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Is there a Role for Antibiotics in the Treatment of Chronic Rhinosinusitis?

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Abstract

Rhinosinusitis is one of the most common reasons for adult outpatient antibiotic prescriptions, though there is little clinical evidence to support this practice, especially for chronic rhinosinusitis. Despite considerable research, the etiology of chronic rhinosinusitis, including the pathogenic role of microbes, remains poorly understood. Rigorous studies of the efficacy of antibiotic treatment of chronic sinusitis are surprisingly few in number and the results are somewhat conflicting. This article will review the rationales for and against the treatment of chronic rhinosinusitis with antibiotics, based on current evidence and understanding of pathophysiology, and will also summarize the current guidelines.

Keywords

Chronic Rhinosinusitis; Antibiotics; Review Article

INTRODUCTION

If acute and chronic cases are combined, rhinosinusitis (RS) is currently the most common indication for adult outpatient antibiotic prescriptions in the United States.(1) There are several randomized controlled trials (RCTs)(2–7) and meta-analyses(8–10) demonstrating no evidence of benefit from antibiotics for the common cold/acute RS (ARS).(8) and some evidence supporting the efficacy of antibiotics in the treatment of a select group of patients with symptoms and signs suggestive of acute bacterial rhinosinusitis (ABRS), (11, 12) However, there are only two published placebo-controlled randomized trials of antibiotic efficacy for chronic RS (CRS), defined as RS symptoms lasting >12 weeks.(13)

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Guidelines differ regarding whether antibiotics should be included as part of the regimen for medical therapy for CRS,(13–18) which reflects both the paucity of rigorous and consistent evidence supporting their efficacy and the persisting uncertainty about the role of microbes in the pathogenesis of CRS. This article will review the rationale for and against antibiotic treatment of CRS based on available clinical evidence as well as the current understanding of the pathophysiology of this condition. We will focus primarily on diffuse primary CRS in adults but antibiotic recommendations for some special considerations will be discussed also. The review will not cover the role of antifungals in the treatment of fungal sinusitis.

CRS encompasses a complex, heterogeneous group of debilitating chronic inflammatory sinonasal diseases.(13, 15) The changing of treatment recommendations over time reflects the evolving understanding of the pathogenesis of the various phenotypes and endotypes. Despite being the subject of considerable research, the etiology of CRS remains poorly understood. A wide range of potential causative agents have been investigated: microbes, aberrant inflammatory patterns, anatomic variations, the genetics underlying the innate immune system and epithelial barrier integrity and mucociliary clearance, hypersensitivities associated with asthma, hormonal imbalance, autoimmune disorders and immunodeficiency.(19) There is little doubt that the condition is multifactorial. Defining the therapeutic role of antibiotics requires some understanding of the pathogenic role of bacteria in CRS.

Pathophysiology and the Role of Microbes

The role of microbes in the pathogenesis of ARS is reasonably well established, and ARS can be divided into acute viral rhinosinusitis, post-viral rhinosinusitis and acute bacterial rhinosinusitis.(13) However, the relationship between CRS and microbes is far less certain. No single bacterial species fulfils Koch's postulates for this condition, even although pathogenic species such as *Staphylococcus aureus* are frequently cultured from the middle meatus of CRS patients (as indeed they are from a significant percentage of normal controls).(20) Research over the last couple of decades has suggested that bacteria may be involved in the pathogenesis of CRS without actually causing an infection. A great deal of interest in biofilms as a cause of CRS was generated by observations using an array of different imaging modalities of biofilms on the sinus mucosa. Subsequently, carefully performed microscopy studies have revealed micro-colonies of bacteria growing within the mucosa of up to half of patients with idiopathic CRS.(21) The actual pathogenic link between the presence of bacteria in biofilms on the mucosal surface and micro-colonies within the mucosa is not clear, as these bacterial colonies often do not appear to provoke a local inflammatory response.(21, 22) Many studies have shown that bacteria in biofilms are much more resistant to antibiotics than are bacteria in planktonic form, partly due to the extracellular matrix of the biofilm structure inhibiting the diffusion of antibiotics and partly due to metabolic changes adopted by the bacteria in biofilms.(23–25)

Another mechanism whereby bacteria could cause mucosal inflammation without causing an infection is by releasing super-antigens.(26) The best evidence for this process occurring in CRS has been found in the mucosa of patients colonised with *Staphylococcus aureus*, particularly in cases of CRS with nasal polyps (CRSwNP).(27–30) However, if super-antigens were a key component of the pathogenesis of CRS, it may reasonably be

anticipated that CRS would respond more consistently to anti-Staphylococcal agents than it does in clinical practice.

The clinical relevance of a single, cultured bacterial species within the context of the polymicrobial communities of the sinonasal mucosa, many members of which are recalcitrant to standard culture efforts, remains unclear and such an approach may poorly represent the *in vivo* processes involved in the pathogenesis of CRS.(19) Standard culture techniques provide a limited range of conditions for microbial growth and thus may fail to detect taxa that require specific conditions. The disparity between the identification of microbes by culture and those (viable but nonculturable) identified by molecular methods has been termed “the great plate count anomaly,” with estimates of the nonculturable portion of microbial communities ranging between 25% and 99%.(31, 32)

Modern culture-independent (molecular) techniques have vastly improved our understanding of the microbiology of CRS. Recent studies have better captured the complexity of the microbial communities associated with CRS, rather than focusing on the effects of a single isolated (and culturable) organism, and have reintroduced the potential importance of the microbial community either as a direct driver of disease or as being involved in exacerbations.(19, 33) Culture-independent sequencing-based studies regularly identify up to an order of magnitude more distinct taxa per individual subject.(34–36) Additional studies are needed to clarify the extent to which viruses, bacteria, and fungi play roles as antecedent factors, chronic colonizers, or exacerbating factors for underlying sinusitis. There is however an increasing body of research using molecular microbiological techniques that suggests that CRS is associated with an imbalance (or dysbiosis) of the complex community of micro-organisms that live on the sinonasal mucosa. How this dysbiosis influences mucosal inflammation is uncertain, but it is clear that normal mucosal integrity and local immune function are both influenced by the presence of commensal bacteria. Disruption of this complex commensal community may lead to a loss of mucosal integrity and loss of local immune tolerance.

Given that a clear link between bacteria and CRS has not yet been established, an increasing number of researchers have shifted the focus of their research to immunological factors underlying CRS. Some have postulated that CRS is a purely immune-mediated disease in which the observed microbial changes are either secondary or limited to causing exacerbations. Increasingly sophisticated analysis of the inflammatory pathways altered in CRS has revealed many new potential targets for pharmacological intervention, encouraging further research in this field.

Inflammatory Mechanisms

CRS has been historically classified by simple clinical phenotyping into CRSwNP and CRS without nasal polyps (CRSsNP). In the contemporary model of CRS pathogenesis, research focus has moved toward the identification of the molecular pathways (or endotypes) that have been activated.(13) In cases of CRS, mucosal barrier disruption may initiate a chronic inflammatory response that fails to resolve. The inflammatory changes may utilize types 1, 2 or 3 inflammatory pathways, either alone or in combination.

Type 1 responses are directed against intracellular pathogens, most commonly viruses, and are characterized by cytokine interferon-γ. Type 2 responses are directed against large, extracellular parasites, and are characterized by cytokines IL-4, IL-5 and IL-13 as well as activation and recruitment of eosinophils and mast cells. Type 3 responses are directed against extracellular bacteria and fungi and are characterized by cytokines IL-17 and IL-22. Each type of response is mediated by an innate lymphocyte subset (ILC1, 2 and 3 respectively) that is linked to a corresponding delayed T helper subset (Th1, Th2 and Th17 respectively).(13)

Studies have revealed that patients with a pure or mixed type 2 endotype tend to be much more resistant to current therapies and exhibit a higher recurrence rate when compared to pure type 1 or 3 endotypes.(13) Furthermore, subtypes may exist wherein discrete aspects of the pathway are relatively enhanced (e.g. mast cell activation, eosinophil activation, and plasma cells activity).(13) Depending on the endotype, treatment can be tailored to a more type 2 or a non-type-2 profile.

Recent successful trials of biological agents support the hypothesis that type 2 inflammation)is responsible for the majority of severe CRSwNP disease in the US.(37–39) However, CRSsNP is much more common (80% of CRS cases), and CRSsNP is more endotypically heterogeneous, with subgroups of type 1 and type 3 inflammatory patterns.(13, 15, 40–42) Although earlier studies suggested that CRSsNP is characterized by type 1 inflammation, with elevated interferon-γ, and CRSwNP is mediated by type 2 inflammation, driven by IL-5 and IL-13, more recent work suggests that this view is an oversimplification. Although type 2 appears to be the most common endotype in both CRSwNP and CRSsNP, type 1 and type 3 inflammation also occur frequently occur, especially in CRSsNP.(42) Type 3 inflammation is associated with bacterial disease, and may possibly indicate a subgroup of CRSsNP that responds better to antibacterial therapy.(43) Although CRSwNP is generally characterized by type 2 inflammation with eosinophilia, a subset of CRSwNP patients is known to have neutrophilic inflammation: in an analysis of tissue from 134 CRSwNP patients, 17% and 18% of CRSwNP patients had type 1 and type 3 inflammation respectively.(42)

A more in-depth review of the evolving perspective of genetics, epigenetics, immunity, microbiology, remodelling and endotypes is beyond the scope of this review. However, we emphasize that the pathogenic mechanisms of CRS vary between subgroups,(16, 44, 45) and anticipate that future guidelines will emphasize different treatment options accordingly.

Antibiotic Utilization and Role

Historically, the antibiotics prescribed for CRS have been chosen empirically as swabs for culture have not been routinely taken in clinical practice. The choice of agent and the duration of its prescription has varied considerably based on the clinician’s training and experience and the clinical setting. A number of guidelines have been developed to rationalize antibiotic prescription for this indication, but there are practical challenges in applying treatment guidelines (particularly those developed in different healthcare environments), including variable treatment costs and antibiotic resistance rates.(46) The global consumption of broader spectrum antibiotics nearly doubled from 2000 to 2015(47)

and prescribing for CRS remains one of the most common indications. Furthermore, in some countries, many antibiotics are dispensed without a prescription.(13)

Although a number of antibiotics are approved by the Food and Drug Administration (FDA) for treating ARS or unspecified RS, no antibiotic has FDA approval for specifically treating CRS. Despite this, antibiotics are still commonly prescribed for this indication.(1, 48, 49) The antibiotic classes most commonly prescribed for CRS consultations in the United States between 2006–2010 were penicillins/beta-lactams (33%), macrolides (26%) and quinolones (19%).(1) In a 2015 survey, amoxicillin/clavulanic acid was the drug of choice for adult and pediatric CRS patients among private practitioners in South Korea, whereas hospital-based doctors preferred macrolides for adult CRS patients and third-generation cephalosporins for pediatric CRS patients.(46) In a 2018 survey of members of the American Rhinologic Society, most respondents prescribed non-macrolide antibiotics and macrolide antibiotics “occasionally” for CRSwNP, and non-macrolide antibiotics “sometimes” and macrolide antibiotics “occasionally” for CRSsNP (with sometimes defined as more often than occasionally).(50) Presumably, these antibiotic choices reflect sensitivities for the most commonly cultured organisms and the influence of some early studies that suggested efficacy of amoxicillin/clavulanate.(51, 52)

Macrolides inhibit protein synthesis, exerting their antimicrobial effect by preventing the bacterial ribosome from translating messenger ribonucleic acid (RNA) into new proteins.(53) Macrolide antibiotics have a range of activities, being bacteriostatic against many strains of commonly cultured respiratory tract pathogens. However, macrolides also possess several anti-inflammatory and immunomodulatory activities that may be important in their role in the treatment of CRS.(53–55) (56, 57) The immunomodulatory properties of macrolides are shared by the 14-membered lactone ring macrolides (erythromycin, clarithromycin, and roxithromycin) and the 15-membered lactone ring macrolides (azithromycin).(58) The precise mechanism of the immunomodulatory properties is unknown, though it has been proposed that macrolides inhibit mucus hypersecretion,(59) activate mucociliary function,(60) modulate the production of cytokines and chemokines,(61) have a suppressive effect on lymphocytic activity(54) and inhibit bacterial functions such as quorum-sensing and biofilm formation.(62, 63)

Antibiotic penetration into the sinonasal mucosa and mucus beyond the minimum inhibitory concentrations (MIC) would be anticipated to be required for efficacy. While a few studies report observing MIC,(64–66) there is limited evidence of correlation with clinical efficacy. A small randomized controlled trial(67) of patients undergoing endoscopic sinus surgery who were given either doxycycline or roxithromycin immediately preoperatively were found to have therapeutic concentrations in the sinus tissue and serum, but not in mucus. This finding provides another reason why non-macrolide antibiotics have not been found to be effective for the treatment of CRS

SUMMARY OF EVIDENCE

Despite the high utilization of antibiotic treatment of CRS, there is a paucity of high quality prospective studies. For treatment of CRS with antibiotics for less than 3 weeks, the majority

of studies focus on the treatment of AECRS. While there are several non-placebo controlled studies and two published double-blind randomized controlled trials (DBRCTs) on the role of prolonged treatment with macrolide antibiotics for CRS, there are few studies evaluating nonmacrolide therapies. Herein we will review the available evidence.

For the purposes of this discussion, three to four weeks or less is considered a 'short-term' antibiotic course and greater than three to four weeks is a considered a 'long-term' course. (13, 15) In general practice, the duration of courses is usually shorter than 10 days. The aim of short-term antibiotic courses is to treat suspected acute bacterial infections causing exacerbations. (13)

There have been only two small placebo-controlled studies investigating the effect of short-term antibiotics in CRS,(13) excluding studies focused only on acute exacerbations of CRS (AECRS). Sabino *et al.*, studied patients with acute exacerbations of CRS with or without polyps and found that after a two-week course of amoxicillin-clavulanate 875 mg/125 mg twice daily (n = 21) or placebo (n=11), both groups exhibited overall improvement on day 14 compared to day 0 ($p < 0.01$).(68) Van Zele conducted a three-arm study comparing a 20-day course of doxycycline, oral methylprednisolone and placebo in 47 patients with CRSwNP (either recurrent after surgery or with grade 3 or 4 polyps) and found reduced postnasal drip symptom scores at week 2, but no significant differences for all other symptoms and time points.(69) Van Zele demonstrated significantly greater polyp shrinkage in the antibiotic treatment arm vs. placebo at 12 weeks post-treatment. The antibiotic effects were of a much lower magnitude than those seen in the corticosteroid arm and were probably not of clinical significance.

Several other non placebo-controlled randomized studies compared parallel, short term antibiotics regimes in cases of CRS.(51, 52, 70–74) Fan *et al.* found that patients in a higher dose clarithromycin group demonstrated better nasal symptom, Lund-Kennedy and Sino-Nasal Outcome Test-20 (SNOT-20) scores at weeks 2 and 4 compared with both baseline values and the low dose clarithromycin group.(72) Namyslowski *et al.* showed improvement in CRS or AECRS symptoms at days 3 to 5 in patients taking amoxicillin/clavulanate, compared to those taking cefuroxime.(51) However, by days 15 to 18, there was no significant difference in clinical cure rates or bacteriologic eradication between the groups. The other five studies had some nuanced results, but to summarize, showed no difference in symptomatology outcomes between head-to-head comparisons of various antibiotics given in short term courses. The absence of a placebo arm in these studies precludes substantive conclusions. A minority of these studies evaluated outcomes after one month.

There have been a number of studies of the efficacy of long-term macrolide and non-macrolide antibiotics in CRSsNP and CRSwNP. Several phase 4 studies have demonstrated symptom improvement, but each study has methodological flaws that limit the conclusions that can be drawn from the results. These studies have been reviewed in great detail elsewhere.(13, 15, 43, 75)

To date, there have been only two published DBRCTs(76, 77)of long-term antibiotic therapy for CRS. Both studies evaluated 12-week treatment with macrolides: Wallwork *et al.* evaluated roxithromycin at 150mg daily in 64 patients with CRSsNP, while Videler *et al.* evaluated azithromycin (AZM) 500mg once per week in 60 patients with CRS with or without polyps.

Wallwork *et al.* observed a significant improvement in SNOT-20 scores, saccharin transit time and nasal endoscopy in the treatment group (all $p<0.05$). When the groups were subdivided *post hoc* into low (<200μg/L) and high (>200μg/L) immunoglobulin E (IgE) levels, the low IgE group treated with roxithromycin had significant improvements in saccharin transit time, endoscopy and IL-8 in nasal lavage. Some patients maintained this improvement for more than three months but others did not, and the initial improvement in symptoms failed to maintain significance at long term follow up.(76)

The study of a 12-week course of azithromycin failed to show a significant improvement in subjective or objective outcomes at the completion of the course.(77) However, 12 weeks after completion of the antibiotics, 50% of the AZM group reported an improvement or cure compared to 9% in the placebo group ($p<0.05$). The single dosing per week is a notable feature of this study and the authors felt that AZM may have been ineffective due to underdosage. (77)

Macrolides have been shown to reduce TH1-mediated non-eosinophilic inflammation when used for durations of at least three months.(78) It may be that there are specific endotypes that will respond better to macrolides than others.

There are no published DBRCTs of long-term non-macrolide antibiotics in CRS, but there are a few studies with less rigorous experimental designs. Dubin *et al.* performed a study of non-macrolide antibiotics for the treatment of CRSsNP.(79) In this study, culture-directed antibiotics (clindamycin, or amoxicillin/clavulanate) were given to patients with CRSsNP. Sequential computerized tomography (CT) scans were obtained at 3 and 6 weeks and compared to baseline scans. There was an improvement in CT scores between baseline and week 3, but no significant improvements between week 3 and week 6. The authors concluded that a longer course of antibiotics may achieve radiographic improvement and disease resolution in some patients. Study weaknesses included a small analysable sample size ($n = 16$), a lack of a washout period and the inclusion of patients who were already on antibiotics (an average of four previous antibiotics courses).

There are few published studies of long-term oral non-macrolide antibiotics for the treatment of CRSwNP. Several open-label studies studied the effects of doxycycline but the results have been inconsistent.(80, 81)

SYNOPSIS OF GUIDELINE RECOMMENDATION

Table I provides a synopsis of recommendations regarding systemic oral antibiotics from several recently published guidelines: the International Consensus Statement on Allergy and Rhinology: Rhinosinusitis (ICAR) 2021,(15) the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020,(13) the Chinese Society of Allergy and Chinese Society

of Otorhinolaryngology-Head and Neck Surgery Guideline (CSACSO) from 2020,(16) the Clinical Practice Guideline (Update): Adult Sinusitis (CPGAS) from 2015,(18) and the Joint Task Force on Practice Parameters (JTFPP) update from 2014.(17) Oral and topical corticosteroids are often recommended in combination with antibiotics.

Whereas earlier guidelines usually included antibiotics as a recommended treatment of CRS, more recent guidelines suggest antibiotics be regarded as an optional treatment for CRS, in association with topical and/or systemic corticosteroids, saline rinses and surgery.(2, 48, 82–88) Whereas in 2007, long term macrolide therapy received a class A recommendation from the EPOS for the treatment of CRSsNP,[307] after subsequent publications by Wallwork *et al.*(76) and Videler *et al.*,(77) the EPOS recommendation was downgraded from A to C (not including exacerbations) in 2012.(89) The EPOS 2020 steering group made recommendations using the GRADE system, and their overall recommendation was "uncertain" due to the relatively low quality of the available evidence. EPOS 2020 called for studies with larger population sizes, and placebo-controlled randomized trials of long-term macrolides are currently underway.(13)

ICAR 2021 recommended against non-macrolide antibiotics for CRSwNP, except in acute exacerbations. Macrolides were considered as an option for treatment of both CRSsNP and CRSwNP, but the optimal drug, dosage and treatment duration were not defined due to the limited published data.(15)

The Chinese Society of Allergy and Chinese Society of Otorhinolaryngology-Head and Neck Surgery guidelines recommend long-term, low-dose macrolide therapy for CRSsNP patients with neutrophilic inflammatory patterns and low IgE levels, but no antibiotics for CRSwNP patients.(16) Long-term, low-dose macrolide therapy post-surgery was discussed to improve the subjective and objective symptom scores, reduce polyp size and delay polyp recurrence. Long-term, low-dose macrolide therapy was recommended for corticosteroid-resistant CRSwNP patients, neutrophil-dominant nasal polyps, persistent edema of nasal mucosa, and purulent nasal discharge.

The CPGAS recommends systemic antibiotics for acute exacerbations of CRS, particularly in patients with persistent purulent drainage. The CPGAS also notes that some patients with CRSsNP may benefit from prolonged antibiotic treatment.(18)

The JTFPP recommends antibiotics as an option in the treatment of CRS, noting that greater benefit with antibiotics has been reported in CRSsNP than in CRSwNP. The JTFPP also notes that the role of antibiotics in CRS is controversial. (17)

SPECIAL CONSIDERATIONS

Cystic fibrosis

Cystic fibrosis (CF) is a genetic condition caused by a mutation in the CF transmembrane regulator (CFTR) protein, which leads to impaired chloride ion transport and consequently viscous mucus, mucociliary dysfunction and bacterial colonization of the upper and the lower airway tract.(90) CRS is almost universal in patients with CF,(91, 92) and the resulting

morbidity and impact on quality of life have become better recognized in recent years. The increasingly longer lifespan of CF patients may result in more patients requiring treatment for CF-related CRS.

The lower airway of CF patients tends to have polymicrobial colonization,(93–95) and there is a growing appreciation of the close correlation between upper and lower airway microbial populations.(90, 91, 96, 97) Clinical experience suggests that reducing the bacterial load in the airways leads to symptom improvement. However, achieving this can be particularly challenging as, apart from the polymicrobial nature, bacteria exist in different phenotypes and niches, which may have a great impact on their sensitivity to antibiotics. Bacteria can be in a planktonic state in the mucus and within surface biofilms,[21, 98, 99] and the number of intramucosal bacteria in CF CRS patients has been observed to be significantly higher than in idiopathic CRS.(100)

Longitudinal studies of the microbiota of CF patients suggest that the bacterial organisms in the lower airway tract of CF patients tend to be relatively constant over time, other than during temporary changes associated with acute infections or treatment.(101–103) Given the strong correlation between upper and lower airway microbial populations, it could be inferred from these observations that the CF CRS bacterial population is also resistant to change.[104]

There is little consensus on the optimal use of antibiotics in CF-related CRS.(105) Nebulized tobramycin(106) and oral fluoroquinolones are often prescribed. Macrolides have demonstrated some efficacy in both upper(107, 108) and lower airways,(109) but there are limited studies specifically performed in CF CRS patients. There is some evidence that adding CFTR modulating agents such as Ivacaftor(110) and Trikafta(111) or DNAse mucolytics such as Dornase alpha(112) to concurrent antibiotic courses increases the therapeutic efficacy.

Pediatric CRS

Generally accepted medical treatment algorithms in the pediatric CRS population are not dissimilar to adults with idiopathic CRS, but there is even less evidence on which to base recommendations. No high-level evidence supports short or long term antibiotics,(13) but an empiric broad-spectrum systemic antibiotic trial may be trialled.(15)

Topical antibiotics

Topically administered antibiotics would potentially have the advantages of minimal systemic absorption and associated adverse effects while managing to deliver significantly greater concentrations to the desired site. However, topical therapies in un-operated sinuses have limited penetrance(113, 114) and are usually not included in medical regimens prescribed for CRS. With the recognition of *S. aureus* as a pathogenic disease modifier of CRS, the effect of treating surgically recalcitrant postoperative patients with topical mupirocin has been studied and some efficacy has been demonstrated.(115, 116) However, there is also evidence that mupirocin irrigation may lead to resistance and the predominance of resistant bacteria such *as P. aeruginosa*.(117) After mupirocin lavages are stopped, colonisation with *S. aureus* tends to recur.(118)

In patients with a background of CF or primary dyskinesia, in whom *P. aeruginosa* is often the dominant pathogen, topical gentamicin may be administered either by nebulisation or addition to lavage bottles. However, long-term treatment has been shown to induce a moderate incidence of gentamicin resistance.(119) In both the idiopathic CRS population and in CF population, the available evidence does support short term treatment with topical antibiotics for exacerbations.

Novel topical antibiotic delivery methods, such as co-delivering antibiotics with fibrin sealant at the completion of functional endoscopic sinus surgery,(120) and applying a drug-eluting stent containing ivacaftor-ciprofloxacin mixture(121) are being studied.

There is also an expanding body of *in vitro* evidence on efficacy of topical antiseptics and anti-biofilm agents such as povidone-iodine,(122, 123) quaternary ammonium compounds(124) and antimicrobial peptides.(125) These agents have the potential benefit of being much less likely to cause resistance than antibiotics.

Perioperative antibiotics

There are no clinical studies whose results support the administration of systemic antibiotics immediately prior to sinus surgery.

According to the classification of surgical wounds, endoscopic sinus surgery is a ‘clean-contaminated’ operative field, although the grading would be changed to ‘contaminated’ if acute, non-purulent inflammation were encountered.(126) Although an acute inflammatory flare up, or acute sinusitis with purulence would warrant prophylactic antibiotic, a clean contaminated wound does not require prophylactic antibiotic. A survey among the American Rhinologic Society members revealed 54% gave antibiotics on induction routinely(50) but there is no evidence to support this practice.

The same survey revealed that 62% of the respondents routinely gave postoperative antibiotics, 76% quoting reduction of postoperative infection risk as the reason.(50) Culture-directed antibiotic usage in the setting of overt purulence is generally accepted, but there is limited evidence for this. The culturing of *S. aureus* from intraoperative swabs has been associated with worse surgical outcomes,(127) but a randomized study demonstrated that the general short-term outcomes of surgery did not alter with a course of postoperative antibiotics.(128) Furthermore, while some have observed a reduction in early postoperative crusting,(129) others used Sino-Nasal Outcome Test-22 (SNOT-22) scores to demonstrate that non-culture dependent empiric antibiotics led to reduction in quality-of-life gain in the early postoperative period.(130)

FUTURE DIRECTIONS AND CONCLUDING REMARKS

Some unanswered questions in CRS antibiotic research are listed in Table II. Several expert guidelines call for RCTs to study the widespread practice of antibiotics for CRS.[3,72] Due to the variable quality of much of the existing evidence, it remains uncertain whether the use of short or long-term antibiotics have an impact on patient outcomes in adults with CRS. Further randomised studies with larger population sizes are needed. Unlike

macrolides, the combination of amoxicillin and clavulanate is not believed to have direct sinonasal anti-inflammatory properties, and so studies are needed to determine conclusively its effectiveness in CRS given the frequency of its prescription for CRS.

Antibiotic resistance is a major threat to public health that demands ongoing attention. The Centers for Disease Control and Prevention (CDC) estimates that more than 2 million patients suffer from complications of antibiotic resistance, with 23,000 patients dying from such complications annually in the United States.[73] Furthermore, the CDC estimates that at least 1 in 3 prescriptions for antibiotics are unnecessary, and the majority of the unnecessary antibiotics are prescribed for respiratory disease caused by viruses.[73] Reducing inappropriate antibiotic use is critical to combating antibiotic resistance. CRS is an ideal condition to clarify the appropriateness and efficacy of antibiotic prescriptions, which is very pertinent in the context of the global crisis of resistance to antibiotics.[3]

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Abbreviations used:

AECRS	acute exacerbations of CRS
ARS	acute rhinosinusitis
AZM	azithromycin
CDC	Centers for Disease Control and Prevention
CSACSO	Chinese Society of Allergy and Chinese Society of Otorhinolaryngology-Head and Neck Surgery Guideline
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane regulator
CPGAS	Clinical Practice Guideline (Update): Adult Sinusitis
CRS	chronic rhinosinusitis
CRSsNP	chronic rhinosinusitis without nasal polyps
CRSwNP	chronic rhinosinusitis with nasal polyps
CT	computerized tomography
DBRCTs	double-blind randomized controlled trials
EPOS	European Position Paper on Rhinosinusitis and Nasal Polyps
FDA	Food and Drug Administration

JTFPP	Joint Task Force on Practice Parameters
ICAR	International Consensus Statement on Allergy and Rhinology: Rhinosinusitis
IgE	immunoglobulin E
IL	interleukin
MIC	minimum inhibitory concentrations
RCT	randomized controlled trial
RNA	ribonucleic acid
RS	rhinosinusitis
SNOT-20	Sino-Nasal Outcome Test-20
SNOT-22	Sino-Nasal Outcome Test-22

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Table I:

Summary of Recent Guideline Recommendations Regarding Antibiotic Treatment of CRS

Guideline	Level of evidence/ Grade	Recommendations and Key Excerpts
ICAR, 2021(15)	B	Option: Macrolides for patients with CRSsNP. Optimal drug, dosage, and treatment duration are not known. Option: Macrolides are likely beneficial in CRSwNP. Optimal drug, dosage and treatment duration are not known. Recommendation against non-macrolide antibiotics (<3 weeks) should generally not be prescribed for CRSwNP except in acute exacerbations
EPOS, 2020(13)	1b (−)	Recommendation against antibiotics for diffuse, bilateral CRS in the primary care setting. EPOS 2020 acknowledges international variations in recommendations, and the steering group "is uncertain" whether or not the use of a short course of antibiotics has an impact on patient outcomes.
	1a (−)	Option: long term antibiotics for patients with CRSsNP and CRSwNP. The EPOS 2020 steering group "is uncertain" whether or not the use of long-term antibiotics has an impact on patient outcomes.
CSA/CSO, 2020(16)	Not specified	Recommendation: long-term, low-dose macrolide therapy for CRSsNP patients with neutrophilic inflammatory patterns and low IgE levels. Recommendation: Long-term, low-dose macrolide therapy for corticosteroid-resistant CRSwNP patients, neutrophil-dominant NPs, persistent edema of the nasal mucosa, and purulent nasal discharge. "Currently, there is no evidence supporting the use of CRS (CRSsNP and CRSwNP) patients with (non-macrolide) antibiotic therapy in CRSsNP or CRSwNP."
CPGAS, 2015(18)	Not specified	Recommendation: antibiotic treatment for acute exacerbations of CRS and for patients with persistent purulent drainage. Option: Some patients with CRSsNP may benefit from prolonged antibiotic treatment.
JTFPP, 2014(17)	A	Option: antibiotics plus a short course of oral corticosteroids in the treatment of CRS. A greater benefit with antibiotics has been reported in CRSsNP than in CRSwNP. Recommendation: >10–14 days of antibiotic therapy for CRS associated with suspected bacterial infection; the choice of antibiotic therapy may need to consider the possible presence of anaerobic pathogens.

CPGAS = Clinical practice guideline (update): adult sinusitis; CSA/CSO = Chinese Society of Allergy and Chinese Society of Otorhinolaryngology-Head and Neck Surgery Guideline; EPOS = European Position Paper on Rhinosinusitis and Nasal Polyps 2020; ICAR = International consensus statement on allergy and rhinology: rhinosinusitis 2021; JTFPP = Diagnosis and management of rhinosinusitis: a practice parameter update (from the Joint Task Force on Practice Parameters)

Table II.

Outstanding questions in CRS antibiotic research

Question
What is the effect of long-term systemic antibiotics, particularly non-macrolides, on CRS outcomes? Do outcomes vary by endotype and/or phenotype?
What is the effect of systemic antibiotics on the sinonasal microbiota in both healthy and CRS subjects?
What is the efficacy of standard vs. culture-directed antibiotics in the treatment of CRS?
Can DNA and RNA (metagenome and metatranscriptome) sequencing approaches furnish a more complete picture of the role of bacteria, viruses, and fungi in the microbiota?

CRS = chronic rhinosinusitis