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

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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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Chronic rhinosinusitis (CRS) is a common clinical syndrome characterized by symptomatic inflammation of the mucosa of the nose and paranasal sinuses. This disorder is most commonly divided into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) based on endoscopic evaluation. Symptoms lasting greater than 3 months differentiates CRS from acute rhinosinusitis (ARS), the vast majority of which are presumed to be viral in origin, with a minority (1%) complicated by secondary acute bacterial infection.[1] In contrast, the etiology of CRS is believed to be multifactorial and the relationship between ARS and CRS remains unclear.

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.[2–34] 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.[5] 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[6] 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 Rudmik and Smith.[7] The Clinical Practice Guideline Manual,[8] Conference on Guideline Standardization (COGS),[9] and the Appraisal of Guidelines and Research Evaluation (AGREE)[10] instrument recommendations were followed to improve quality, transparency, and reporting of results.

TABLE 1. Antibiotic approaches for CRS evaluated in review

Antibacterial
Oral antibiotics (non-macrolide; shorter than 3 weeks treatment duration)
Oral antibiotics (non-macrolide; longer than 3 weeks treatment duration)
Macrolide class of antibiotics
Intravenous antibiotics
Topical antibiotics
Antifungal
Oral antibiotics
Intravenous antibiotics
Topical antibiotics

CRS = chronic rhinosinusitis.

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[6] and the European Position Paper on Rhinosinusitis and Nasal Polyposis (EPOS).[11]

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

methodology according to the Center for Evidence-Based Medicine.[12] 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).[13] 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).[14–19] Four of these studies were randomized controlled trials (RCTs),[14,16,17,19] each with a double-blind design. However, in 3 of the 4 clinical trials[16,17,19] 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[15,18] were observational cohort studies. The study by Gehanno and Cohen[18] 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.[14] 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 consider a major research priority.

TABLE 2. Recommendations based on defined grades of evidence

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

RCT = randomized controlled trial.

TABLE 3. Summary of oral antibacterial antibiotic studies for CRS (non-macrolide; shorter than 3 weeks treatment duration)

Study	Year	Study design	LOE	Definition of CRS	n	Study group(s)	Antibiotic protocol	Clinical endpoint(s)	Conclusion
Van Zele et al.[14]	2010	RCT	1b	Bilateral polyps	33	1) Doxycycline; 2) Placebo	Doxycycline 200 mg once, followed by 100 mg 1 × /day for 20 days	1) Polyp size; 2) PNIF; 3) olfaction; 4) congestion; 5) rhinorrhea; 6) postnasal drainage	Reduction in polyp size at week 12. Reduction in postnasal drainage at week 2
Galioto et al.[15]	1995	Observational cohort	4	None	5	1) Flurithromycin	1) Flurithromycin 375 mg 2 × /day for ≥5days	Clinical "cure" or "improvement"	All cured or improved
Dellanomica et al.[16]	1994	RCT	1b	Symptoms + X-ray findings	171	1) Cefotiam; 2) Cefixime	1) Cefotiam 200 mg 2 × /day for 10 days; 2) Cefixime 200 mg 2 × /day for 10 days	Clinical "cure" or "improvement"	No difference between groups
Legent et al.[17]	1994	RCT	1b	3 months symptoms + CT findings	251	1) Amoxicillin/ clavulanate; 2) Ciprofloxacin	1) Amoxicillin/clavulanate 500 mg 3 × /day for 9 days; 2) Ciprofloxacin 500 mg 2 × /day for 9 days	1) Clinical "cure"; 2) nasal drainage	No difference between groups
Gehanno and Cohen[18]	1993	Observational cohort	4	None	198	1) Ofloxacin	Ofloxacin 200 mg 2 × /day for 12 days	Clinical "cure" or "improvement"	Majority of patients cured/improved at 8 days
Huck et al.[19]	1993	RCT	1b	"Nonresolving sinus disease"	15	1) Cefaclor; 2) Amoxicillin	1) Cefaclor 500 mg 2 × /day for 10 days; 2) Amoxicillin 500 mg 3 × /day for 10 days	1) "Success/failure"; 2) X-ray findings	No difference between groups

CRS = chronic rhinosinusitis; CT = computed tomography; LOE = level of evidence; PNIF = peak nasal inspiratory flow; RCT = randomized controlled trial.

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

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

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

The (non-macrolide) studies examining oral antibacterial antibiotics for CRS reviewed above used a treatment regimen lasting 3 weeks or less. Only a single study by Dubin et al.[20] could be identified that examined different durations of oral antibiotic use for CRS. In this observational study of CRS without polyps, 35 patients with >3 months of symptoms and evidence of disease on computed tomography (CT) scan were treated with oral clindamycin, amoxicillin/clavulanate, or doxycycline for 6 weeks. CT scans were obtained after 3 weeks and 6 weeks of therapy and compared to previous scans at baseline using the Lund-Mackay scoring system. A total of 16 of 35 patients completed all 6 weeks of therapy and had CT data available for each time point. A statistically significant improvement in CT scores was seen between baseline and 3 weeks, with average scores improving from 8.9 to 4.38. No difference was seen between 3-week and 6-week CT scores (4.38 vs 4.125; $p = 0.9$). Although average CT scans failed to improve after 3 weeks, the authors noted that 38% of patients actually had some improvement in CT scores between 3 and 6 weeks, whereas 62% had no change or worsening over time. The fact that 38% of patients improved was taken as potential evidence supporting a longer duration of therapy by the authors, although this conclusion seems questionable. GI upset severe enough to require discontinuation of therapy after 3 weeks was noted in 3 patients. No cases of *Clostridium difficile* colitis or allergic reaction were observed.

Because only 1 study is available for review, an aggregate quality of evidence could not be generated. At present, there is no data demonstrating benefit from oral, non-macrolide antibiotic courses lasting greater than 3 weeks. This fact must be balanced with the known risks of oral antibiotics previously described, as well as additional costs associated with extended antibiotic courses. When considering this evidence, the summary *recommendation* is *against* a prolonged (>3 weeks) course of oral antibacterial antibiotics

(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.
3. Harm: GI upset. Potential for *Clostridium difficile* colitis. Anaphylaxis. Bacterial resistance. Rash.
4. Cost: Variable (low to high).
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 studies[23,34] 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 ($p \leq 0.01$ 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, PNIF, 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] Moriayama 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] Moriayama 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 had worsening of imaging findings. Suzuki et al.[32] used a computer software program to measure the

TABLE 4. Summary of macrolide class antibiotics for CRS

Study	Year	Study design	LOE	Definition of CRS	N	Study group(s)	Macrolide protocol	Clinical end-point(s)	Conclusion
Videler et al.[21]	2011	RCT, blinded	1b	EPOS	60	1) Azithromycin; 2) Placebo	Azithromycin 500mg QD × 3 days, then 500 mg/week × 11 weeks	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	No significant benefit was found over placebo
Cervin et al.[22]	2009	Observational cohort	4	Persistent nasal symptoms after FESS	25	Clarithromycin	Clarithromycin 250 mg QD × 12 weeks	1) Mediators in nasal mucous (IL-8, ECP, α2-macroglobulin)	Reduction in mediator levels histamine-induced secretion
Haruna et al.[23]	2009	Observational cohort	4	Symptoms and CT findings	29	1) Roxithromycin; 2) Clarithromycin	Roxithromycin 150 mg QD or clarithromycin 200 mg QD × 8-20 weeks	1) Clinical symptom questionnaire; 2) CT scores	Symptom and CT scores improved or unchanged in all patients. Better improvement if no polyps or lower initial CT score
Song et al.[24a]	2009	Observational cohort	4	None	47	Roxithromycin	Roxithromycin "low dose" × 3-6 months	1) Symptoms; 2) Apoptotic rate of nasal polyp mucosa	Improved symptoms and polyp cell apoptosis
Wallwork et al.[25]	2006	RCT, blinded	1b	CRS Task Force Criteria, CT scores	59	1) Roxithromycin; 2) Placebo	Roxithromycin 150 mg QD × 3 months	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	Improved patient response, SNOT-20 and endoscopy but no improvement in other outcomes; Better response in patients without elevated IgE
Cervin et al.[26]	2002	Observational cohort	4	AAO-HNS criteria failed surgical and medical management	17	Erythromycin	Erythromycin 250 mg BID × 12 months	1) Symptoms (VAS 0-100); 2) Endoscopic findings; 3) STT; 4) Ciliary beat frequency; 5) Nitric oxide levels	Improved symptoms, endoscopy and STT; No change in CBF or NO levels
Katsuta et al.[27a]	2002	Observational cohort	4	Nasal polyposis	56	Roxithromycin	Roxithromycin 300 mg QD × 3 months	1) Symptoms; 2) Endoscopy; 3) CT findings; 4) Microscopy	More than 50% of patients improved in symptoms, endoscopy, and CT
MacLeod et al.[28]	2001	Observational cohort	4	History, physical and CT findings	25	Clarithromycin	Clarithromycin 500 mg BID × 14 days	1) Mucosal biopsy specimens with immunohistochemical stains for several markers	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

(*Continued*)

TABLE 4. Continued

Study	Year	Study design	LOE	Definition of CRS	N	Study group(s)	Macrolide protocol	Clinical end-point(s)	Conclusion
Rhee et al.[29]	2000	Observational cohort	4	Persistent signs, symptoms and CT changes despite medical therapy	18	Clarithromycin	Clarithromycin 500 mg BID × 4 weeks	1) Physical characteristics of nasal mucous before and after treatment	Increased spinability and percent solid component of mucous with decreased ratio of viscosity to elasticity
Yamada et al.[30]	2000	Observational cohort	4	Symptoms, X-ray, polyps on endoscopy	20	Clarithromycin	Clarithromycin 400 mg QD × 8-12 weeks	1) Endoscopic polyp grade; 2) Mediator levels from nasal lavage	Improved polyp grade in 40% and decreased IL-8 after treatment
Kimura et al.[31]	1997	Observational cohort	4	None	30	Roxithromycin	Roxithromycin 150 mg QD × 3 months	1) Subjective symptoms; 2) endoscopic signs; 3) Sinus X-rays	Improved symptoms and endoscopy scores ($p <$ 0.001). X-rays all improved or no change.
Suzuki et al.[32]	1997	Observational cohort	4	Symptoms, signs, CT, nasal smears without eosinophils	12	Roxithromycin	Roxithromycin 150 mg QD × 4-11 months	1) Sinus aeration on CT (%); 2) nasal smear analysis of IL-8 and neutrophil count	Improved aeration of all sinuses, decreased PMN score and decreased IL-8 levels ($p < 0.05$)
Hashiba and Baba[33]	1996	Observational cohort	4	Symptoms >2 years despite medical & surgical therapy	45	Clarithromycin	Clarithromycin 200 mg BID × 8-12 weeks	1) Subjective symptoms; 2) objective findings	Improvement in all factors in over 50% of patients except for nasal edema; efficacy increased with duration of treatment from 2-12 weeks
Kita et al.[34a]	1995	Observational cohort	4	None	71	1) Erythromycin; 2) Roxithromycin	Erythromycin 600 mg QD × 3 months; Roxithromycin 150 mg QD × 3 months	1) Nasal symptoms; 2) Endoscopic findings; 3) Maxillary sinus X-ray	Significant improvement in symptoms, endoscopy and X-ray; no difference between macrolides
Minami et al.[35a]	1995	Observational cohort	4	None	21	Roxithromycin	Roxithromycin 150 mg QD × 6 months	1) Nasal symptoms; 2) X-ray mucociliary function	Improved symptoms and mucociliary function in >67% of patients
Moriyama et al.[36]	1995	Retrospective case-control	3b	Pansinusitis requiring FESS	149	1) Erythromycin postoperatively; 2) No postoperative erythromycin	Erythromycin 600 mg TID × 1-2 months then 400 mg BID × 1-2 months, then 200 mg QD × 1-2 months	1) Subjective symptoms; 2) Endoscopic findings in maxillary, ethmoid, and frontal sinuses	Greater improvement in symptoms ($p < 0.01$) and endoscopy (no p value given) with postoperative erythromycin
Kikuchi et al.[37a]	1991	Observational cohort	4	Symptoms after Caldwell-Luc and medical therapy	26	Erythromycin	Erythromycin 400-600 mg QD × 7 months	1) Subjective symptoms; 2) Rhinoscopy exam findings	Improved symptoms and rhinoscopy findings without significant side effects

[a]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 = eosinophilic cationic protein; EG2 = eosinophil granule protein-2; EPOS = European Position Paper on Rhinosinusitis and Nasal Polyposis; 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.[22,25,28,30,32] Three studies[22,28,30] demonstrated a significant decrease in interleukin 8 (IL-8) following macrolide treatment, with the study by Suzuki et al.[32] showing a correlative decrease in neutrophils from nasal smears. Cervin et al.[22] 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).[26] Moreover, Yamada et al.[30] 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.[29] 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. Uncontrolled studies showed additional improvements in imaging findings, characteristics of nasal mucous, and reduction of inflammatory mediators in mucous.
3. Harm: GI upset. Rash. Taste disturbance. Hand numbness. All graded as mild to moderate and none required discontinuation of the medication. Potential liver function abnormalities. Theoretical risk of antibiotic resistance but none confirmed in the above studies.
4. Cost: Moderate to high. Treatment duration ranged from 2 weeks to 12 months. Most treated for at least 3 months.
5. Benefits-harm assessment: Balance of benefit vs harm.
6. Value judgments: Consistent benefit shown in multiple observational studies and 1 controlled study vs cost and minimal side effects. No evidence for superiority of any individual macrolides.
7. Recommendation level: Option (especially in patients with low IgE levels).

Intravenous antibacterial antibiotics

Two studies examined intravenous (IV) administration of antibacterial antibiotics for CRS (Table 5).[38,39] Anand et al.[38] reported outcomes from a prospective, observational cohort of 45 patients with osteitis of the paranasal sinuses on CT scan treated with 6 weeks of IV antibiotics. A mix of 21 different antibiotic combinations was used in this patient population, with clinical endpoints that included patient-reported symptom scores and the Rhinosinusitis Disability Index (RSDI) QOL measure. A statistically significant improvement in all 15 symptoms evaluated was reported at week 9 (3 weeks after completion of therapy), with $p < 0.003$ for all. No difference was seen in the RSDI, although this outcome was measured in only 7 patients and therefore was underpowered. This study was considered Level 4 evidence because it failed to include a comparator group. Fowler et al.[39] reported a retrospective case series of 31 patients receiving culture-directed IV antibacterial antibiotics. In this patient population, CRS was defined as 3 months or greater of clinical symptoms with

TABLE 5. Summary of intravenous antibacterial antibiotics for CRS

Study	Year	Study design	LOE	Definition of CRS	n	Study group(s)	Antibiotic protocol	Clinical end-point(s)	Conclusion
Anand et al.[38]	2003	Observational cohort	4	Osteitis on CT scan	45	1) IV antibiotics	21 different antibiotic formulations for 6 weeks	1) Symptom scores; 2) RSDI	Improvement in symptom scores at 9 weeks; change in RSDI not significant (underpowered; n = 7)
Fowler et al.[39]	2003	Retrospective case series	4	3 months symptoms + CT or endoscopy	31	1) IV antibiotics (culture-directed)	Several different formulations for average of 4.8 weeks (ceftriaxone most common)	1) Resolution (defined by CT or endoscopy); 2) Relapse rate	29% with resolution; 89% with relapse at average of 11.5 weeks

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.[38] reported complications in 16% of patients, including elevations in liver function enzymes, neutropenia/septicemia, bleeding, and rash. Fowler et al.[39] 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.[40] 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.
3. Harm: Thrombophlebitis. Deep venous thrombosis. Elevated liver function tests. Neutropenia/septicemia. Drug reaction. Rash. Bleeding.
4. Cost: High.
5. Benefits-harm assessment: Preponderance of harm over benefit.
6. Value judgments: Clear risk of harmful side effects and high cost vs modest benefits reported in uncontrolled studies.
7. 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).[41–49] Every published case series and observational cohort reported improvement in patient-reported clinical symptoms compared to pretreatment baseline scores. Kobayashi and Baba[48] 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.[41] 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[43–45,47] 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.[42,46,49] 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.[49] 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[46] 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.[42] 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[45] documented a sore throat and cough in 9.5% and 7.5% of patients, respectively, whereas patients in the Neher et al.[43] 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[50,51] 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[52]

TABLE 6. Summary of topical antibacterial antibiotic studies for CRS

Study	Year	Study design	LOE	Definition of CRS	n	Study group(s)	Antibiotic protocol	Method	Clinical endpoint(s)	Conclusion
Uren et al.[41]	2008	Observational cohort	4	Failed medical and surgical treatment + staphylococcal culture	16	1) Mupirocin	1) Mupirocin 100 mL (500 μg/mL in lactated ringers) 2 × /day for 3 weeks	Large volume irrigation	1) Nasal endoscopy; 2) VAS symptoms; 3) SNOT-20	Significant improvement in endoscopy, symptom scores, and QOL compared to baseline
Videler et al.[42]	2008	RCT	1b	3 months symptoms + objective findings + staphylococcal culture	14	1) Bacitracin/colimycin; 2) Placebo	1) Bacitracin/colimycin 8 mL (830/640 μg/mL) 2 × /day for 8 weeks + oral levofloxacin for 2 weeks; 2) Saline 2 × /day for 8 weeks + oral levofloxacin for 2 weeks	Nebulizer	1) VAS symptoms; 2) Short Form-36; 3) Disease-Specific Symptom Score	No difference between groups
Neher et al.[43]	2005	Observational cohort	4	3 months symptoms + objective findings	12	1) N-chlorotaurine	1) N-chlorotaurine 10-20 mL of 1% in lactated ringers via catheter 3 × /week for 4 weeks	Low volume irrigation	1) Olfaction (Zurich); 2) CT scores; 3) Symptoms; 4) Polyp size; 5) Pain	Improvement in olfaction; no change in CT scores; increased pain compared to baseline; no analysis of symptoms or endoscopy
Scheinberg and Otsuji[44]	2002	Retrospective case series	4	2 years symptoms	41	1) Multiple antibiotics	1) One of several different antibiotics 2 × /day for 3 weeks	Nebulizer	1) Symptom scores (individual and aggregate)	Aggregate score improved from 2.39 to 0.49; each individual symptom scores improved.
Vaughan and Carvalho[45]	2002	Retrospective case series	4	Failed prior sinus surgery	46	1) Multiple antibiotics	1) One of several different antibiotics 2 × /day for 3 weeks	Nebulizer	1) RSOM symptoms (timing of follow-up unclear)	Improvement in postnasal drainage, nasal drainage, facial pain/pressure, and emotional consequences
Desrosiers and Salas-Prato[46]	2001	RCT	1b	3 months symptoms	20	1) Tobramycin; 2) Placebo	1) Tobramycin 4 mL (20 mg/mL) 3 × /day for 4 weeks; 2) Saline + 1 mg/mL quinine	Nebulizer	1) RQLQ; 2) Pain; 3) Mucosal edema; 4) Secretions; 5) Postnasal drainage; 6) Congestion	No difference between groups in all measures except congestion; congestion worse in tobramycin arm
Desrosiers and Salas-Prato[46]	2001	RCT	1b	3 months symptoms	20	1) Tobramycin; 2) Placebo	1) Tobramycin 4 mL (20 mg/mL) 3 × /day for 4 weeks; 2) Saline + 1 mg/mL quinine	Nebulizer	1) RQLQ; 2) Pain; 3) Mucosal edema; 4) Secretions; 5) Postnasal drainage; 6) Congestion	No difference between groups in all measures except congestion; congestion worse in tobramycin arm

(Continued)

TABLE 6. Continued

Study	Year	Study design	LOE	Definition of CRS	n	Study group(s)	Antibiotic protocol	Method	Clinical endpoint(s)	Conclusion
Kamijyo et al.[47]	2001	Observational cohort	2c	3 months symptoms	28	1) Fosfomycin	1) Fosfomycin 2 mL (3% wt/vol) 3 × /day for 4 weeks	Nebulizer	1) Symptoms; 2) Endoscopy; 3) Cytokines (IL-1B, IL-6, IL-8)	60% with "fair" improvement in symptoms and endoscopic appearance; significant decrease in IL-6 and IL-1B, but not IL-8
Kobayashi and Baba[48]	1992	Observational cohort	2c	None	208	1) Fosfomycin; 2) Dideoxy-kanamycin; 3) Cefmenoxime	Low, mid, and high dosages administered 3 × /week for 8 weeks	Nebulizer	1) Overall improvement (excellent, good, fair, poor); 2) X-ray changes	61% to 72% with fair or better improvement; X-ray improvement in 47% to 59% on highest dosages; no statistical comparisons among antibiotics
Sykes et al.[49]	1986	RCT	2b	None	50	1) Dexametha-sone, tramazoline, and neomycin; 2) Dexametha-sone, 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	Metered dose spray	1) Symptoms; 2) Nasal resistance; 3) Mucociliary clearance	No difference between groups

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.

and polymyxin E[53]; 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 Carvalho[45] reported an average of 20 minutes per nebulization, whereas Sheinberg and Otsuji[44] 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.

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.

5. Benefits-harm assessment: Potential for harm over benefit.
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).[54–56] The highest-level evidence was presented by Kennedy et al.[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.[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[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.
5. Benefits-harm assessment: Preponderance of harm over benefit.
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).[57–69] Eight of these studies were Level 1b placebo-controlled randomized trials,[57–59,61,63,64,66,67] and all but 2 studies[59,66] were blinded. One report was a non–placebo-controlled RCT[60] and an additional 4 studies were prospective observational cohorts without placebo.[62,65,68,69] Fluconazole nasal spray was used in 1 study[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[58,59,61,62,64,65,67,68]; 5 were RCTs and used validated sinusitis symptom scoring tools[58,59,61,64,67] whereas 3 were observational cohorts[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.[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 Weschta et al.[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

Study	Year	Study design	LOE	Definition of CRS	N	Study group(s)	Antibiotic protocol	Clinical end-point(s)	Conclusion
Sieberling and Wormald[54]	2009	Retrospective case series	4	Allergic fungal sinusitis; nonallergic fungal eosinophilic sinusitis	23	1) Itraconazole	Itraconazole 100 mg 2 × /day for 6 months	1) Physician evaluation of response	69.6% with favorable response
Chan et al.[55]	2008	Retrospective case series	4	Allergic fungal sinusitis refractory to ESS and medical management	32	1) Itraconazole	Itraconazole 100 mg TID for 1 month then BID for 2 months	1) Endoscopy scores (Kupferberg); 2) Symptom scores (RSOM-31)	Endoscopy improved in 37.5%, no change in 47%, and worsened in 16%; symptoms improved in 56%. Elevated LFTs in 19%
Kennedy et al.[56]	2005	RCT	1b	AAO-HNS criteria	53	1) Terbinafine; 2) Placebo	Terbinafine 625 mg po 1 × /day for 6 weeks	1) CT score; 2) QOL; 3) Patient evaluation; 4) Physician evaluation	No difference between groups

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 placebo.[58,61,67]

Endoscopic findings were examined in 9 studies[58,59,61,62,64,65,67–69]; 5 were RCTs[58,59,61,64,67] 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 studies.[58,59,61,67] 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 studies[58,64,68] 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 RCT[64] 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 group[68] 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 mucous, 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 studies[59,64] 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.
3. Harm: Nasal burning. GI upset. Rash. Asthma attack.
4. Cost: Moderate to high.
5. Benefits-harm assessment: Preponderance of harm over benefit.
6. Value judgments: No demonstrable benefit over placebo in multiple RCTs vs side effects and cost.

TABLE 8. Summary of topical antifungal antibiotics for CRS

Study	Year	Study design	LOE	Definition of CRS	n	Study group(s)	Antifungal protocol	Clinical end-point(s)	Conclusion
Ebbens et al.[57]	2009	RCT, blinded, multicenter	1b	Symptoms, endoscopy, CT findings, previous FESS	99	1) Amphotericin B irrigation; 2) Placebo	Amphotericin B 2500 mg BID × 13 weeks	Levels of secreted mediators from nasal lavage fluid	No difference between groups
Gerlinger et al.[58]	2009	RCT, blinded	1b	EAACI criteria all patients postpolypectomy	30	1) Amphotericin B nasal spray; 2) Placebo	Amphotericin B 2 mg BID × 12 months	1) Modified Lund-Mackay; 2) Symptoms (SNAQ-11); 3) QOL questionnaire; 4) Endoscopic scoring (Malm)	No difference between groups; both groups had improvement in symptoms, QOL, and endoscopy; no change in CT scores
Liang et al.[59]	2008	RCT, unblinded	1b	CRS Task Force 2003 criteria (all without polyps)	64	1) Amphotericin B irrigation; 2) Placebo	Amphotericin B 20 mg daily × 4 weeks	1) Symptoms questionnaire (RSOM-31); 2) Endoscopy (Lund); 3) Nasal lavage cultures	No difference between groups; both groups showed improvement
Corradini et al.[60]	2006	RCT	1b	Polyps plus positive fungal cultures	89	1) Ethmoidectomy and LAS irrigation; 2) Ethmoidectomy and LAS/ Amphotericin B irrigation; 3) Steroids and LAS irrigation; 4) Steroids and LAS/Amphotericin B irrigation	Amphotericin B 0.8 mg 6 times per week × 1 month then 0.16 mg 6 times per week × 19 months	Recurrence of nasal polyps	No difference between groups 1 vs 2 or 3 vs 4, but groups with Ampho irrigations (2 + 4) had decreased recurrence collectively than groups without Ampho (1 + 3), $p = 0.018$
Ebbens et al.[61]	2006	RCT, blinded, multicenter	1b	Symptoms, endoscopy, CT findings, previous FESS	99	1) Amphotericin B irrigation; 2) Placebo	Amphotericin B 2500 mg BID × 13 weeks	1) Symptoms (VAS score and RSOM-31); 2) Endoscopic exam; 3) QOL (SF-36); 4) Peak nasal inspiratory flow; 5) Polyp score	No differences between groups for any parameter.
Helbling et al.[62]	2006	Observational cohort	4	Malm stage II or III polyps	21	Amphotericin B nasal spray	Amphotericin B 1 mg TID × 3 months	1) Endoscopic polyp score; 2) Symptom questionnaire	Symptom improvement in 1/3 of patients, no significant polyp improvement
Weschta et al.[63]	2006	RCT, blinded	1b	Nasal polyps, symptom, endoscopy and CT scores	60	1) Amphotericin B nasal spray; 2) Placebo	Amphotericin B 1.2 mg QID × 2 months	Measurement of tryptase and eosinophil cationic protein from nasal lavage	No difference between groups
Ponikau et al.[64]	2005	RCT, blinded	1b	AAO-HNS 1997 Guidelines	24	1) Amphotericin B irrigation; 2) Placebo	Amphotericin B 5 mg BID × 6 months	1) Percent mucosal thickening change on CT; 2) Endoscopic edema; 3) Symptoms (SNOT-20); 4) IL-5, EDN, and *Alternaria* levels in nasal mucous	Improved CT and endoscopy findings in Amphotericin group but no change in nasal mucous markers or patient symptoms between groups
Jen et al.[65]	2004	Observational cohort	4	AFS with worsening symptoms	16	Fluconazole nasal spray	Fluconazole 0.5 mg BID × 3 months	1) Endoscopic edema and polyps; 2) Symptoms (not defined)	Symptoms and endoscopic exam stable or improved in 75% of patients
Shin and Ye[66]	2004	RCT, unblinded	1b	AAO-HNS 1996 Task Force Criteria	41	1) Amphotericin B irrigation; 2) Placebo	Amphotericin B 5-10 mg BID × 4 weeks	Cytokine levels from nasal polyps surgically removed	No difference between groups

(*Continued*)

TABLE 8. Continued

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

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.[2] 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.[70–72] Other researchers have explored the roles of osteomyelitis and mucosal biofilms as infectious conditions that might promote inflammation.[73,74] 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

Antibiotic strategy	Grade of evidence	Balance of benefit to harm	Recommendation
Oral antibacterial (≤3 weeks)[a]	C	Equal	Option
Oral antibacterial (>3 weeks)[a]	N/A (single study)	Harm	Recommend against
IV antibacterial	C	Harm	Recommend against
Topical antibacterial	B	Harm	Recommend against
Oral antifungal	B	Harm	Recommend against
IV antifungal	N/A (no studies)	Unknown	Recommend against
Topical antifungal	A	Harm	Recommend strongly against
Macrolide class	B	Equal	Option

[a]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 antibiotic strategies for CRS, particularly oral and topical antibacterial antibiotics. Moreover, future clinical studies also need to evaluate optimal dosing durations, as this may significantly 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 histopathologic features to further classify subgroups, and little consensus 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 treatment efficacy in specific subtypes. For this reason it may be reasonable, based on the individual case, to use antibiotic strategies that were not recommended by this review. It is anticipated that future research will more clearly define 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 diagnostic 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 antibiotics as therapeutic "options" (Table 9). The inability to formally recommend these strategies stems from the lack of high-quality controlled clinical data, which is balanced against known side effects and associated costs. The strongest individual data is for oral doxycycline in nasal polyposis patients and prolonged oral macrolides in patients with low IgE. Interestingly, both of these medications have known anti-inflammatory properties in addition to their antimicrobial effects. However, evidence is lacking for either treatment in terms of providing long-term benefit (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 intended 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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