

Antimicrobial Therapy in Chronic Rhinosinusitis

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Antimicrobial therapy has been a mainstay of treatment for chronic rhinosinusitis (CRS). The roles of bacterial and fungal infection in the primary pathogenesis of CRS recently have been called into question. Although many different bacteria and fungi can be isolated from CRS patients, antimicrobial treatment directed at their eradication has met with mixed clinical results. Overall, macrolide antibiotics hold the most promise before surgery. Topical antibiotics are safe, efficient, and effective for treating acute bacterial exacerbations of CRS after endoscopic sinus surgery and may prevent the development of subsequent bacterial resistance. Topical treatment of CRS with antifungal agents both before and after sinus surgery is of limited benefit and should not be considered as a primary treatment modality before surgery. Further research into the role of bacterial and fungal infection in the pathophysiology of CRS may offer better insights into appropriate antimicrobial choices, dosing, and treatment duration.

Introduction

Chronic rhinosinusitis (CRS) affects an estimated 20 million Americans, and more than 100,000 surgical procedures are performed specifically for CRS each year [1]. CRS is responsible for significant morbidity among sufferers, with fatigue and bodily pain scores that rival those for other serious, chronic conditions, such as osteoarthritis and depression [2]. Unfortunately, despite the prevalence of CRS, its pathophysiology, optimal medical treatment regimens, and selection criteria for surgical treatment of refractory cases all remain controversial and poorly understood.

Historically, antibiotics have been widely used in the medical management of CRS. Traditionally, this has centered around antibacterial therapy and has been based on

historical data regarding the microbiology of CRS and extrapolation of data from acute bacterial rhinosinusitis. Recently, however, interest has increased in antimicrobial therapy directed at potential fungal causes, as well as in the investigation of topical antimicrobial agents such as topical antibacterials and other nonpharmacologic microbicidal agents.

In this article, we examine the effectiveness of antibiotics in the treatment of CRS in the unoperated, presurgical state, as well as the effectiveness of antibiotics in cases of recurrent or persistent CRS after endoscopic sinus surgery (ESS). Furthermore, we examine the effectiveness of antifungal therapy and anti-inflammatory aspects of antimicrobials for CRS.

CRS Prior to ESS

Most antibiotic therapy for CRS is administered before consideration for ESS under the rubric of maximum medical management. Antibiotics are usually one component of medical therapy and are most commonly used in conjunction with topical nasal steroid sprays, systemic steroids, mucolytic agents, and decongestants [3]. Many variables exist in regard to antibiotic therapy, including choice of agent, dose, and duration of therapy. All these variables may influence the effectiveness of antibiotics in treating CRS.

Antibacterials

Oral antibacterial agents have been the main antimicrobials used in the medical treatment of CRS. In several prospective studies concerning the diagnosis of CRS, investigators have shown that antibiotic use in the medical treatment of CRS is significant [1]. Patients presenting for otolaryngologic evaluation of CRS typically have already received 2.6 courses of antibiotics and have taken oral antibiotics for more than 5 weeks of the preceding 12 months [4•]. Annual antibiotic costs for treatment of CRS are approximately \$250 per patient [5]. Highlighting the widespread prevalence in the treatment of CRS, a recent survey study found that 94% of otolaryngologists prescribed oral antibiotics in the medical treatment of CRS [6].

Based on various microbiologic studies, the spectrum of bacterial organisms linked to CRS has evolved significantly. In addition to the standard aerobic respira-

tory pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, investigators have increasingly implicated *Staphylococcus aureus*, possibly as a superantigen; *Pseudomonas aeruginosa*; and anaerobes. However, despite microbiologic investigations of the bacteria recovered in presurgical CRS, the true efficacy of antibacterials in CRS has been only partially determined.

Although the most common antimicrobial treatment modality for CRS incorporates long-term (> 2 weeks) treatment with antibiotics, a few comparative studies have been published regarding short-term therapy of CRS with various agents. Namyslowski et al. [7] compared 14-day courses of amoxicillin clavulanate and cefuroxime. Clinical cures were achieved in 95% and 88% of patients, respectively. However, the absence of a control group makes interpretation of these results difficult. Interestingly, as opposed to clinical cure, only 65% of patients treated with amoxicillin clavulanate and 68% treated with cefuroxime achieved bacterial eradication. Other more remote studies of short-term therapy produced similar results [8,9••].

Although long-term oral antibiotic therapy duration varies significantly, most authorities agree with a 3- to 6-week course of antibacterial therapy in CRS. Again, these recommendations have been based primarily on historical practice rather than levels of evidence. In fact, a review of the literature demonstrates that very few prospective trials of antibacterial treatment of CRS have been conducted, and none were placebo controlled.

The one group of antibacterial agents that has been studied in CRS is the macrolide group. Pioneered by the Japanese in the 1990s, the macrolide class of antibiotics was initially used with some success to treat diffuse panbronchiolitis on a long-term basis. Subsequently, investigators reported successful treatment of polypoid and nonpolypoid CRS with low-dose macrolide therapy on a long-term basis. In many instances, treatment durations during studies range from 8 to 12 weeks and even beyond. Various studies of macrolides in the treatment of CRS demonstrated clinical improvements ranging from 50% to 71% of patients as determined by clinical symptoms scores [9••]. These studies were conducted before the establishment of disease-specific survey estimates for CRS and before the widespread availability of CT.

Two studies merit specific mention regarding macrolides and CRS. Ragab et al. [10] randomly assigned 90 patients to a medical treatment arm with erythromycin for 3 months or ESS and observed them sequentially for 1 year with validated outcome assessment instruments. The medical and surgical treatment arms improved significantly on almost all parameters, and no significant difference between groups was noted at 1 year. Rather than suggesting the ineffectiveness of surgery, this study may alternatively suggest the selective effectiveness of the macrolide agents in treating CRS. Furthermore, this study is one of the few randomized trials to compare medical management with surgical management in CRS. In a randomized, double-blind, placebo-controlled clinical trial of 64 patients with

CRS (but without nasal polyposis) by Wallwork et al. [11•], participants received roxithromycin, 150 mg daily for 12 weeks, or placebo. Patients treated with roxithromycin showed significant improvement in global symptom scores and Sinonasal Outcomes Tool-20 scores.

Thus, of all the classes of antibiotics used empirically to treat presurgical CRS, the best medical evidence exists for fairly long-term macrolide therapy. One major failing in the analysis of antibiotic effectiveness for CRS lies in the fact that no antibiotic has US Food and Drug Administration approval for a CRS indication. Pharmaceutical companies in the United States therefore have been unmotivated to study treatment outcomes for antibacterial agents in CRS. Because of the widespread variability in treatment practice concerning antibiotics for CRS, there is a significant need for prospective, randomized, placebo-controlled trials of this component of antibacterial therapy.

Antifungals

The potential role of fungus in CRS has emerged as a significant area of controversy. Several authors have identified the presence of ubiquitous fungi in a very high proportion of patients afflicted with CRS, as well as in normal controls [12]. Investigators have hypothesized that an immune (nonallergic) response to this fungal presence may lead to chronic eosinophilic rhinosinusitis and, possibly, sinonasal polyposis [9••]. Although the original findings were novel and interesting, subsequent investigations have failed to validate a significant role for ubiquitous fungi in the true etiology of CRS [13].

The potential associations between fungal elements and inflammation in CRS have prompted several investigators to conduct controlled trials of antifungals for the treatment of CRS. Unfortunately, most of these studies have enrolled patients with and without a history of previous sinus surgery. This makes interpretation of the results significantly more difficult because of the likely differential penetration of the antifungal agent into the sinus cavities themselves, particularly in presurgical patients. Alternatively, enrollment of patients with a prior history of sinus surgery also may select a more refractory patient population that is less likely to respond to antifungal therapy.

Liang et al. [14•] recently carried out a randomized, placebo-controlled, double-blind study on the treatment of nonpolypoid CRS with amphotericin B irrigations. In both the amphotericin and placebo arms, significant improvements were noted on Rhinosinusitis Symptom Outcomes Measure-31 scores at weeks 2 and 4 of treatment. However, no significant differences between treatment arms were noted, suggesting the benefit rose from the mechanical action of the irrigation rather than from the amphotericin B itself. Of note, this was one of the few studies to examine nonpolypoid patients without any history of prior surgery with respect to antifungal treatment. One potential drawback to this study was the relatively low concentration of amphotericin B in the irrigant (5 mg/mL).

Oral antifungal agents also have been tested as potential antimicrobials based on the fungal hypothesis. Kennedy et al. [15] reported results of a rigorously conducted, randomized, double-blind, placebo-controlled, multicenter trial that examined the efficacy of the high-dose oral antifungal agent terbinafine in treatment of CRS. They found that oral terbinafine failed to improve the symptoms or radiographic appearance of CRS even when nasal irrigation samples were positive for fungal culture.

Recently, a membership survey of the American Rhinologic Society was conducted to determine practice patterns for maximum medical management of CRS [16•]. Among 308 respondents, only 17% reported any significant use of oral antifungal agents in the treatment of CRS. The vast majority of these used oral antifungals in 10% to 50% of their CRS cases. Similarly, only 11.8% reported 10% to 50% use of antifungal spray, and 1% reported 50% to 100% use in their CRS patients. Finally, 6.6% of respondents reported 10% to 50% use of antifungal nebulizer spray in CRS patients. Thus, it would seem that rhinologists use antifungal agents infrequently to treat CRS. This most likely reflects their familiarity with the literature, personal experience, and overall dissatisfaction with the success of antifungal agents in the treatment of CRS.

Intravenous therapy

Interest in intravenous antibiotic therapy for refractory CRS has increased relatively recently. In 2003, Anand et al. [17] reported on the use of intravenous antibiotics to treat refractory rhinosinusitis and “nonsurgical” patients. These “nonsurgical” patients were either not surgical candidates or were unwilling to undergo revision sinus surgery. Thus, an inherent significant selection bias may exist. Also, all patients had evidence of diffuse bony thickening on CT of the paranasal sinuses, suggesting osteitis as a potential marker for more severe sinonasal disease. Nonetheless, the authors reported a significant benefit from intravenous antibiotic therapy with antibacterial agents (eg, ceftriaxone, clindamycin, Levaquin [Ortho-McNeil-Janssen Pharmaceuticals, Raritan, NJ], tobramycin, cefepime) in Rhinosinusitis Disability Index scores and, in a subselected group of patients, improvement in endoscopic examination and CT findings. Despite a follow-up study showing relatively few catheter- and antibiotic-related complications from intravenous antibacterial therapy in the same group, this treatment paradigm has not been widely adopted in the United States [18].

CRS After ESS

Oral agents

Very few studies have examined the effectiveness of oral antibiotic agents in the treatment of acute bacterial exacerbation and/or chronic bacterial exacerbation of CRS after ESS. Bacterial infection after ESS may be affected by many different types of bacterial species, including

multiple drug-resistant species [19]. Although the postoperative sinonasal cavity may be colonized by bacteria after ESS, acute bacterial infections arising after ESS most commonly represent de novo infections by noncolonizing bacteria [20]. When treating acute bacterial exacerbations after ESS, clinicians should strongly consider culture-directed therapy. Bhattacharyya and Kepnes [21] recently demonstrated in a multiyear study of 90 adult patients with serial cultures for their acute bacterial exacerbations that using culture-directed therapy for these exacerbations may prevent development of bacterial resistance in individual patients. Cincik and Ferguson [22] also demonstrated that culture-directed therapy changed subsequent antimicrobial management in 51.4% of their patients.

Topical agents

Antibacterials

Although oral agents may be very convenient for the treatment of acute bacterial exacerbations of CRS after ESS, the ability to deliver high concentrations of antibiotics directly to the sinonasal cavities while also potentially limiting systemic adverse reactions from antibiotics has renewed interest in topical antibacterial therapy in these situations. Topical antibacterial agents may be delivered by nebulization or irrigation. Lim et al. [23••] recently compiled an excellent review of topical antimicrobials in the management of CRS.

Nebulization

In the earlier part of this decade, there was renewed interest in nebulized antimicrobials, in particular antibiotics, for the maintenance of CRS patients after surgery and the treatment of CRS exacerbations after surgery. Desrosiers and Salas-Prato [24] and Kamijyo et al. [25] demonstrated significant symptomatic improvement with the use of topical antimicrobials. However, the former controlled trial failed to show any significant difference between tobramycin and a control arm with saline nebulization alone in maintenance therapy. Subsequently, Vaughan and Carvalho [26] demonstrated in a multiple-arm controlled study that CRS exacerbations after surgery could be successfully treated with a greater infection-free period with culture-directed nebulized antibiotics as opposed to standard intravenous or oral therapy. Since then, no substantial trials have been published regarding the effectiveness of nebulized therapy for acute exacerbations of CRS.

Irrigation

Solares et al. [27•] evaluated topical treatment with mupirocin in a small study of a specific population of patients with CRS exacerbations due to methicillin-resistant *S. aureus* (MRSA). Among 24 MRSA patients, 26 of 27 post-treatment cultures showed no MRSA, suggesting the effectiveness of topical mupirocin in eradicating such exacerbations caused by MRSA. This study is important because MRSA sinusitis has demonstrated a continued prevalence rate approximating 19% in *S. aureus* CRS, a rate that has been stable over time [28•].

Antifungals

Because of the fungal hypothesis described previously, several investigators have been interested in the topical application of antifungals for the postsurgical management of CRS. Unfortunately, few well-conducted trials have been published on this topic. Of the topical antifungal trials, most intermingle postsurgical patients with nonsurgical or remotely prior surgical patients, making interpretation of the results difficult. Antifungals have been applied via irrigation or nasal spray and have most commonly tested amphotericin B as the antifungal agent.

Weschta et al. [29] conducted a randomized trial of amphotericin B versus placebo with concomitant nasal steroid therapy in a patient population with nasal polyposis. Approximately 50% of patients had sinus surgery previously. They evaluated a puff-spray administration of amphotericin four times daily for 8 weeks with an equivalent daily dose of 4.8 mg. They found no significant improvement in several objective markers, such as eosinophil cationic protein, trypsin, and cellular activation markers according to fungal presence. Furthermore, symptoms seemed to actually wane in individuals in the amphotericin B arm.

Ponikau et al. [30] conducted a double-blind, randomized, controlled trial of 30 patients comparing amphotericin B with placebo. In this somewhat longer trial (6 months of follow-up), the investigators showed statistically significant improvements in mucosal thickening according to CT and endoscopic mucosal disease but could not show statistically significant improvements in patient symptom scores. Finally, Ebbens et al. [31] completed a double-blind, multicenter, randomized, controlled trial of amphotericin B versus placebo in 51 patients over a course of 3 months. No statistically significant differences in the visual analogue scale, endoscopic findings, or disease-specific outcome measures were elicited.

Thus, the role of topical antifungal agents remains controversial and nebulous in the setting of CRS after surgery. Published studies are confounded by substantial heterogeneity that is marked by widely varying patient populations that intermix surgical and nonsurgical patients and patients with and without polyposis, often without recommended CT corroboration [4•]. Substantial variability also exists in dosing regimens and duration of follow-up [23••]. As a result, trial-to-trial comparison of results is difficult. Other difficulties with comparing results are the variability and outcome measures. Because of the inherent discordance between CT findings and patients' reported symptom scores, in future trials, it may be beneficial to report both as standard outcomes measures [32,33]. Adding further to the controversy is a recent *in vitro* study that suggests that the concentration of commercially available amphotericin B (currently available at 100 µg/mL) may be insufficient to be fungicidal [34]. Clearly, standardization of many of the above parameters, including multicenter trials with appropriate follow-up, is urgently needed if we are to better understand the role of topical antifungal therapy in CRS [9••].

Special Situations

A few special situations merit specific mention with respect to antimicrobial management of CRS. One neglected group of patients with CRS are those with chronic recurrent rhinosinusitis, also termed *recurrent acute rhinosinusitis* [35]. Although this group of patients has been better characterized recently, an understanding of the microbiology and pathogenesis of this disease is still lacking [36]. Optimal antimicrobial treatment options also have yet to be studied.

Cystic fibrosis patients are known to be chronically colonized with a variety of bacteria, the most prominent of which is *P. aeruginosa*. Nebulized antibiotics, antibiotics delivered via irrigation, and chronic suppressive doses of oral antibiotics all have been used in this patient population to suppress baseline symptoms and acute exacerbations of CRS. As lung function is often influenced by sinus status in cystic fibrosis, further work is warranted in this patient population [37]. Although it is beyond the scope of this article, immunocompromised patients, such as those with immunoglobulin deficiencies, also suffer from frequent exacerbations of CRS. The optimization of antimicrobial management in this patient population also requires further study.

Conclusions

The roles of bacterial and fungal infection in the primary pathogenesis of CRS recently have been called into question. Nonetheless, certain antibiotic classes, in particular the macrolides, seem to have a beneficial effect in treating CRS. Although there has been renewed interest in topical antimicrobial treatment of CRS, clinical trials have been heterogeneous, inconsistent, and disappointing overall for this modality. However, topical antibacterial agents have a role in the treatment of acute bacterial exacerbations of CRS after ESS.

Disclosure

No potential conflict of interest relevant to this article was reported.

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