusitis. *Clin Exp Immunol*. 2004;137:366-372.
240. Tan BK, Chandra RK, Pollak J, et al. Incidence and associated premorbid diagnoses of patients with chronic rhinosinusitis. *J Allergy Clin Immunol*. 2013;131:1350-1360.
241. Wilson KF, McMains KC, Orlandi RR. The association between allergy and chronic rhinosinusitis with and without nasal polyps: an evidence-based review with recommendations. *Int Forum Allergy Rhinol*. 2014;4:93-103.
242. Bernstein IL, Storms WW. Practice parameters for allergy diagnostic testing. Joint Task Force on Practice Parameters for the Diagnosis and Treatment of Asthma. *Ann Allergy Asthma Immunol*. 1995;75:543-625.
243. Oksenhendler E, Gérard L, Fieschi C, et al. Infections in 252 patients with common variable immunodeficiency. *Clin Infect Dis*. 2008;46:1547-1554.
244. Zurlo JJ, Feuerstein IM, Lebovics R, et al. Sinusitis in HIV-1 infection. *Am J Med*. 1992;93:157-162.
245. Orange JS, Ballou M, Stiehm ER, et al. Use and interpretation of diagnostic vaccination in primary immunodeficiency. *J Allergy Clin Immunol*. 2012;130(3)(suppl):S1-24.
246. Bonilla FA, Bernstein IL, Khan DA, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *Ann Allergy Asthma Immunol*. 2005;94(5)(suppl 1):S1-S63.
247. Lange B, Holst R, Thilsing T, et al. Quality of life and associated factors in persons with chronic rhinosinusitis in the general population. *Clin Otolaryngol*. 2013;38(6):474-480.
248. Samter M, Beers RF. Concerning the nature of intolerance to aspirin. *J Allergy*. 1967;40:281-293.
249. Settignano GA, Chafee FH. Nasal polyps in asthma and rhinitis: a review of 6,037 patients. *J Allergy Clin Immunol*. 1977;59:17-21.
250. Drake-Lee AB, Lowe D, Swanston A, et al. Clinical profile and recurrence of nasal polyps. *J Laryngol Otol*. 1984;98:783-793.
251. Caplin I, Haynes JT, Spahn J. Are nasal polyps an allergic phenomenon? *Ann Allergy*. 1971;29:631-634.
252. Settignano GA. Epidemiology of nasal polyps. *Allergy Asthma Proc*. 1996;17:231-236.
253. Bhattacharyya N, Lee LN. Evaluating the diagnosis of chronic rhinosinusitis based on clinical guidelines and endoscopy. *Otolaryngol Head Neck Surg*. 2010;143:147-151.

254. Meltzer EO, Hamilos DL. Rhinosinusitis diagnosis and management for the clinician: a synopsis of recent consensus guidelines. *Mayo Clin Proc.* 2011;86:427-443.
255. Soler ZM, Oyer SL, Kern RC, et al. Antimicrobials and chronic rhinosinusitis with or without polyposis in adults: an evidenced-based review with recommendations. *Int Forum Allergy Rhinol.* 2013;3:31-47.
256. Joe SA, Thambi R, Huang J. A systematic review of the use of intranasal steroids in the treatment of chronic rhinosinusitis. *Otolaryngol Head Neck Surg.* 2008;139:340-347.
257. Kalish L, Snidvongs K, Sivasubramaniam R, et al. Topical steroids for nasal polyps. *Cochrane Database Syst Rev.* 2012;12:CD006549.
258. Wei CC, Adappa ND, Cohen NA. Use of topical nasal therapies in the management of chronic rhinosinusitis. *Laryngoscope.* 2013;123:2347-2359.
259. Hissaria P, Smith W, Wormald PJ, et al. Short course of systemic corticosteroids in sinonasal polyposis: a double-blind, randomized, placebo-controlled trial with evaluation of outcome measures. *J Allergy Clin Immunol.* 2006;118:128-133.
260. Benitez P, Alobid H, Berenguer M, et al. A short course of oral prednisone followed by intranasal budesonide is an effective treatment of severe nasal polyps. *Laryngoscope.* 2006;116:770-775.
261. Poetker DM, Jakubowski LA, Lal D. Oral corticosteroids in the management of adult chronic rhinosinusitis with and without nasal polyps: an evidence-based review with recommendations. *Int Forum Allergy Rhinol.* 2012;3:104-120.
262. Lildholdt T, Rundcrantz H, Lindqvist N. Efficacy of topical corticosteroid powder for nasal polyps: a double-blind, placebo-controlled study of budesonide. *Clin Otolaryngol.* 1995;20:26-30.
263. Aukema AAC, Mulder PGH, Fokkens WJ. Treatment of nasal polyposis and chronic rhinosinusitis with fluticasone propionate nasal drops reduces need for sinus surgery. *J Allergy Clin Immunol.* 2005;115:1017-1023.
264. Harvey R, Hannan SA, Badia L, et al. Nasal saline irrigations for the symptoms of chronic rhinosinusitis. *Cochrane Database Syst Rev.* 2007;3:CD006394.
265. van den Berg JW, de Nier LM, Kaper NM, et al. Limited evidence: higher efficacy of nasal saline irrigation over nasal saline spray in chronic rhinosinusitis—an update and reanalysis of the evidence base. *Otolaryngol Head Neck Surg.* 2014;150:16-21.
266. Pynnonen MA, Mukerji SS, Kim HM, et al. Nasal saline for chronic sinonasal symptoms: a randomized controlled trial. *Arch Otolaryngol Head Neck Surg.* 2007;133:1115-1120.
267. Tomooka LT, Murphy C, Davidson TM. Clinical study and literature review of nasal irrigation. *Laryngoscope.* 2000;110:1189-1193.
268. Fokkens W, Lund V, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps 2007. *Rhinology Suppl.* 2007;(20):1-136.
269. Mullol J, Obando A, Pujols L, et al. Corticosteroid treatment in chronic rhinosinusitis: the possibilities and the limits. *Immunol Allergy Clin North Am.* 2009;29:657-668.
270. Snidvongs K, Kalish L, Sacks R, et al. Topical steroid for chronic rhinosinusitis without polyps. *Cochrane Database Syst Rev.* 2011;(8):CD009274.
271. Rudmik L, Hoy M, Schlosser RJ, et al. Topical therapies in the management of chronic rhinosinusitis: an evidence-based review with recommendations. *Int Forum Allergy Rhinol.* 2013;3:281-298.
272. Scadding GK, Durham SR, Mirakian R, et al. BSACI guidelines for the management of rhinosinusitis and nasal polyposis. *Clin Exp Allergy.* 2008;38:260-275.
273. LaForce C, Journeay GE, Miller SD, et al. Ocular safety of fluticasone furoate nasal spray in patients with perennial allergic rhinitis: a 2-year study. *Ann Allergy Asthma Immunol.* 2013;111:45-50.
274. Giger R, Pasche P, Cheseaux C, et al. Comparison of once-versus twice-daily use of beclomethasone dipropionate aqueous nasal spray in the treatment of allergic and non-allergic chronic rhinosinusitis. *Eur Arch Otorhinolaryngol.* 2003;260:135-140.
275. Sacks P-L, Harvey RJ, Rimmer J, et al. Topical and systemic antifungal therapy for the symptomatic treatment of chronic rhinosinusitis. *Cochrane Database Syst Rev.* 2011;8:CD008263.
276. Isaacs A, Fakhri S, Luong A, et al. meta-analysis of topical amphotericin B for the treatment of chronic rhinosinusitis. *Int Forum Allergy Rhinol.* 2011;4:250-254.
277. Ponikau JU, Sherris DA, Kephart GM, et al. Striking deposition of toxic eosinophil major basic protein in mucus: implications for chronic rhinosinusitis. *J Allergy Clin Immunol.* 2005;116:362-369.
278. Ponikau JU, Sherris DA, Kern EB, et al. The diagnosis and incidence of allergic fungal sinusitis. *Mayo Clin Proc.* 1999;74:877-884.
279. Taylor MJ, Ponikau JU, Sherris DA, et al. Detection of fungal organisms in eosinophilic mucin using a fluorescein-labeled chitin-specific binding protein. *Otolaryngol Head Neck Surg.* 2002;127:377-383.
280. Kim ST, Choi JH, Jeon HG, et al. Comparison between polymerase chain reaction and fungal culture for the detection of fungi in patients with chronic sinusitis and normal controls. *Acta Otolaryngol.* 2005;125:72-75.
281. Shin S-H, Ponikau JU, Sherris DA, et al. Chronic rhinosinusitis: an enhanced immune response to ubiquitous airborne fungi. *J Allergy Clin Im.* 2004;114:1369-1375.
282. Ponikau JU, Sherris DA, Kephart GM, et al. The role of ubiquitous airborne fungi in chronic rhinosinusitis. *Clin Rev Allergy Immunol.* 2006;30:187-194.
283. Thanasumpun T, Batra PS. Oral antifungal therapy for chronic rhinosinusitis and its subtypes: a systematic review. *Int Forum Allergy Rhinol.* 2011;1:382-389.
284. Gosepath J, Grebneva N, Mossikhin S, et al. Topical antibiotic, antifungal, and antiseptic solutions decrease ciliary activity in nasal respiratory cells. *Am J Rhinol.* 2002;16:25-31.
285. Shirazi MA, Stankiewicz JA, Kammeyer P. Activity of nasal amphotericin B irrigation against fungal organisms in vitro. *Am J Rhinol.* 2007;21:145-148.
286. Centers for Disease Control and Prevention. Get smart: know when antibiotics work. [http://www.cdc.gov/drugresistance/community/campaign\\_materialshtm#3](http://www.cdc.gov/drugresistance/community/campaign_materialshtm#3). Accessed March 23, 2007.