Antimicrobials and chronic rhinosinusitis with or without polyposis in adults: an evidenced-based review with recommendations

Zachary M. Soler, MD, MSc1; Samuel L. Oyer, MD1; Robert C. Kern, MD2; Brent A. Senior MD3; Stilianos E. Kountakis, MD, PhD4; Bradley F. Marple, MD5 and Timothy L. Smith, MD, MPH6

Background: Chronic rhinosinusitis (CRS) is characterized by inflammation of the mucosa of the nose and paranasal sinuses. The role of bacterial or fungal infection in CRS is unclear, yet antimicrobials are commonly prescribed for this condition. Published guidelines offer little direction regarding antibiotic strategies for CRS. The purpose of this article is to provide an evidence-based approach to the use of antibacterial and antifungal antibiotics in the management of CRS.

Methods: A systematic review of the literature was performed following recommendations of the Clinical Practice Guideline Manual, Conference on Guideline Standardization (COGS), and the Appraisal of Guidelines and Research Evaluation (AGREE). Inclusion criteria were: age ≥18 years old, chronic rhinosinusitis with or without polyps, antibiotic treatment as the experimental group, and clearly defined primary clinical endpoint. Studies involving patients with cystic fibrosis or acute invasive fungal sinusitis were excluded.

Results: The review identified and evaluated the literature on 8 classes of antimicrobials for CRS: oral antibacterial antibiotics ≤3 weeks, oral antibacterial antibiotics >3 weeks, macrolide antibiotics, intravenous antibacterial antibiotics, topical antibacterial antibiotics, oral antifungals, intravenous antifungals, and topical antifungals.

Conclusion: Based on the available evidence, oral antibacterial antibiotics and prolonged macrolide antibiotics are considered therapeutic options in the treatment of CRS while the use of topical antibacterial antibiotics, intravenous antibacterial antibiotics and oral, topical, or intravenous antifungals would be recommended against. These evidence-based recommendations should not necessarily be applied to all patients with CRS and are not intended to supersede clinical judgment based on individual patient circumstances. © 2013 ARS-AAOA, LLC.

Key Words: chronic rhinosinusitis; antibiotics; antifungals; macrolides; evidence-based medicine

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1Division of Rhinology and Sinus Surgery, Department of Otolaryngology–Head and Neck Surgery, Medical University of South Carolina, Charleston, SC; 2Department of Otolaryngology–Head and Neck Surgery, Feinberg School of Medicine, Northwestern University, Chicago, IL; 3Division of Rhinology, Allergy, and Endoscopic Skull Base Surgery, Department of Otolaryngology–Head and Neck Surgery, University of North Carolina at Chapel Hill, Chapel Hill, NC; 4Department of Otolaryngology, Georgia Health Sciences University, Augusta, GA; 5Department of Otolaryngology–Head and Neck Surgery, University of Texas Southwestern Medical Center, Dallas, TX; 6Division of Rhinology and Sinus Surgery, Oregon Sinus Center, Department of Otolaryngology–Head and Neck Surgery, Oregon Health and Science University, Portland, OR

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

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Historically, CRSwNP was believed to be associated with severe allergy, whereas CRSsNP was thought to represent a state of persistent infection of the paranasal sinuses. An abundance of data, however, demonstrates that bacteria and fungi can typically be cultured from the nose and sinuses of patients with both forms of CRS, suggesting that these microbial agents may be drivers of the chronic inflammation which broadly defines the disorder. Hence, it is not surprising that antibiotics are a fundamental treatment strategy for patients with CRS. A recent survey of over 300 American Rhinologic Society members reveals that antibiotics continue to be a mainstay of CRS medical therapy. Over 90% of respondents to this anonymous survey reported using antibiotics “almost always” for CRS, usually with treatment courses lasting 3 to 4 weeks. Antibiotics were also considered an essential component of medical therapy prior to consideration of surgical treatment. Despite the widespread use of antibiotics for CRS, available guidelines such as the 2007 American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) Sinusitis Guideline offer little direction regarding antibiotic strategies for CRS.

The purpose of this study was to review the published literature evaluating the efficacy of antibiotics for patients with CRS, both with and without polyposis. This review covers both antibacterial and antifungal antibiotics, as well as routes of administration to include oral, topical, and intravenous formulations. For each antibiotic strategy, this article provides a focused summary of the literature and, when possible, recommendations are introduced based on the supporting evidence. This review is not intended to replace professional judgment; rather, it is meant to assist clinicians with understanding the available evidence and the potential tradeoffs associated with each treatment strategy. It must be highlighted that clinical studies, by their nature, report mean characteristics of specific study populations. Although CRS can be specifically defined, important heterogeneity likely exists among individual patients who may or may not be represented by the mean. Therefore, these evidence-based recommendations should not necessarily be applied to all patients, and individual clinician judgment remains critical to determining the most appropriate care in accordance with the specific clinical scenario and individual patient values.

### Materials and methods

An ad hoc committee of the American Rhinologic Society was formed after questions pertaining to antibiotic usage for CRS were raised at the 57th Annual Meeting in September, 2011. Eight distinct antibiotic approaches were identified and felt to warrant further investigation (Table 1). The purpose of this committee was to develop an evidence-based review with recommendations for each of these strategies, following the iterative algorithm outlined by Rudnik and Smith. The Clinical Practice Guideline Manual, Conference on Guideline Standardization (COGS), and the Appraisal of Guidelines and Research Evaluation (AGREE) instrument recommendations were followed to improve quality, transparency, and reporting of results. A screening literature search was performed using PubMed and Cochrane Review Databases up through November 1, 2011. An initial search strategy including keywords “chronic,” “sinusitis,” “rhinosinusitis,” and “antibiotics” resulted in 1100 potential abstracts. Sequential secondary search strategies were then employed using additional focused keywords including “bacterial,” “fungal,” “intravenous,” “topical,” and “macrolide,” as well as individual antibiotic names. All abstracts were reviewed and the following inclusion criteria applied: adult population ≥18 years old; chronic rhinosinusitis; antibiotic as the experimental group; and clearly defined primary clinical endpoint in humans. If studies were uncontrolled (case series, cohort designs) then the treatment regimen must have included antibiotics alone and not be a constellation of multiple therapeutic strategies or have taken place in the postsurgical setting. Because many studies predate formal definitions of CRS, all studies that classified patients as “chronic” were included, with authors’ criteria recorded if given. Those studies that included a mix of ARS and CRS patients were excluded if CRS data could not be extracted separately. Additional exclusion criteria included studies with <5 patients and those that pertained solely to cystic fibrosis, as this was felt to be a distinct patient population unlikely to reflect CRS patients as a whole. The references from each included article were then reviewed to identify potential missing studies, as were the references from the Clinical Practice Guideline of the AAO-HNS and the European Position Paper on Rhinosinusitis and Nasal Polyposis (EPOS).

Included studies were evaluated and level of evidence (LOE) was applied based on reported research

### TABLE 1. Antibiotic approaches for CRS evaluated in review

<table>
<thead>
<tr>
<th>Antibacterial</th>
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<tbody>
<tr>
<td>Oral antibiotics (non-macrolide; shorter than 3 weeks treatment duration)</td>
<td></td>
</tr>
<tr>
<td>Oral antibiotics (non-macrolide; longer than 3 weeks treatment duration)</td>
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<tr>
<td>Macrolide class of antibiotics</td>
<td></td>
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<tr>
<td>Intravenous antibiotics</td>
<td></td>
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<tr>
<td>Topical antibiotics</td>
<td></td>
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<tr>
<td>Antifungal</td>
<td></td>
</tr>
<tr>
<td>Oral antibiotics</td>
<td></td>
</tr>
<tr>
<td>Intravenous antibiotics</td>
<td></td>
</tr>
<tr>
<td>Topical antibiotics</td>
<td></td>
</tr>
</tbody>
</table>

CRS = chronic rhinosinusitis.
methodology according to the Center for Evidence-Based Medicine. After quality evaluation for each study, a summary was produced that includes the aggregate grade of evidence and recommendations based on the American Academy of Pediatrics (AAP) guidelines (Table 2). When there was only a single study evaluating an antibiotic strategy, an aggregate grade of evidence was not provided because grades are derived from the findings of multiple studies.

Three authors (Z.M.S., S.L.O., and T.L.S.) reviewed the literature and produced the initial manuscript. One at a time, subsequent authors (R.J.K., B.A.S., S.E.K., and B.F.M.) were asked to identify any potential missing studies, review available evidence, and critically appraise the summary recommendations. Each invited reviewer was blinded to the number and names of earlier authors to encourage honest feedback and minimize unintended pressure from earlier authors. Author selection was based on a literature review, identifying individuals with an interest in evidence-based medicine and/or prior participation with guideline development. Recommendations incorporate the quality of research methodology, balance of benefit vs harm, and value judgments of the authors. When the evidence was sufficient to develop a recommendation for an antibiotic strategy, a suggested role for the intervention was provided.

Results

Oral antibacterial antibiotics (non-macrolide; less than 3 weeks treatment duration)

A total of 6 studies met inclusion criteria and had an experimental arm that included oral antibacterial antibiotics for CRS (Table 3). Four of these studies were randomized controlled trials (RCTs) each with a double-blind design. However, in 3 of the 4 clinical trials the experimental arms were comprised of 2 different antibiotic regimens without a placebo control group. None of these studies demonstrated a statistically significant difference between antibiotic regimens. The failure to include a placebo control makes it difficult to quantify the true clinical benefit of any of the specific regimens. Two of the identified studies were observational cohort studies. The study by Gehanno and Cohen followed 198 patients with CRS after being treated with ofloxacin for 8 days. The majority of patients were deemed to be “cured” or “improved” after this regimen, although no objective criteria were given by which these outcomes were measured. The lack of a control group also significantly weakens the conclusions that can be drawn from these short-term studies.

The highest evidence available is a Level 1b study by Van Zele et al. comparing 20 days of oral doxycycline to separate arms of methylprednisolone and placebo in patients with bilateral nasal polyposis. Compared to placebo, the authors were able to show a significant reduction in polyp size in the doxycycline group as evaluated by nasal endoscopy that persisted to 12 weeks. Secondary analysis also demonstrated a reduction of postnasal drainage at 2 weeks, although this improvement was not present at other follow-up time points. Despite a reduction in visible polyp size, no difference was seen in patient-reported nasal congestion scores, an arguably more clinically relevant outcome measure. Similarly, no difference between doxycycline and placebo was seen for peak nasal inspiratory flow (PNIF) or symptoms of rhinorrhea and loss of smell. The authors were unsure whether the improvement in polyp size was secondary to the antibacterial properties of doxycycline or related to its intrinsic anti-inflammatory effects, potentially through inhibition of matrix-metalloproteinases, inflammatory cytokines, or local immunoglobulin E (IgE) production.

The relative weakness of the evidence supporting oral antibacterial antibiotics is surprising given how commonly they are used to treat CRS. The potential clinical benefits outlined above are offset by known side effects such as gastrointestinal upset, liver enzyme disruptions, and more rarely Clostridium difficile colitis and (occasionally severe) allergic reactions. The cost associated with antibiotic use is not trivial, although this expenditure is quite variable depending on the specific antibiotic chosen and its duration. Clinicians must also keep in mind community effects from antibiotic usage, including the development of bacterial resistance patterns. When evaluating the evidence in aggregate, the summary recommendation is to consider oral antibacterial antibiotics an option for CRS. Bearing in mind the frequency with which oral antibiotics are currently used, adequately powered RCTs evaluating the efficacy of oral antibacterial antibiotics either alone or in combination with other medications should be considered a major research priority.

### TABLE 2. Recommendations based on defined grades of evidence

<table>
<thead>
<tr>
<th>Grade</th>
<th>Research quality</th>
<th>Preponderance of benefit over harm</th>
<th>Balance of benefit over harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Well-designed RCTs</td>
<td>Strong recommendation</td>
<td>Option</td>
</tr>
<tr>
<td>B</td>
<td>RCT with minor limitations; overwhelming consistent evidence from observational studies</td>
<td>Strong recommendation/recommendation</td>
<td>Option</td>
</tr>
<tr>
<td>C</td>
<td>Observational studies (case control and cohort designs)</td>
<td>Recommendation</td>
<td>Option</td>
</tr>
<tr>
<td>D</td>
<td>Expert opinion; case reports; reasoning from first principles</td>
<td>Option</td>
<td>No recommendation</td>
</tr>
</tbody>
</table>

RCT = randomized controlled trial.
Table 3. Summary of oral antibacterial antibiotic studies for CRS (non-macrolide; shorter than 3 weeks treatment duration)

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study design</th>
<th>LOE</th>
<th>Definition of CRS</th>
<th>n</th>
<th>Study group(s)</th>
<th>Antibiotic protocol</th>
<th>Clinical endpoint(s)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Zele et al.14</td>
<td>2010</td>
<td>RCT</td>
<td>1b</td>
<td>Bilateral polyps</td>
<td>33</td>
<td>1) Doxycycline; 2) Placebo</td>
<td>Doxycycline 200 mg once, followed by 100 mg 1 × /day for 20 days</td>
<td>1) Polyp size; 2) PNIF; 3) oifaction; 4) congestion; 5) rhinorrhea; 6) postnasal drainage</td>
<td>Reduction in polyp size at week 12; Reduction in postnasal drainage at week 2</td>
</tr>
<tr>
<td>Galioto et al.15</td>
<td>1995</td>
<td>Observational cohort</td>
<td>4</td>
<td>None</td>
<td>5</td>
<td>1) Flurithromycin</td>
<td>1) Flurithromycin 375 mg 2 × /day for ≥5days</td>
<td>Clinical “cure” or “improvement”</td>
<td>All cured or improved</td>
</tr>
<tr>
<td>Dellanoimica et al.16</td>
<td>1994</td>
<td>RCT</td>
<td>1b</td>
<td>Symptoms + X-ray findings</td>
<td>171</td>
<td>1) Cefotiam; 2) Cefixime</td>
<td>1) Cefotiam 200 mg 2 × /day for 10 days; 2) Cefixime 200 mg 2 × /day for 10 days</td>
<td>Clinical “cure” or “improvement”</td>
<td>No difference between groups</td>
</tr>
<tr>
<td>Legent et al.17</td>
<td>1994</td>
<td>RCT</td>
<td>1b</td>
<td>3 months symptoms + CT findings</td>
<td>251</td>
<td>1) Amoxicillin/clavulanate; 2) Ciprofloxacin</td>
<td>1) Amoxicillin/clavulanate 500 mg 3 × /day for 9 days; 2) Ciprofloxacin 500 mg 2 × /day for 9 days</td>
<td>1) Clinical “cure”; 2) nasal drainage</td>
<td>No difference between groups</td>
</tr>
<tr>
<td>Gehanno and Cohen18</td>
<td>1993</td>
<td>Observational cohort</td>
<td>4</td>
<td>None</td>
<td>198</td>
<td>1) Ofloxacin</td>
<td>Ofloxacin 200 mg 2 × /day for 12 days</td>
<td>Clinical “cure” or “improvement”</td>
<td>Majority of patients cured/improved at 8 days</td>
</tr>
<tr>
<td>Huck et al.19</td>
<td>1993</td>
<td>RCT</td>
<td>1b</td>
<td>“Nonresolving sinus disease”</td>
<td>15</td>
<td>1) Cefaclor; 2) Amoxicillin</td>
<td>1) Cefaclor 500 mg 2 × /day for 10 days; 2) Amoxicillin 500 mg 3 × /day for 10 days</td>
<td>1) “Success/failure”; 2) X-ray findings</td>
<td>No difference between groups</td>
</tr>
</tbody>
</table>

CRS = chronic rhinosinusitis; CT = computed tomography; LOE = level of evidence; PNIF = peak nasal inspiratory flow; RCT = randomized controlled trial.
(excluding macrolide class) for routine CRS. Although the recommendation is against prolonged antibiotics, we acknowledge that situation-specific cases may arise in which extended courses would be reasonable, particularly those who have demonstrated a partial response. Evaluating the optimal duration of oral antibacterial therapy should be an important consideration for future clinical trials evaluating antibiotic strategies.

Oral antibacterial antibiotic (non-macrolide; longer than 3 weeks treatment duration)

1. Aggregate quality of evidence: N/A (single study).
2. Benefit: No clear benefit demonstrated for prolonged course.
5. Benefits-harm assessment: Preponderance of harm over benefit: known risk of medication side effects, quantifiable costs, and potential for bacterial resistance vs unproven benefit of prolonged course.
6. Value judgments: None
7. Recommendation level: Recommend against a prolonged (>3week) course of oral antibacterial antibiotics (except for macrolide class) for routine CRS cases.

Macrolide antibiotics

There were 17 studies identified that evaluated the use of macrolide antibiotics in CRS for their anti-inflammatory properties (Table 4).21–37 Two were placebo-controlled RCTs,21,25 one was a retrospective case-control study,36 and the remaining 14 were prospective observational studies (Level 4). Five of the studies were non-English texts with English abstracts.24,27,34,35,37 The abstracts were reviewed and the studies were included in this review because a suitable amount of detail was contained in the abstract to meet the inclusion criteria; all of these articles were Level 4 studies. Specific macrolide use and their daily doses are as follows: erythromycin in 4 studies (400-1800 mg); clarithromycin in 5 studies (150-300 mg); roxithromycin in 9 studies (150-300 mg); and azithromycin in 1 study (500 mg per week). Two observational studies23,34 compared treatment with 2 separate macrolides and neither found a significant benefit of 1 macrolide over another. Duration of therapy ranged from 2 weeks to 12 months.

The best available evidence supporting macrolide use comes from Wallwork et al.25 in a placebo-controlled RCT of roxithromycin 150 mg daily for 3 months in patients with refractory CRS. Sixty-four patients were randomized and patients in the macrolide group demonstrated a significant improvement in subjective response, disease-specific quality of life (QOL), endoscopy findings, and measured saccharine transit time compared to placebo (p < 0.01 for all) at the conclusion of therapy. No improvement was seen in objective olfactory function, peak nasal inspiratory flow, or mediators measured from nasal lavage. Improvement in QOL was no longer significant at 12 weeks following completion of therapy. A subgroup analysis based on serum IgE levels revealed most of the benefit seen in the study was in patients with low (<200 μg/L) IgE levels (p < 0.01) and in this group QOL improvement was significant at completion of therapy and trended toward significance at 12 weeks following completion (p = 0.06). No macrolide resistant organisms developed during treatment.

Videler et al.21 recently published a double-blind RCT comparing azithromycin to placebo in patients with CRS according to EPOS criteria. Patients were treated with 500 mg per day of azithromycin for 3 days, followed by 500 mg per week for 11 weeks, and monitored until 3 months following completion of therapy. No significant difference was seen in a comprehensive battery of evaluations, including the 22-item Sino-Nasal Outcome Test (SNOT-22), Short Form (36) Health Survey (SF-36), Visual Analogue Scale (VAS) for symptoms, Patient Response Rating Scale, sinonasal endoscopy, PNIIF, or olfaction. This study differed from Wallwork et al.25 in that over 50% of patients had nasal polyposis, the study drug was dosed weekly, and total IgE levels were not evaluated.

Of the remaining 15 observational studies, 10 evaluated symptom resolution following macrolide treatment.23,24,26,27,31,33–37 None of the studies used previously validated sinusitis symptom tools (5 of the studies were available only as abstracts and the method of evaluating symptoms was not described). All studies showed symptom improvement in over 50% of patients; however, none of the 4 studies that specifically assessed olfaction (subjectively or objectively) found an improvement following macrolide therapy.25,26,31,34 Moriyama et al.36 performed a retrospective case-control study of 149 patients following functional endoscopic sinus surgery (FESS) and compared 57 patients who had received postoperative long-term erythromycin compared to 92 patients who did not receive erythromycin. The authors found a statistically significant improvement in symptoms among the group that received erythromycin (p < 0.01).

Objective endoscopic exam findings were evaluated in 8 studies.25–28,30,31,36,37 Again, each author described a standardized method for grading endoscopic exams, but none used a previously validated scale. There was general improvement reported in objective findings in 40% to 70% of patients. Three studies found improvement in all findings except mucosal edema,33,34,37 and 1 study found no improvement in amount of post nasal discharge.28 Moriyama et al.36 noted consistently higher rates of improved endoscopy findings in the patients who received erythromycin but no p values were reported to assess the statistical significance of these differences.

Six studies evaluated imaging findings before and after macrolide treatment with improvement seen in 51% to 75% of patients.23,24,27,32,34,36 None of the patients reported worsening of imaging findings. Suzuki et al.32 used a computer software program to measure the
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study design</th>
<th>LOE</th>
<th>Definition of CRS</th>
<th>N</th>
<th>Study group(s)</th>
<th>Macrolide protocol</th>
<th>Clinical end-point(s)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Videler et al.²¹</td>
<td>2011</td>
<td>RCT, blinded</td>
<td>1b</td>
<td>EPOS</td>
<td>60</td>
<td>1) Azithromycin; 2) Placebo</td>
<td>Azithromycin 500mg QD × 3 days, then 500 mg/week × 11 weeks</td>
<td>1) SNOT-22; 2) Patient Response Rating Scale; 3) VAS symptoms; 4) Nasal endoscopy; 5) Peak nasal inspiratory flow; 6) Olfaction; 7) Short Form-36; 8) Sinonasal cultures</td>
<td>No significant benefit was found over placebo</td>
</tr>
<tr>
<td>Cervin et al.²²</td>
<td>2009</td>
<td>Observational cohort</td>
<td>4</td>
<td>Persistent nasal symptoms after FESS</td>
<td>25</td>
<td>Clarithromycin</td>
<td>Clarithromycin 250 mg QD × 12 weeks</td>
<td>1) Mediators in nasal mucous (IL-8, ECP, α2-macroglobulin)</td>
<td>Reduction in mediator levels histamine-induced secretion</td>
</tr>
<tr>
<td>Haruna et al.²³</td>
<td>2009</td>
<td>Observational cohort</td>
<td>4</td>
<td>Symptoms and CT findings</td>
<td>29</td>
<td>1) Roxithromycin; 2) Clarithromycin</td>
<td>Roxithromycin 150 mg QD or clarithromycin 200 mg QD × 8-20 weeks</td>
<td>1) Clinical symptom questionnaire; 2) CT scores</td>
<td>Symptom and CT scores improved or unchanged in all patients. Better improvement if no polyps or lower initial CT score</td>
</tr>
<tr>
<td>Song et al.²⁴ᵃ</td>
<td>2009</td>
<td>Observational cohort</td>
<td>4</td>
<td>None</td>
<td>47</td>
<td>Roxithromycin “low dose” × 3-6 months</td>
<td></td>
<td>1) Symptoms; 2) Apoptotic rate of nasal polyp mucosa</td>
<td>Improved symptoms and polyp cell apoptosis</td>
</tr>
<tr>
<td>Wallwork et al.²⁵</td>
<td>2006</td>
<td>RCT, blinded</td>
<td>1b</td>
<td>CRS Task Force Criteria, CT scores</td>
<td>59</td>
<td>1) Roxithromycin; 2) Placebo</td>
<td>Roxithromycin 150 mg QD × 3 months</td>
<td>1) Symptoms (SNOT-20); 2) Patient response scale; 3) Peak nasal inspiratory flow; 4) STT; 5) Nasal endoscopy; 6) Olfactory function; 7) Markers from nasal lavage</td>
<td>Improved patient response, SNOT-20 and endoscopy but no improvement in other outcomes; Better response in patients without elevated IgE</td>
</tr>
<tr>
<td>Cervin et al.²⁶</td>
<td>2002</td>
<td>Observational cohort</td>
<td>4</td>
<td>AAO-HNS criteria failed surgical and medical management</td>
<td>17</td>
<td>Erythromycin</td>
<td>Erythromycin 250 mg BID × 12 months</td>
<td>1) Symptoms (VAS 0-100); 2) Endoscopic findings; 3) STT; 4) Ciliary beat frequency; 5) Nitric oxide levels</td>
<td>Improved symptoms, endoscopy and STT; No change in CBF or NO levels</td>
</tr>
<tr>
<td>Katsuta et al.²⁷ᵃ</td>
<td>2002</td>
<td>Observational cohort</td>
<td>4</td>
<td>Nasal polyposis</td>
<td>56</td>
<td>Roxithromycin</td>
<td>Roxithromycin 300 mg QD × 3 months</td>
<td>1) Symptoms; 2) Endoscopy; 3) CT findings; 4) Microscopy</td>
<td>More than 50% of patients improved in symptoms, endoscopy, and CT</td>
</tr>
<tr>
<td>MacLeod et al.²⁸</td>
<td>2001</td>
<td>Observational cohort</td>
<td>4</td>
<td>History, physical and CT findings</td>
<td>25</td>
<td>Clarithromycin</td>
<td>Clarithromycin 500 mg BID × 14 days</td>
<td>1) Mucosal biopsy specimens with immunohistochemical stains for several markers</td>
<td>Significant decrease in CD68, EG2, elastase, IL-6, IL-8, TNF-α, and edema; improvement in headache and sinus pain but not in nasal congestion or discharge</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study design</th>
<th>LOE</th>
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<th>Macrolide protocol</th>
<th>Clinical end-point(s)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhee et al.²⁹</td>
<td>2000</td>
<td>Observational cohort</td>
<td>4</td>
<td>Persistent signs, symptoms and CT changes despite medical therapy</td>
<td>18</td>
<td>Clarithromycin</td>
<td>Clarithromycin 500 mg BID × 4 weeks</td>
<td>1) Physical characteristics of nasal mucous before and after treatment</td>
<td>Increased spinability and percent solid component of mucous with decreased ratio of viscosity to elasticity</td>
</tr>
<tr>
<td>Yamada et al.³⁰</td>
<td>2000</td>
<td>Observational cohort</td>
<td>4</td>
<td>Symptoms, X-ray, polyps on endoscopy</td>
<td>20</td>
<td>Clarithromycin</td>
<td>Clarithromycin 400 mg QD × 8-12 weeks</td>
<td>1) Endoscopic polyp grade; 2) Mediator levels from nasal lavage</td>
<td>Improved polyp grade in 40% and decreased IL-8 after treatment</td>
</tr>
<tr>
<td>Kimura et al.³¹</td>
<td>1997</td>
<td>Observational cohort</td>
<td>4</td>
<td>None</td>
<td>30</td>
<td>Roxithromycin</td>
<td>Roxithromycin 150 mg QD × 3 months</td>
<td>1) Subjective symptoms; 2) endoscopic signs; 3) Sinus X-rays</td>
<td>Improved symptoms and endoscopy scores (p &lt; 0.001), X-rays all improved or no change</td>
</tr>
<tr>
<td>Suzuki et al.³²</td>
<td>1997</td>
<td>Observational cohort</td>
<td>4</td>
<td>Symptoms, signs, CT, nasal smears without eosinophils</td>
<td>12</td>
<td>Roxithromycin</td>
<td>Roxithromycin 150 mg QD × 4-11 months</td>
<td>1) Sinus aeration on CT (%); 2) nasal smear analysis of IL-8 and neutrophil count</td>
<td>Improved aeration of all sinuses, decreased PMN score and decreased IL-8 levels (p &lt; 0.05)</td>
</tr>
<tr>
<td>Hashiba and Baba³³</td>
<td>1996</td>
<td>Observational cohort</td>
<td>4</td>
<td>Symptoms &gt; 2 years despite medical &amp; surgical therapy</td>
<td>45</td>
<td>Clarithromycin</td>
<td>Clarithromycin 200 mg BID × 8-12 weeks</td>
<td>1) Subjective symptoms; 2) objective findings</td>
<td>Improvement in all factors in over 50% of patients except for nasal edema; efficacy increased with duration of treatment from 2-12 weeks</td>
</tr>
<tr>
<td>Kita et al.³⁴a</td>
<td>1995</td>
<td>Observational cohort</td>
<td>4</td>
<td>None</td>
<td>71</td>
<td>1) Erythromycin; 2) Roxithromycin</td>
<td>Erythromycin 600 mg QD × 3 months; Roxithromycin 150 mg QD × 3 months</td>
<td>1) Nasal symptoms; 2) Endoscopic findings; 3) Maxillary sinus X-ray</td>
<td>Significant improvement in symptoms, endoscopy and X-ray; no difference between macrolides</td>
</tr>
<tr>
<td>Minami et al.³⁵a</td>
<td>1995</td>
<td>Observational cohort</td>
<td>4</td>
<td>None</td>
<td>21</td>
<td>Roxithromycin</td>
<td>Roxithromycin 150 mg QD × 6 months</td>
<td>1) Nasal symptoms; 2) X-ray mucociliary function</td>
<td>Improved symptoms and mucociliary function in &gt;67% of patients</td>
</tr>
<tr>
<td>Moriya a et al.³⁶</td>
<td>1995</td>
<td>Retrospective case-control</td>
<td>3b</td>
<td>Pansinusitis requiring FESS</td>
<td>149</td>
<td>Erythromycin</td>
<td>Erythromycin 600 mg TID × 1-2 months then 400 mg BID × 1-2 months, then 200 mg QD × 1-2 months</td>
<td>1) Subjective symptoms; 2) Endoscopic findings in maxillary, ethmoid, and frontal sinuses</td>
<td>Greater improvement in symptoms (p &lt; 0.01) and endoscopy (no p value given with postoperative erythromycin)</td>
</tr>
<tr>
<td>Kikuchi et al.³⁷a</td>
<td>1991</td>
<td>Observational cohort</td>
<td>4</td>
<td>Symptoms after Caldwell-Luc and medical therapy</td>
<td>26</td>
<td>Erythromycin</td>
<td>Erythromycin 400-600 mg QD × 7 months</td>
<td>1) Subjective symptoms; 2) Rhinoscopy exam findings</td>
<td>Improved symptoms and rhinoscopic findings without significant side effects</td>
</tr>
</tbody>
</table>

*Studies written in foreign language with English summary.

AAO-HNS = American Academy of Otolaryngology-Head and Neck Surgery; BID = twice per day; CRS = chronic rhinosinusitis; CT = computed tomography; ECP = eosinophil cationic protein; EG2 = eosinophil granule protein-2; EPOS = European Position Paper on Rhinosinusitis and Nasal Polyps; FESS = functional endoscopic sinus surgery; IgE = immunoglobulin E; IL-6 = interleukin-6; IL-8 = interleukin-8; LOE = level of evidence; NO = nitric oxide; PMN = polymorphonuclear leukocyte; PNIF = peak nasal inspiratory flow; QD = once per day; RCT = randomized controlled trial; SNOT-20 = 20-item Sino-Nasal Outcome Test; SNOT-22 = 22-item Sino-Nasal Outcome Test; STT = saccharine transit time; TID = three times per day; TNF = tumor necrosis factor; VAS = Visual Analogue System.
percent of sinus aeration on CT and found significant improvements in aeration of maxillary, ethmoid, sphenoid, and frontal sinuses in 10 patients after treatment with roxithromycin (p < 0.05 for all).

Additionally, chemical mediators from nasal mucous or lavage samples were evaluated in 5 studies. Two studies demonstrated a significant decrease in interleukin 8 (IL-8) following macrolide treatment, with the study by Suzuki et al. showing a correlative decrease in neutrophils from nasal smears. Cervin et al. demonstrated an additional decrease in eosinophilic cationic protein (ECP) and α-2 macroglobulin with a reduction in histamine-induced plasma exudation following clarithromycin treatment. An additional article from the same group, however, failed to show a change in nitric oxide levels (NO) or ciliary beat frequency (CBF). Moreover, Yamada et al. demonstrated a decrease in IL-8 levels, but not in IL-4, IL-6, IL-10, or monocyte chemotactic protein-1 (MCP1) following 2 to 3 months of macrolide therapy. Finally, Rhee et al. found improvement in several physical characteristics of mucous in macrolide-treated patients with decreased viscosity and more liquid mucous.

An abundance of Level 4 evidence supports the clinical utility of macrolide antibiotics for CRS. A single RCT demonstrated modest improvements in patient symptoms, QOL, and endoscopy compared to placebo, particularly in those without atopy. These potential clinic benefits must be weighed against the costs of prolonged macrolide therapy, mild side effects, and theoretical potential for bacterial resistance. Considering the inherent tradeoffs, a summary recommendation is to consider prolonged macrolides as an option for CRS patients, particularly those with low IgE levels. It remains unclear whether the clinical benefit of macrolide antibiotics is a result of direct antimicrobial effects, a byproduct of their intrinsic anti-inflammatory properties, or a combination of both mechanisms.

Macrolide antibiotics
1. Aggregate quality of evidence: B (Level 1b: 2 studies; Level 3b: 1 study; Level 4: 14 studies).
2. Benefit: Improved patient symptoms and endoscopy findings vs placebo in 1 controlled study.

Table 5. Summary of intravenous antibacterial antibiotics for CRS

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>LOE</th>
<th>Definition of CRS</th>
<th>n</th>
<th>Antibiotic protocol</th>
<th>Clinical end-point(s)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anand et al.</td>
<td>2003</td>
<td>Observational cohort</td>
<td>4</td>
<td>Osteitis on CT scan</td>
<td>45</td>
<td>21 different antibiotic formulations for 6 weeks</td>
<td>1) Symptom scores; 2) RSDI</td>
<td>Improvement in symptom scores at 9 weeks; change in RSDI not significant (underpowered; n = 7)</td>
</tr>
<tr>
<td>Fowler et al.</td>
<td>2003</td>
<td>Retrospective case series</td>
<td>4</td>
<td>3 months symptoms + CT or endoscopy</td>
<td>31</td>
<td>Several different formulations for average of 4.8 weeks (ceftriaxone most common)</td>
<td>1) Resolution (defined by CT or endoscopy); 2) Relapse rate</td>
<td>29% with resolution; 89% with relapse at average of 11.5 weeks</td>
</tr>
</tbody>
</table>

CRS = chronic rhinosinusitis; CT = computed tomography; IV = intravenous; LOE = level of evidence; RSDI = Rhinosinusitis Disability Index.
objective evidence of mucosal disease on CT scan or endoscopy. After an average of 4.8 weeks of antibiotics, only 29% were felt to have disease resolution (defined by CT or endoscopy) and 89% relapsed at an average of 11.5 weeks.

Both of the included studies reported complication rates secondary to IV antibiotic therapy. Anand et al. reported complications in 16% of patients, including elevations in liver function enzymes, neutropenia/sepsis, bleeding, and rash. Fowler et al. reported a 26% incidence of complications including line-related infections, deep venous thrombosis, and acute drug reactions. The largest review of complication rates for outpatient IV antibiotic therapy for CRS was published by Lin et al. in 2005. In this retrospective chart review, 29 of 177 (16%) patients developed a treatment-related complication, 10 of which required a change in therapy.

The complications secondary to IV antibacterial antibiotics are potentially serious in nature and the associated costs are high. Given that only a single, uncontrolled study reports potential clinical value, there appears to be a preponderance of harm over benefit for IV antibacterial antibiotics in CRS. A summary recommendation against routine use of IV antibacterial antibiotics is made for CRS. Use should be considered on an individual clinical basis, with the physician and patient weighing available information regarding efficacy, risks, and inherent value judgments. This recommendation would not apply to acute infectious complications that may infrequently arise secondary to CRS, such as intracranial or intraorbital infections.

**Intravenous antibacterial antibiotics**

1. Aggregate quality of evidence: C (Level 4: 2 studies).
2. Benefit: Potential for improvement in patient-reported symptoms in uncontrolled studies.
5. Value judgments: Clear risk of harmful side effects and high cost vs modest benefits reported in uncontrolled studies.
6. Recommendation level: Recommend against use of intravenous antibiotics for uncomplicated CRS cases.

**Topical antibacterial antibiotics**

Nine studies examined topical antibacterial antibiotic use for CRS, with study designs ranging from retrospective case series to randomized placebo-controlled clinical trials (Table 6). Every published case series and observational cohort reported improvement in patient-reported clinical symptoms compared to pretreatment baseline scores. Kobayashi and Baba published the largest observational cohort, following outcomes of 208 patients treated with varying dosages of 3 aminoglycoside antibiotics administered via nebulizer for 8 weeks. On the highest dosages, 61% to 72% of patients reported their improvement as either “fair” or better. A statistical comparison of specific antibiotics or dosages was not done. More recently, Uren et al. reported outcomes of 16 patients treated with mupirocin twice daily via large-volume irrigations. A statistically significant improvement in nasal endoscopy, VAS for symptoms, and 20-item SNOT (SNOT-20) scores was observed at the end of 3 weeks. Improvement in clinical symptoms was reported in 4 other observational studies with LOEs ranging from 2c to 4; however, none of these studies included a control group.

Three RCTs have examined topical antibacterial antibiotic use for CRS, with all failing to document a significant clinical effect. Each of these studies was relatively small in size and none provide information regarding the intrinsic power of the study to show a clinically relevant difference between groups. The first and largest study was published by Sykes et al. In this study, 50 patients with CRS were randomized to either a regimen of neomycin, dexamethasone, and tramazoline or a regimen of dexamethasone and tramazoline without neomycin. Patients administered the medication as a metered-dose spray every 6 hours for 2 weeks. At the end of the treatment period, no difference in clinical symptoms, nasal resistance, or mucociliary clearance could be detected. Desrosiers and Salas-Prato examined topical administration of tobramycin via nebulizer 3 times a day for 4 weeks compared to placebo nebulization of saline and quinine in 20 patients. No difference was seen between groups in the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score (primary outcome measure) or assessment of pain, mucosal edema, secretions, or postnasal drainage. Of note, the tobramycin group actually reported worse congestion than the placebo arm. The most recent study by Videler et al. treated 14 patients with CRS with 2 weeks of oral levofloxacin followed by either nebulized bacitracin/colimycin or saline for 8 weeks. No difference was seen in individual symptoms or overall QOL.

The majority of reported studies either observed no treatment-related complications or failed to report this data. Vaughan and Carvalho documented a sore throat and cough in 9.5% and 7.5% of patients, respectively, whereas patients in the Neher et al. study reported increased pain related to catheter placement. None of these potential side effects resulted in a change in treatment. Systemic bioavailability and optimal dosing regimens are not well established for topically applied antibacterial antibiotics, thus dosages and routes of administration have not been U.S. Food and Drug Administration (FDA)-approved in most cases. Two small pilot studies have demonstrated that gentamicin can be detected in the serum after nasal irrigations, although no complications were noted. Prior studies have also documented bronchospasm after nebulization of several antibiotics, including tobramycin.
TABLE 6. Summary of topical antibacterial antibiotic studies for CRS

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study design</th>
<th>LOE</th>
<th>Clinical study</th>
<th>Definition of CRS</th>
<th>n</th>
<th>Study group(s)</th>
<th>Antibiotic protocol</th>
<th>Method</th>
<th>Clinical endpoint(s)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uren et al.41</td>
<td>2008</td>
<td>Observational cohort</td>
<td>4</td>
<td>Failed medical and surgical treatment + staphylococcal culture</td>
<td>16</td>
<td>1) Mupirocin</td>
<td>1) Mupirocin 100 mL (500 μg/mL in lactated ringers) 2 × /day for 3 weeks</td>
<td>Large volume irrigation</td>
<td>1) Nasal endoscopy; 2) VAS symptoms; 3) SNOT-20</td>
<td>Significant improvement in endoscopy, symptom scores, and QOL compared to baseline</td>
<td></td>
</tr>
<tr>
<td>Videler et al.42</td>
<td>2008</td>
<td>RCT</td>
<td>1b</td>
<td>3 months symptoms + objective findings + staphylococcal culture</td>
<td>14</td>
<td>1) Bacitracin/colimycin; 2) Placebo</td>
<td>1) Bacitracin/colimycin 8 mL (830/640 μg/mL) 2 × /day for 8 weeks; 2) Saline 2 × /day for 8 weeks + oral levofloxacin for 2 weeks; 3) Saline 2 × /day for 8 weeks + oral levofloxacin for 2 weeks</td>
<td>Nebulizer</td>
<td>1) VAS symptoms; 2) Short Form-36; 3) Disease-Specific Symptom Score</td>
<td>No difference between groups</td>
<td></td>
</tr>
<tr>
<td>Neher et al.43</td>
<td>2005</td>
<td>Observational cohort</td>
<td>4</td>
<td>3 months symptoms + objective findings</td>
<td>12</td>
<td>1) N-chlorotaurine</td>
<td>1) N-chlorotaurine 10-20 mL of 1% in lactated ringers via catheter 3 × /week for 4 weeks</td>
<td>Low volume irrigation</td>
<td>1) Olfaction (Zurich); 2) CT scores; 3) Symptoms; 4) Polyp size; 5) Pain</td>
<td>Improvement in olfaction; no change in CT scores; increased pain compared to baseline; no analysis of symptoms or endoscopy</td>
<td></td>
</tr>
<tr>
<td>Scheinberg and Otsuji44</td>
<td>2002</td>
<td>Retrospective case series</td>
<td>4</td>
<td>2 years symptoms</td>
<td>41</td>
<td>1) Multiple antibiotics</td>
<td>1) One of several different antibiotics 2 × /day for 3 weeks</td>
<td>Nebulizer</td>
<td>1) Symptom scores (individual and aggregate)</td>
<td>Aggregate score improved from 2.39 to 0.49; each individual symptom scores improved.</td>
<td></td>
</tr>
<tr>
<td>Vaughan and Carvalho45</td>
<td>2002</td>
<td>Retrospective case series</td>
<td>4</td>
<td>Failed prior sinus surgery</td>
<td>46</td>
<td>1) Multiple antibiotics</td>
<td>1) One of several different antibiotics 2 × /day for 3 weeks</td>
<td>Nebulizer</td>
<td>1) RSOM symptoms (timing of follow-up unclear)</td>
<td>Improvement in postnasal drainage, nasal drainage, facial pain/pressure, and emotional consequences</td>
<td></td>
</tr>
<tr>
<td>Desrosiers and Salas-Prato46</td>
<td>2001</td>
<td>RCT</td>
<td>1b</td>
<td>3 months symptoms</td>
<td>20</td>
<td>1) Tobramycin; 2) Placebo</td>
<td>1) Tobramycin 4 mL (20 mg/mL) 3 × /day for 4 weeks; 2) Saline + 1 mg/mL quinine</td>
<td>Nebulizer</td>
<td>1) RQLQ; 2) Pain; 3) Mucosal edema; 4) Secretions; 5) Postnasal drainage; 6) Congestion</td>
<td>No difference between groups in all measures except congestion; congestion worse in tobramycin arm</td>
<td></td>
</tr>
<tr>
<td>Desrosiers and Salas-Prato46</td>
<td>2001</td>
<td>RCT</td>
<td>1b</td>
<td>3 months symptoms</td>
<td>20</td>
<td>1) Tobramycin; 2) Placebo</td>
<td>1) Tobramycin 4 mL (20 mg/mL) 3 × /day for 4 weeks; 2) Saline + 1 mg/mL quinine</td>
<td>Nebulizer</td>
<td>1) RQLQ; 2) Pain; 3) Mucosal edema; 4) Secretions; 5) Postnasal drainage; 6) Congestion</td>
<td>No difference between groups in all measures except congestion; congestion worse in tobramycin arm</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
and polymyxin E53; however, most of these protocols utilized the oral route of inhalation and were done in specialized populations such as cystic fibrosis patients. Depending on route of administration, topical sinonasal medications may also require an appreciable time commitment from patients. Vaughan and Carvalho45 reported an average of 20 minutes per nebulization, whereas Sheinberg and Otsuji44 estimate 10 to 15 minutes per dose.

The potential clinical benefit reported only in uncontrolled studies balances against the cost of topical antibacterial antibiotics, the time necessary for administration, a mostly unknown safety and dosing profile, and to a lesser extent the minor complications that have been reported. In our judgment the potential for harm outweighs the as-yet-unproven benefits, leading to a summary recommendation against use of topical antibacterial antibiotics for routine CRS cases. Despite this recommendation, the authors acknowledge that topical application of antibiotics may be an appropriate option in select instances and individual clinicians should consider the risks, benefits, and value judgments carefully. Future adequately powered RCTs are needed to clarify the therapeutic benefit of topical antibacterial antibiotics, assess optimal delivery strategies, and establish clear safety profiles and individual dosing regimens.

### Table 6. Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study design</th>
<th>LOE</th>
<th>Definition of CRS</th>
<th>n</th>
<th>Study group(s) protocol</th>
<th>Method</th>
<th>Clinical endpoint(s)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kamiyo et al.47</td>
<td>2001</td>
<td>Observational cohort</td>
<td>2c</td>
<td>3 months symptoms</td>
<td>28</td>
<td>1) Fosfomycin 2 mL (3% wt/vol) 3 × /day for 4 weeks</td>
<td>Nebulizer</td>
<td>1) Symptoms; 2) Endoscopy; 3) Cytokines (IL-1B, IL-6, IL-8)</td>
<td>60% with “fair” improvement in symptoms and endoscopic appearance; significant decrease in IL-6 and IL-18, but not IL-8</td>
</tr>
<tr>
<td>Kobayashi and Baba48</td>
<td>1992</td>
<td>Observational cohort</td>
<td>2c</td>
<td>None</td>
<td>208</td>
<td>1) Fosfomycin; 2) Dideoxykanamycin; 3) Cefmenoxime Low, mid, and high dosages administered 3 × /week for 8 weeks</td>
<td>Nebulizer</td>
<td>1) Overall improvement (excellent, good, fair, poor); 2) X-ray changes</td>
<td>61% to 72% with fair or better improvement; X-ray improvement in 47% to 59% on highest dosages; no statistical comparisons among antibiotics</td>
</tr>
<tr>
<td>Sykes et al.49</td>
<td>1986</td>
<td>RCT</td>
<td>2b</td>
<td>None</td>
<td>50</td>
<td>1) Dexamethasone, tramazoline, and neomycin; 2) Dexamethasone, tramazoline 1) Dexamethasone 20 μg, tramazoline 120 μg, neomycin 100 μg per nostril 4 × /day for 2 weeks; 2) Dexamethasone 20 μg, tramazoline 120 μg per nostril 4 × /day for 2 weeks</td>
<td>Metered dose spray</td>
<td>1) Symptoms; 2) Nasal resistance; 3) Mucociliary clearance</td>
<td>No difference between groups</td>
</tr>
</tbody>
</table>

CRS = chronic rhinosinusitis; CT = computed tomography; IL-6 = interleukin-6; LOE = level of evidence; QOL = quality of life; RCT = randomized controlled trial; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; RSOM = Rhinosinusitis Outcome Measure; SNOT-20 = 20-item Sino-Nasal Outcome Test; VAS = Visual Analogue Scale.

Topical antibacterial antibiotics

1. Aggregate quality of evidence: B (Level 1b: 2 studies; Level 2b: 1 study; Level 2c: 2 studies; Level 4: 4 studies).
2. Benefit: Potential for improvement in patient-reported symptoms and QOL in uncontrolled studies. Controlled clinical trials failed to show a benefit; however, it is unclear whether studies were adequately powered.
3. Harm: Increased congestion was seen with nebulized tobramycin. Nebulized forms of some antibiotics can cause bronchospasm. Topically applied antibiotics have been detected systemically in serum, and bioavailability of most antibiotics and ideal dosing regimens remain unknown. Topical regimens can be time consuming for patients, depending on frequency and route of administration.
4. Cost: Moderate to high.
Soler et al.

6. Value judgments: Clinical benefit seen only in uncontrolled observational studies vs monetary expense, time commitment, and unknown safety profile.
7. Recommendation level: Recommendation against use of topical antibiotics for routine CRS cases.

Oral antifungal antibiotics

Only 3 studies examining oral antifungal antibiotics for CRS met inclusion criteria for review (Table 7).\textsuperscript{54–56} The highest-level evidence was presented by Kennedy et al.\textsuperscript{56} In this randomized, double-blind, placebo-controlled trial, 53 patients received either oral terbinafine or placebo daily for 6 weeks. All patients had CRS according to AAO-HNS criteria. At the end of treatment, no difference was seen for CT scores, QOL, or overall physician and patient evaluations. No difference in complications was observed between treatment arms.

Two additional uncontrolled retrospective studies described outcomes of itraconazole use in patients with allergic fungal sinusitis (AFS). Chan et al.\textsuperscript{55} reported outcomes of 32 patients with AFS treated with 100 mg itraconazole 3 times per day (TID) for 1 month, followed by 100 mg twice per day (BID) for 2 months. Nasal endoscopy findings improved in 37.5%, with the remainder showing either no change or worsening. Symptom scores were improved in 56%; however, there was no correlation between subjective and endoscopic changes. Elevation in liver function studies was seen in 19%, with 1 patient requiring discontinuation of therapy.

Seiberling and Wormald\textsuperscript{54} reported a retrospective case series of 23 patients with disease classified as either AFS or nonallergic eosinophilic fungal sinusitis. Patients refractory to other treatments were dosed with oral itraconazole twice daily for 6 months. After treatment, 69.6% were felt to have a favorable response in clinical symptoms or endoscopy based on chart review, although it is unclear what constituted a favorable response because no objective criteria were described. Of note, 11 of 16 patients who completed the full course of therapy were felt to be free of disease at the last follow-up visit. Elevated liver function studies were noted in 4 of 23 patients, with 3 patients requiring discontinuation of therapy.

With the highest-level evidence indicating no clinical benefit, the moderate to high cost associated with prolonged oral antifungal treatments, and potential for medication-related complications, the available data represents a preponderance of harm over benefit. As such, the summary recommendation is against routine use of oral antifungal antibiotics for cases of CRS. Use should be considered on an individual clinical basis, with the physician and patient weighing available information regarding efficacy, risks, and inherent value judgments. This recommendation would not apply to cases of chronic invasive fungal sinusitis, wherein tissue destruction is evident and fungal hyphae are seen invading sinonasal tissues.

Oral antifungal antibiotics

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

Intravenous antifungal antibiotics

No published studies have examined IV antifungal antibiotics for CRS patients without clear invasive fungal disease. Intravenously-administered antifungal medications are costly and have side effects that are potentially serious in nature. Without any evidence demonstrating utility, a preponderance of harm over benefit must be assumed and a recommendation against IV antifungal medications made.

Topical antifungal antibiotics

A total of 13 studies evaluating the use of topical antifungals for CRS met inclusion criteria (Table 8).\textsuperscript{57–69} Eight of these studies were Level 1b placebo-controlled randomized trials,\textsuperscript{57–59,61,63,64,66,67} and all but 2 studies\textsuperscript{59,66} were blinded. One report was a non–placebo-controlled RCT\textsuperscript{60} and an additional 4 studies were prospective observational cohorts without placebo.\textsuperscript{62,65,68,69} Fluconazole nasal spray was used in 1 study\textsuperscript{65} of AFS patients whereas all other studies evaluated the use of amphotericin B nasal spray or irrigation. Antifungal dosing was widely variable, with daily doses of amphotericin B ranging from 0.8 mg to 5 gm and duration of therapy from 4 weeks to 20 months.

Symptomatic improvement was measured in 8 studies,\textsuperscript{58,59,61,62,64,65,67,68} 5 were RCTs and used validated sinusitis symptom scoring tools,\textsuperscript{58,59,61,64,67} whereas 3 were observational cohorts\textsuperscript{62,65,68} and only 1 used a validated symptom tool. Symptomatic improvement was seen in 25% to 75% of patients in uncontrolled studies, although 25% of the AFS population studied by Jen et al.\textsuperscript{65} had a worsening of symptoms while on fluconazole therapy. None of the controlled studies demonstrated an improvement in symptoms above and beyond that seen with placebo. In fact, the amphotericin B group in the study by Wescota et al.\textsuperscript{67} demonstrated less symptomatic improvement than the placebo group (p < 0.005). Three studies specifically measured QOL results (all but 1 using...
TABLE 7. Summary of oral antifungal antibiotics for CRS

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study design</th>
<th>LOE</th>
<th>Definition of CRS</th>
<th>N</th>
<th>Study group(s)</th>
<th>Antibiotic protocol</th>
<th>Clinical end-point(s)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sieberling and Wormald⁶⁴</td>
<td>2009</td>
<td>Retrospective case series</td>
<td>4</td>
<td>Allergic fungal sinusitis; nonallergic fungal eosinophilic sinusitis</td>
<td>23</td>
<td>1) Itraconazole</td>
<td>Itraconazole 100 mg 2 × /day for 6 months</td>
<td>1) Physician evaluation of response</td>
<td>69.6% with favorable response</td>
</tr>
<tr>
<td>Chan et al.⁵⁵</td>
<td>2008</td>
<td>Retrospective case series</td>
<td>4</td>
<td>Allergic fungal sinusitis refractory to ESS and medical management</td>
<td>32</td>
<td>1) Itraconazole</td>
<td>Itraconazole 100 mg TID for 1 month then TID for 2 months</td>
<td>1) Endoscopy scores (Kupferberg); 2) Symptom scores (RSOM-31)</td>
<td>Endoscopy improved in 37.5%, no change in 47%, and worsened in 16%; symptoms improved in 56%. Elevated LFTs in 19%</td>
</tr>
<tr>
<td>Kennedy et al.⁶⁶</td>
<td>2005</td>
<td>RCT</td>
<td>1b</td>
<td>AAO-HNS criteria</td>
<td>53</td>
<td>1) Terbinafine; 2) Placebo</td>
<td>Terbinafine 625 mg po 1 × /day for 6 weeks</td>
<td>1) CT score; 2) QOL; 3) Patient evaluation; 4) Physician evaluation</td>
<td>No difference between groups</td>
</tr>
</tbody>
</table>

AAO-HNS = American Academy of Otolaryngology–Head and Neck Surgery; BID = 2 times per day; CRS = chronic rhinosinusitis; CT = computed tomography; ESS = endoscopic sinus surgery; LFT = liver function test; LOF = level of evidence; po = by mouth; QOL = quality of life; RCT = randomized controlled trial; RSOM-31 = 31-item Rhinosinusitis Outcome Measure; TID = 3 times per day.

a validated QOL assessment tool) and none demonstrated improvement compared to placebo⁵⁸,⁶¹,⁶⁷.

Endoscopic findings were examined in 9 studies⁵⁸,⁵⁹,⁶¹,⁶²,⁶³,⁶⁴,⁶⁵,⁶⁶,⁶⁷-⁶⁹; 5 were RCTs⁵⁸,⁵⁹,⁶¹,⁶⁴,⁶⁷ and 4 were observational cohorts.⁶²,⁶⁵,⁶⁸,⁶⁹ All but 1 study (Jen et al.⁶⁵) used a standardized endoscopic grading system, with 4 studies using previously validated staging systems. Among the controlled studies, there was a trend toward improvement in the amphotericin B patients compared to placebo but this did not reach statistical significance in 4 of 5 studies⁵⁸,⁵⁹,⁶¹,⁶⁷. The study of 24 patients by Ponikau et al.⁶⁴ demonstrated a 70% improvement in median endoscopy scores in the amphotericin B group compared to no change in the placebo group (p = 0.038), but this study did not use a previously validated endoscopic scoring system.

Three studies⁵⁸,⁶⁴,⁶⁶ evaluated CT findings before and after treatment, with mixed results. Gerlinger et al.⁵⁸ utilized the modified Lund-Mackay score to evaluate CT scans before and after 12 months of amphotericin B irrigations vs placebo in a RCT of 30 patients. A trend toward improvement in the placebo group was seen compared to the amphotericin B arm, but this did not reach statistical significance (p = 0.052). The Mayo Clinic group conducted both an RCT and observation cohort study using a software program that calculated the percent of mucosal inflammation compared to total sinus area. In their RCT⁶⁴ comparing 6 months of amphotericin B irrigation to placebo, the authors found an 8.8% reduction in percent mucosal thickening in the antifungal group compared to a 2.5% increase in the placebo arm (p = 0.03). An observational study of 51 patients by the same group⁶⁶ demonstrated a significant improvement in maxillary sinus opacification from 65% to 23% following amphotericin B irrigations in the 13 patients with posttreatment scans (p < 0.0001). No significant improvement was found in the opacification of either the sphenoid or frontal sinuses. The authors did not explain why only 13 of 51 patients received a second CT scan.

Inflammatory mediators from nasal mucus, lavage samples, or polyp biopsies were studied in 4 Level 1b RCTs.⁵⁷,⁶³,⁶⁴,⁶⁶ One study by Ponikau et al.⁶⁴ found a significant decrease in eosinophil-derived neurotoxin (EDN) in amphotericin B–treated patients compared to placebo (p = 0.046), but none of the remaining 24 mediators measured in the 4 studies demonstrated a significant difference compared to placebo. Two of the studies⁵⁹,⁶⁴ included quantification of fungi before and after treatment with no significant difference in fungal eradication between groups, and no alteration in chemical mediators among the patients whose fungus was cleared compared to those in which fungus persisted.

An abundance of Level 1b data has failed to show a consistent clinical benefit from topical antifungal antibiotics for CRS. The lack of demonstrable clinical efficacy is countered by moderate-to-high costs and minor side effects. The summary recommendation is strongly against topical antifungal antibiotics for patients with routine CRS.

Topical antifungal antibiotics

1. Aggregate quality of evidence: A (Level 1b: 9 studies; Level 4: 4 studies).
2. Benefit: No consistent benefit in clinical symptoms, endoscopy, or CT scans compared to placebo controls.
4. Cost: Moderate to high.
6. Value judgments: No demonstrable benefit over placebo in multiple RCTs vs side effects and cost.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study design</th>
<th>LOE</th>
<th>Definition of CRS</th>
<th>n</th>
<th>Study group(s)</th>
<th>Antifungal protocol</th>
<th>Clinical end-point(s)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ebbens et al.57</td>
<td>2009</td>
<td>RCT, blinded,</td>
<td>1b</td>
<td>Symptoms, endoscopy, CT findings, previous FESS</td>
<td>99</td>
<td>1) Amphotericin B irrigation; 2) Placebo</td>
<td>Amphotericin B</td>
<td>Levels of secreted mediators from nasal lavage fluid</td>
<td>No difference between groups</td>
</tr>
<tr>
<td>Gerlinger et al.58</td>
<td>2009</td>
<td>RCT, blinded</td>
<td>1b</td>
<td>EAACI criteria all patients postpolyectomy</td>
<td>30</td>
<td>1) Amphotericin B nasal spray; 2) Placebo</td>
<td>Amphotericin B 2 mg</td>
<td>1) Modified Lund-Mackay; 2) Symptoms (SNAQ-11); 3) QOL questionnaire; 4) Endoscopic scoring</td>
<td>No difference between groups; both groups had improvement in symptoms, QOL, and endoscopy; no change in CT scores</td>
</tr>
<tr>
<td>Liang et al.59</td>
<td>2008</td>
<td>RCT, unblinded</td>
<td>1b</td>
<td>CRS Task Force 2003 criteria (all without polyps)</td>
<td>64</td>
<td>1) Amphotericin B irrigation; 2) Placebo</td>
<td>Amphotericin B 20</td>
<td>1) Symptoms questionnaire (RSOM-31); 2) Endoscopy (Lund); 3) Nasal lavage cultures</td>
<td>No difference between groups; both groups showed improvement</td>
</tr>
<tr>
<td>Corradini et al.60</td>
<td>2006</td>
<td>RCT</td>
<td>1b</td>
<td>Polyps plus positive fungal cultures</td>
<td>89</td>
<td>1) Ethmoidectomy and LAS irrigation; 2) Ethmoidectomy and LAS/Amphotericin B irrigation; 3) Steroids and LAS irrigation; 4) Steroids and LAS/Amphotericin B irrigation</td>
<td>Amphotericin B 0.8 mg 6 times per week then 0.16 mg 6 times per week × 19 months</td>
<td>Recurrence of nasal polyps</td>
<td>No difference between groups 1 vs 2 or 3 vs 4, but groups with Amphotericin irrigations (2 + 4) had decreased recurrence collectively than groups without Amphotericin (1 + 3), p = 0.018</td>
</tr>
<tr>
<td>Ebbens et al.61</td>
<td>2006</td>
<td>RCT, blinded,</td>
<td>1b</td>
<td>Symptoms, endoscopy, CT findings, previous FESS</td>
<td>99</td>
<td>1) Amphotericin B irrigation; 2) Placebo</td>
<td>Amphotericin B 2500 mg BID × 13 weeks</td>
<td>1) Symptoms (VAS score and RSOM-31); 2) Endoscopic exam; 3) QOL (SF-36); 4) Peak nasal inspiratory flow; 5) Polyp score</td>
<td>Improved CT and endoscopy findings in Amphotericin group but no change in nasal mucosal markers or patient symptoms between groups</td>
</tr>
<tr>
<td>Helbling et al.62</td>
<td>2006</td>
<td>Observational</td>
<td>4</td>
<td>Malm stage II or III polyps</td>
<td>21</td>
<td>Amphotericin B nasal spray</td>
<td>Amphotericin B 1 mg</td>
<td>1) Endoscopic polyp score; 2) Symptom questionnaire</td>
<td>Symptom improvement in 1/3 of patients, no significant polyp improvement</td>
</tr>
<tr>
<td>Weschta et al.63</td>
<td>2006</td>
<td>RCT, blinded</td>
<td>1b</td>
<td>Nasal polyps, symptom, endoscopy and CT scores</td>
<td>60</td>
<td>1) Amphotericin B nasal spray; 2) Placebo</td>
<td>Amphotericin B 1.2 mg QID × 2 months</td>
<td>Measurement of tryptase and eosinophil cationic protein from nasal lavage</td>
<td>No difference between groups</td>
</tr>
<tr>
<td>Ponikau et al.64</td>
<td>2005</td>
<td>RCT, blinded</td>
<td>1b</td>
<td>AAO-HNS 1997 Guidelines</td>
<td>24</td>
<td>1) Amphotericin B irrigation; 2) Placebo</td>
<td>Amphotericin B 5 mg</td>
<td>1) Percent mucosal thickening change on CT; 2) Endoscopic edema; 3) Symptoms (SNOT-20); 4) IL-5, EDN, and Alternaria levels in nasal mucus</td>
<td>Improved CT and endoscopy findings in Amphotericin group but no change in nasal mucosal markers or patient symptoms between groups</td>
</tr>
<tr>
<td>Jen et al.65</td>
<td>2004</td>
<td>Observational</td>
<td>4</td>
<td>AFS with worsening symptoms</td>
<td>16</td>
<td>Fluconazole nasal spray</td>
<td>Fluconazole 0.5 mg</td>
<td>1) Endoscopic edema and polyps; 2) Symptoms (not defined)</td>
<td>Symptoms and endoscopic exam stable or improved in 75% of patients</td>
</tr>
<tr>
<td>Shin and Ye66</td>
<td>2004</td>
<td>RCT, unblinded</td>
<td>1b</td>
<td>AAO-HNS 1996 Task Force Criteria</td>
<td>41</td>
<td>1) Amphotericin B irrigation; 2) Placebo</td>
<td>Amphotericin B 5-10 mg BID × 4 weeks</td>
<td>Cytokine levels from nasal polyps surgically removed</td>
<td>No difference between groups</td>
</tr>
</tbody>
</table>

(Continued)
TABLE 8. Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study design</th>
<th>LOE</th>
<th>Definition of CRS</th>
<th>n</th>
<th>Study group(s)</th>
<th>Antifungal protocol</th>
<th>Clinical end-point(s)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weschta et al.67</td>
<td>2004</td>
<td>RCT, blinded</td>
<td>1b</td>
<td>Nasal polyps, symptom, endoscopy and CT scores</td>
<td>60</td>
<td>1) Amphotericin B nasal spray; 2) Placebo</td>
<td>Amphotericin B 1.2 mg QID × 2 months</td>
<td>1) Response = 50% reduction in pretreatment CT score; 2) Symptom score; 3) QOL score (RQL); 4) Fungus from nasal lavage</td>
<td>Symptom scores better in placebo group (p &lt; 0.005); no difference in CT, QOL, or endoscopy between groups</td>
</tr>
<tr>
<td>Ponikau et al.68</td>
<td>2002</td>
<td>Observational cohort</td>
<td>4</td>
<td>AAO-HNS 1997 Guidelines</td>
<td>51</td>
<td>Amphotericin B irrigation</td>
<td>Amphotericin B 4 mg BID × 3-17 months</td>
<td>1) Subjective symptoms; 2) Endoscopic findings; 3) CT findings</td>
<td>Improved CT aeration, endoscopic findings and symptoms in 75%</td>
</tr>
<tr>
<td>Richetti et al.69</td>
<td>2002</td>
<td>Observational cohort</td>
<td>4</td>
<td>Nasal polyps refractory to topical steroids and saline</td>
<td>74</td>
<td>Amphotericin B irrigation, saline irrigation, steroid spray</td>
<td>Amphotericin B 20 mg BID × 4 weeks</td>
<td>1) Endoscopic exam for resolution of polyps</td>
<td>39% overall cured of polyps; higher rates in patients with previous FESS (p &lt; 0.033)</td>
</tr>
</tbody>
</table>

AAO-HNS = American Academy of Otolaryngology–Head and Neck Surgery; AFS = allergic fungal sinusitis; BID = 2 times per day; CT = computed tomography; EAACI = European Academy of Allergy and Clinical Immunology; EDN = eosinophil-derived neurotoxin; FESS = functional endoscopic sinus surgery; IL-5 = interleukin-5; LAS = lysine acetylsalicylate; QID = 4 times per day; QOL = quality of life; RCT = randomized controlled trial; RQL = Rhinoconjunctivitis Quality of Life; RSOM-31 = 31-item Rhinosinusitis Outcome Measure; SNAQ-11 = 11-item Sinonasal Assessment Questionnaire; SNOT-20 = 20-item Sinonasal Outcome Test; TID = 3 times per day.

7. Recommendation level: Strong recommendation against the use of topical antifungals for routine CRS patients.

Discussion

Historically, the rationale for the treatment of CRS with antibiotics was based on the presumed relationship of ARS to CRS, as well as rare but undeniable evidence of microbial tissue invasion and obvious infectious complications in some cases of CRS. Current consensus documents, however, define CRS as a chronic inflammatory rather than a purely infectious disorder, and most lines of research presume that the inflammation seen in CRS results from a dysfunctional host–environment interaction. Identification of the key environmental agent(s) that drive the inflammatory process has been a major research focus for many years.

Currently, the rationale for the routine use of antibiotics in typical uncomplicated cases of CRS is based on 2 assumptions: (1) that bacteria and/or fungi are not only the agents of the rare invasive complications of CRS but also drive the chronic, mucosal inflammatory process; and (2) that antibiotics will reduce the level of colonized microbes in the sinonasal cavity with secondary reduction of the host inflammatory reaction. While the first issue remains controversial, limited evidence suggests a role for Staphylococcus aureus as an environmental agent driving some forms of CRS. Other researchers have explored the roles of osteomyelitis and mucosal biofilms as infectious conditions that might promote inflammation. Even if these hypotheses prove to be correct, it remains to be demonstrated that antibiotics can durably reduce the level of mucosal inflammation and thus improve patient symptomatology. Emerging concepts of mucosal homeostasis would cast

TABLE 9. Summary of evidence for antibiotic utilization in CRS

<table>
<thead>
<tr>
<th>Antibiotic strategy</th>
<th>Grade of evidence</th>
<th>Balance of benefit to harm</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral antibacterial</td>
<td>C</td>
<td>Equal</td>
<td>Option</td>
</tr>
<tr>
<td>(≤3 weeks)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral antibacterial</td>
<td>N/A (single study)</td>
<td>Harm</td>
<td>Recommend against</td>
</tr>
<tr>
<td>(&gt;3 weeks)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV antibacterial</td>
<td>C</td>
<td>Harm</td>
<td>Recommend against</td>
</tr>
<tr>
<td>Topical antibacterial</td>
<td>B</td>
<td>Harm</td>
<td>Recommend against</td>
</tr>
<tr>
<td>Oral antifungal</td>
<td>B</td>
<td>Harm</td>
<td>Recommend against</td>
</tr>
<tr>
<td>IV antifungal</td>
<td>N/A (no studies)</td>
<td>Unknown</td>
<td>Recommend against</td>
</tr>
<tr>
<td>Topical antifungal</td>
<td>A</td>
<td>Harm</td>
<td>Recommend strongly against</td>
</tr>
<tr>
<td>Macrolide class</td>
<td>B</td>
<td>Equal</td>
<td>Option</td>
</tr>
</tbody>
</table>

*Excludes macrolide class of oral antibacterial antibiotics.
CRS = chronic rhinosinusitis; IV = intravenous; N/A = none available.
doubt on this proposition.75,76 Hence, there remains a clear need for additional controlled clinical trials to evaluate an

tibiotic strategies for CRS, particularly oral and topical an-
tibacterial antibiotics. Moreover, future clinical studies also

to evaluate optimal dosing durations, as this may sig-

ingificantly affect not only costs associated with treatment

but also efficacy.

Studies were included in this review if participants had

been diagnosed with CRS. Although specific criteria exist
to define CRS, many researchers currently believe that it
is a heterogeneous group of disorders unified by a similar
clinical presentation. Research guidelines have suggested
a division between CRS patients with and without polyps,
although some investigators focus on clinical or histopatho-

glogic features to further classify subgroups, and little con-
sensus exists.77–79 It remains possible that some antibiotic
strategies will prove efficacious in certain subgroups but
not in others, as was reported with macrolide antibiotics
in those without atopy. The lack of subgroup analysis in
most existing studies would serve to mask possible treat-
ment efficacy in specific subtypes. For this reason it may
be reasonable, based on the individual case, to use anti-
biotic strategies that were not recommended by this review.
It is anticipated that future research will more clearly de-

fine relevant subgroups, and that distinctions in underlying

pathophysiology will guide therapeutic strategies, including

antibiotics. We encourage future antibiotic clinical studies

to include relevant characteristics that will allow current
and future subgroup analysis in studies using general diag-

nostic criteria for CRS.

Conclusion

Based on the available published literature, an evidence-

based strategy for CRS with or without polyps would consider oral antibacterial and prolonged macrolide anti-

biotics as therapeutic “options” (Table 9). The inability
to formally recommend these strategies stems from the
lack of high-quality controlled clinical data, which is bal-
anced against known side effects and associated costs. The
strongest individual data is for oral doxycycline in nasal
polyposis patients and prolonged oral macrolides in pa-

tients with low IgE. Interestingly, both of these medica-

tions have known anti-inflammatory properties in addition
to their antimicrobial effects. However, evidence is lack-
ing for either treatment in terms of providing long-term ben-
fefit (ie, > 12 weeks after completion). An evidence-based

strategy for CRS would not routinely use IV antibacterial

antibiotics or topical antibacterial antibiotics, nor oral, IV,
or topical antifungal medications. This review is not in-
tended to supersede clinical judgment, but rather to assist
clinicians in understanding the available evidence, weighing
the inherent tradeoffs, and developing an evidence-based strategy for antibiotic use.

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18. Gehanno P, Cohen B. Effectiveness and safety of

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of long-term clarithromycin treatment on lavage-fluid
markers of inflammation in chronic rhinosinusitis.


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