Chronic rhinosinusitis and antibiotics: The good, the bad, and the ugly

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ABSTRACT

Background: Despite the recognition that bacteria are universally present in the sinuses of patients with chronic rhinosinusitis (CRS) no compelling role for a primary infectious etiology of CRS has been elucidated. CRS is a constellation of inflammatory diseases that typically involve either noneosinophilic or eosinophilic processes, distinct conditions that must be treated individually.

Methods: The bacteria that are present in the sinuses may be innocuous bystanders but alternatively may contribute to the presence and severity of the disease through their ability to influence immune responses, function as immune adjuvants, provide antigens or superantigens that contribute to adaptive immune activation, or in forming the basis for the frequent acute superinfections. However, those bacteria that do contribute to the persistence and severity of CRS primarily reside in biofilms, and, as such, are not capable of being eradicated with antibiotics at the doses at which they can be used, even when local irrigation is considered.

Results: Biofilms create an inhospitable environment for antibiotic potency by down-regulating the metabolic activity of their "core" bacteria, decreasing the oxygen concentration, and altering the pH at the core of the biofilm.

Conclusion: Ultimately, if topical antibiotics are considered, they should be primarily focused on treating acute exacerbations and choices of antibiotics should optimally be based on endoscopic culture. This should be done with the recognition that while under certain circumstances antibiotics can ameliorate the severity of CRS, even if bacterial eradication were possible, this would not eliminate the underlying primary pathogenic mechanism or the natural history of these conditions.

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Chronic rhinosinusitis (CRS) is a constellation of common and debilitating diseases affecting nearly 14.2% of the U.S. population.¹ Historically, these diseases have been primarily categorized into two groups: CRS with nasal polyps (CRSwNPs) and CRS without NPs, reflecting the recognition that CRSwNPs is more prominently associated with eosinophilia. However, noneosinophilic pathogenic sinus disease is recognized to produce NPs and, similarly, not all patients with eosinophilic sinusitis have NPs (at least at the time they present). Insofar as noneosinophilic and the various eosinophilic presentations of CRS have distinct pathogenic mechanisms, for the purpose of this study, we will primarily focus on the pathology-based terms noneosinophilic and eosinophilic CRS with the recognition that the former comprises most of the CRS without NP and the latter most of the CRSwNP subjects.^{2,3}

Eosinophilic sinusitis comprises at least two conditions, including aspirin-exacerbated respiratory disease (AERD) and, most commonly, chronic hyperplastic eosinophilic sinusitis (CHES). CHES is a disease of the upper respiratory tract that mirrors the disease of the lower airways that is often concomitantly expressed in these patients—asthma.⁴ It is a classically Th2-mediated condition with high levels of interleukin (IL)-4, IL-5, IL-13, and other cytokines and chemokines that together drive the influx of eosinophils into the tissues, cause allergic (IgE) sensitization, and drive goblet cell metaplasia.^{5–7} In addition to their sensitivity to aspirin and other nonselective cyclooxygenase 1 inhibitors,

patients with AERD are distinguished from those with CHES by their less frequent allergic sensitization, usual presentation later in life, and much more robust tissue and blood eosinophilia.^{8–10}

In contrast, inflammatory (noneosinophilic) sinusitis is typically a disease associated with anatomic blockade of the sinus ostia because of congenital malformation or chronic (allergic or nonallergic) rhinitis.^{11,12} These patients develop frequent, protracted episodes of acute sinusitis that ultimately lead to remodeling of the sinus tissue. This remodeling is characterized by denuding of the epithelium, goblet cell, and glandular hypertrophy with increased mucus production and infiltration with a chronic inflammatory (mononuclear cell) infiltrate with or without neutrophils.^{13–15} On occasion, as with eosinophilic sinusitis, these patients will develop polyps secondary to their chronic inflammatory state. These changes promote or exacerbate ostia obstruction and reinfection and together this leads to a persistent proinflammatory vicious cycle. However, with surgical correction of the anatomic blockade, these patients often improve or resolve. For a comparison of the types of CRS, see Table 1.

Current approaches to all of these conditions variously have included nasal saline rinses, topical and systemic corticosteroids (CCSs),¹⁶ surfactants,¹⁷ and, when warranted, functional endoscopic sinus surgery (FESS). The eosinophilic diseases are particularly responsive to oral CCSs, although protracted courses are avoided and shorter courses only provide temporary relief. However, when properly delivered to the sinus cavities (and not just the nares as with nasal sprays), topical CCSs have also proven effective.^{16,18,19} Although often effective in providing long-term remission of noneosinophilic forms of CRS, FESS alone is unlikely to eradicate eosinophilic CRS insofar as these diseases, as with asthma, are self-perpetuating Th2-mediated immune inflammatory processes. In the absence of (or, often, even with) aggressive postoperative medical management, these patients will typically require multiple revision surgeries.²⁰

Importantly, neither the eosinophilic nor noneosinophilic presentations of CRS comprise primary infectious processes. It is possible that the CRS observed in patients with immune deficiencies and perhaps other conditions such as the primary ciliary disorders may have chronic infections. However, this has not been properly studied, and even in these situations, it seems more likely that the frequent, protracted sinus infections that occur primarily act to drive the same noneosinophilic disease observed in patients with ostia blockade. In

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Table 1 Comparison of the types of chronic sinusitis

	Inflammatory (noneosinophilic) Sinusitis	CHES	AERD
Presence of atopy	No more than general population	Increased	No more than general population
Presence of asthma	—	+	++
Sensitivity to aspirin/NSAIDs	—	—	++
CT scan findings	Anatomical defect or inflammatory nasal disease; ± polyps	+ polyps; hyperplastic mucosal disease of sinuses	++ polyps; extensive pansinusitis ⁶¹
Peripheral eosinophils	—	+	++
Prognosis post-FESS alone	Often good	Poor	Very poor

AERD = aspirin-exacerbated respiratory disease; chronic hyperplastic eosinophilic sinusitis; NSAIDs = nonsteroidal anti-inflammatory drugs; FESS = functional endoscopic sinus surgery.

summary, none of the presentations of CRS comprise a primary infectious process and, therefore, even if it were possible to eradicate bacteria from the sinuses (which it is not), antibiotics will never “cure” CRS.

In contrast, although not primarily an infectious process, bacteria are universally present in CRS and likely do contribute to its persistence and severity. In both eosinophilic and noneosinophilic CRS diseases, the presence of an altered epithelium, ciliary dysfunction, and mucus hyperplasia all contribute to bacterial overgrowth and, ultimately, this leads to the formation of bacterial biofilms.^{21,22} Although the role of these bacteria is not completely understood—either as innocuous bystanders or important pathogens, it is recognized that they act as antigens as well as activators of pathogen-associated molecular pattern receptors. Also, superantigens from toxins secreted by these bacteria are important immunologic adjuvants, leading to nonspecific (antigen-independent) adaptive immune responses. For these reasons, topical and systemic antibiotics have been considered for treatment of CRS, but the results of these treatments remain incongruent.

BACTERIA AND BIOFILMS

The bacteria that colonize the diseased sinuses take advantage of the damaged epithelium, reduced innate immune mechanisms (*e.g.*, reduced expression of antimicrobial peptides), and the rich nutrient environment to proliferate. These bacteria may then bond together to form biofilms, and in chronic sinusitis such bacterial biofilms are present in 29–72% of patients.^{21,23–27} Biofilms are structured communities of bacterial cells that exist in a self-produced polymeric matrix that are adherent to an inert foreign body or living surface, in this case, the damaged epithelium.²¹ Whether on a heart valve, infected implant, or damaged sinus epithelium, once present, biofilms are impossible to eradicate. Antibiotics, *e.g.*, are incapable of sterilizing biofilms. It is important to recognize that biofilms are mostly water, and solutes the size of antibiotics should diffuse through the biofilm matrix. However, the bacteria at the center of a biofilm are less metabolically active secondary to hypoxia and nutrient limitation and, therefore, become unresponsive to the cellular mechanisms driving the action of antibiotics (Fig. 1). Many antibiotics (*e.g.*, penicillins) are bactericidal only with active replication, leaving the dormant bacteria impervious to antibiotic killing. The gradients in hypoxia and pH created within the biofilms also may sufficiently alter the antibiotic potency, especially when considering the aminoglycoside family.²⁷ Therefore, bacterial “hibernation” allows for survival in the center of biofilms throughout the course of antibiotic treatment. These bacteria are subsequently available to emerge in their metabolically active infectious (planktonic) state, making reinfection and recurrent acute sinusitis an easy endeavor. In support of this hypothesis, topical antibiotics are, in fact, capable of penetrating and destroying biofilms.

However, treatment requires much higher doses of antibiotics—100–1000× higher than the predicted mean inhibitor concentration.²⁸

Quorum sensing is another defense mechanism afforded to bacteria in biofilms. This unique feature allows bacteria to constitutively produce and secrete certain signaling molecules based on the density of their population. These signals serve to activate transcription of certain genes that would otherwise remain silent without the presence of other similar bacteria.²⁹ A few key organisms found in CRS use this method of defense, including *Pseudomonas aeruginosa* and these signals coordinate their formation into biofilms.³⁰ Similar signals also alter the growth patterns of other organisms, including *Candida albicans*.³⁰

Another advantage provided by the complex matrices that form biofilms to bacterial persistence rests in the ability of the organized system to evade polymorphonuclear cell and complement-mediated cytotoxicity. Even when a neutrophil is able to detect opsonized bacteria within the biofilm, the biofilm acts as a large multicellular complex, incompatible with phagocytosis of individual bacteria. The neutrophil experiences “frustrated phagocytosis,” and instead of degranulating within internalized phagosomes, degranulates externally with secretion of reactive oxygen species, digestive enzymes, antimicrobial peptides, and mitochondrial-derived DNA that form antimicrobial complexes that are termed neutrophil extracellular traps.³¹ Paradoxically, although this immune response will never clear the biofilms, collateral damage to the epithelium does occur, which, along with the concomitant ongoing activation of the complement pathway, contributes to the mucosal inflammation and severity of CRS (Fig. 1). Importantly, the only way to eliminate bacterial biofilms is to remove the foreign body completely, as in the cases of orthopedic hardware or stents. Unfortunately, complete removal of the insulted tissue is not possible in sinus disease. Therefore, neither antibiotics nor surgery are effective in removing the biofilms.

SUPERANTIGENS AND STAPHYLOCOCCUS IgE

In eosinophilic forms of CRS, attempting to reduce bacterial load may have some merit, when considering the actions of bacterial-derived superantigens in potentiating a T helper (Th) 2-mediated pathogenic process. Even in their indolent biofilm-associated state, these bacteria are not innocuous and can be a robust source of superantigens^{32–36} and immune adjuvants, but also of allergenic (IgE inducing) proteins (Fig. 1).³⁷ Superantigens are proteins that bind directly to the β-chain of the T-cell receptor, leading to the nonspecific activation of large numbers of T lymphocytes thereby producing a barrage of cytokine secretion.³⁴ Although numerous bacteria may secrete superantigens, staphylococci are particularly noteworthy for the extent and diversity of their superantigen repertoire. This is particularly important because CRS, especially in its eosinophilic presentations, are singularly characterized by *Staphylococcus* coloni-

Figure 1. Biofilm (yellow) on the surface of sinus epithelium. These biofilms provide a protective advantage to the bacteria that form them (see text for details).

Figure 2. Comparative analysis of the bacterial communities in chronic rhinosinusitis (CRS) and healthy sinus tissue. (Source: Reproduced with permission from Ref. 46.)

zation, which reportedly are present in ~30% of patients with noneosinophilic CRS, 70% with CRSwNPs, and, strikingly, 90% of patients with AERD^{36,38} and, when present, predict worse outcomes postoperatively.³⁹ This preponderance of *Staphylococcus* reflects the specific inhibition of innate immunity against *Staphylococcus* in these Th2-mediated diseases (similar to what is observed in atopic dermatitis).⁴⁰ In eosinophilic CRS the T cells infiltrating the sinuses typically display a Th2 cytokine signature⁴¹; so this superantigen-mediated surge in cytokines will prominently include IL-4, IL-5, and IL-13, again, exacerbating the allergic inflammatory processes and contributing to worsening tissue remodeling. Additionally, components of *Staphylococcus* biofilms alone may be sufficient to skew naïve T cells to the Th2 pathway, independent of the presence of superantigens.⁴²

Besides acting as a source of superantigens, bacterial-derived peptides will also act as antigens that, in this Th2 milieu, will drive IgE responses. Thus, IgE antibodies directed against *Staphylococcus* enterotoxin itself can be identified in 27.8% of subjects with CRSwNPs

and 53.8% of CRS subjects with both NPs and asthma.³⁶ In addition, although not extensively studied, presumably, IgE is also being generated that is directed against other antigens present in the sinuses, including, plausibly, IgE directed against other bacterial peptides, aeroallergens, and, arguably, even self-derived proteins. IgE antibodies to antigens such as *Staphylococcus* enterotoxin cross-link FcεRI on mast cells and basophils, further expanding the inflammatory response. IgE antibodies also engage FcεRI on dendritic cells promoting facilitated antigen uptake and leading to a vicious cycle of ongoing Th2 cytokine secretion.

In summary, the importance of bacteria and especially *Staphylococcus* spp. as sources of antigens and superantigens may explain the observed usefulness of antibiotics, including macrolides, doxycycline, topical antibiotics such as mupirocin, and other antibiotics in some individuals with CRS, independent of their role in treating secondary acute exacerbations.^{43,44} Furthermore, in addition to reducing superantigen load, we would argue that intrinsic anti-inflammatory effects of these medications should also not be discounted as a basis for the improvements observed in these patient populations.⁴⁵ However, these observations should not be misconstrued to suggest that CRS is an infectious disease requiring antibiotics.

SINUS BIOMES AND THE POTENTIAL PARADOXICAL ROLE OF ANTIBIOTICS AS A CAUSE OF CRS

Using microchips that are able to detect both rare and unculturable bacteria, it is now recognized that bacteria are universally present in both healthy and diseased sinuses. In a recent pilot study⁴⁶ CRS patients were paradoxically found to have significantly fewer taxa of bacteria than their healthy control counterparts (Fig. 2). Interestingly, the taxa of the CRS subjects were characterized by unique expression of one single species, *Corynebacterium tuberculostrictum*, and healthy sinuses were characterized by the relative abundance of *Lactobacillus* spp., *Enterococcus* spp., and *Pediococcus* spp. These studies suggest the possibility that an imbalance of immunogenic bacteria as opposed to

those that are more tolerogenic may underlie CRS pathogenesis. To address this concept, this group designed a mouse model of inflammatory sinusitis and did, in fact, indicate that *C. tuberculo*stearium instillation into the sinuses led to hyperplasia of the goblet cells. Significantly, however, this only occurred with the concomitant administration of antibiotics. In this model antibiotics were needed to eliminate the commensal (potentially tolerogenic) bacteria that normally populates the sinuses, allowing the relatively antibiotic-resistant bacteria, *C. tuberculo*stearium, to become pathogenic. In further support of this model, this process was rescued by the addition of the tolerogenic bacterium, *Lactobacillus sakei*.⁴⁶ Although, clearly, additional investigation is needed, this remarkable study suggests that antibiotic treatments, including those given for acute rhinosinusitis (but presumably also for any reason), could paradoxically promote the development, persistence, and/or severity of CRS.

THERAPEUTIC IMPLICATIONS

Antibiotics

As discussed, unlike acute bacterial rhinosinusitis, there are no forms of CRS that are directly linked to infectious causes. Rather, the spectra of conditions that comprise CRS represent ongoing self-perpetuating noninfectious inflammatory diseases. Therefore, other than as already discussed, systemic antibiotics have little role in CRS other than treating—if warranted—acute exacerbations. Although they may in certain circumstances ameliorate disease through their ability to diminish load of bacterial superantigens or through their intrinsic anti-inflammatory effects, however, even under these limited latter circumstances, the use of antibiotics should be tempered with concerns regarding the dangers of promoting expansion of resistant bacteria, given that these bacteria reside in biofilms, can never be eradicated, and will form the nidus for future—inevitable—acute exacerbations that will then be resistant to treatment.

Similarly, topical antibiotics are also most often ineffective when used alone and in the usual doses prescribed, again, reflecting both the absence of bacterial etiology in these disorders and the challenges of influencing the natural history of bacteria that are residing within sinus biofilms or paradoxically those that are residing within phagocytic cells themselves. For example, in an animal model involving *Pseudomonas* biofilms grown on sinus mucosa, these organisms required ~400× the mean inhibitory concentration of tobramycin to be eradicated.²⁸ It is also important to appreciate that although these medications are used locally in the nasal washes, systemic absorption does occur and that with this absorption comes the risk of systemic side effects.

Mupirocin has been used with efficacy in postsurgical patients with positive endoscopically guided cultures for *Staphylococcus aureus*. In one pilot study of recalcitrant CRS, 15/16 patients treated with mupirocin dissolved into their nasal saline irrigations twice daily for 3 weeks showed significant improvement in their nasoendoscopic findings and became culture negative for *S. aureus* after treatment. This study likely reflects, again, either the treatment of an acute exacerbation or the reduction of *Staphylococcus*-associated superantigens.⁴⁷ Importantly, a similar study has now been repeated in a double-blind placebo-controlled fashion. Twenty-two subjects with CRS recalcitrant to surgery received either mupirocin nasal washes or placebo. Although none of the subjects who received placebo had negative *Staphylococcus* cultures, 8/9 of the subjects who were on mupirocin cleared the infection after 1 month of treatment.⁴⁸

Surfactants

In certain situations, specifically in the presence of known bacteria that have been directly cultured from the sinuses and biofilms, some studies suggest that topical antibiotics in combination with a surfactant may be an effective treatment.⁴⁹ In *in vitro* models, surfactants act as a detergent that will break up the biofilm matrix thereby promot-

ing their eradication, including by leading to improved conditions for the antibiotics to work effectively.⁵⁰ However, side effects from surfactants (e.g., baby shampoo) are well described and recent clinical investigations with a synthetic surfactant were discontinued because of the frequent development of (temporary) anosmia in up to 3–5% of subjects.

Biologics

More recently, preliminary studies were published suggesting a role for the IgE-targeting therapy omalizumab in CRS. This is based not only on the frequent presence of IgE directed against *Staphylococcus* superantigens in this disorder⁵¹ but—reflecting the presence of an inflammatory milieu high in IL-4 and IL-13—likely IgE also directed against other bacterial peptides, possibly aeroallergens and, very possibly, even self-antigens. Indeed, investigations show the ability of anti-IgE to activate NP tissue, studies that were unable to identify the specific target for that IgE.⁵² This study of 24 subjects with asthma and NPs showed significant improvements in symptoms and quality of life but also in objective measures of endoscopy and sinus CT scores.^{51,53} Importantly, this improvement occurred irrespective of the presence of sensitization to aeroallergens, again suggesting that it may be IgE sensitization to bystander pathogens (or even self-proteins) that are driving this disease process.

Insofar as CHES is defined by the accumulation of activated eosinophils, it seems reasonable to speculate that interventions designed to attenuate eosinophilic inflammation will be beneficial in this disorder. The experience with humanized anti-IL-5 (mepolizumab) in asthma supports the ability of this intervention to greatly attenuate the bone marrow eosinophilopoietic response associated with asthma.⁵⁴ Arguably, this should also work to reduce the systemic response characteristic of allergic rhinitis and the secondary recruitment of eosinophils into the sinuses of allergic rhinitis sufferers with CHES.^{55,56} However, as a single intervention, this medication was unable to sufficiently reduce tissue eosinophilia to produce a therapeutic benefit in asthma. This was felt to reflect the complementary role of other cytokines, including, especially, granulocyte macrophage colony-stimulating factor, in promoting activation and survival of eosinophils.⁵⁷ This failure may also reflect roles for both constitutive (IL-5 independent) eosinophilopoiesis and the need to attenuate expression of eosinophil-specific chemokines (e.g., inhibition of CCL11 [eotaxin] using chemokine receptor CCR3 antagonists) or eosinophil-specific adhesion molecules (e.g., through the use of VLA-4 antagonists).⁵⁸ Arguably, no single agent is likely to be effective for CHES and, as suggested by the mepolizumab studies, it will be necessary to synergistically block both the systemic bone marrow component of CHES and the local factors critical for inflammatory cell recruitment.

Approach to the Patient with CRS

In summary, proper treatment of CRS needs to be based on the specific histology and pathogenic mechanisms driving the disease. If inflammatory (noneosinophilic) sinusitis is suspected, FESS should be strongly considered to alleviate the closed ostia and other anatomic mechanisms driving this condition. Importantly, surgical intervention may thereby prove curative. In addition, FESS allows entry of saline rinses that can be applied with or without additional agents including CCSs, topical antibiotics, and/or surfactants, as appropriate. This may be particularly important because even if surgery by itself does not break the vicious circle driving this form of CRS, surgery may still be essential to allow this access to the diseased tissue.^{59,60} For eosinophilic sinusitis, as with noneosinophilic sinusitis, surgery may prove essential to permit access to the diseased sinuses of topical agents likely to provide therapeutic benefit. However, unlike noneosinophilic sinusitis, surgery alone is unlikely to produce a cure for a disease that, similar to asthma, is primarily a self-perpetuating sinus mucosa- and immune-driven inflammatory process. For eosinophilic sinusitis, the mainstay of treatment remains nasal saline irrigation

and, as with asthma, this likely will require the addition of topical CCSs.¹⁶ Short courses of systemic CCSs can be effective in “melting” polyp tissue and may thereby allow topical steroids presented in nasal saline irrigations to access the sinuses. However, longer courses of oral CCS, clearly, must be avoided. A discussion of AFS and AERD is beyond the scope of this article but each of these disorders has unique approaches that can be considered.^{8–10,61}

CONCLUSIONS

Despite the fact that bacteria are universally present in the sinuses of patients with CRS, no role for a primary infectious etiology of these diseases has been elucidated. CRS is an inflammatory disease associated with either inflammatory (noneosinophilic) or eosinophilic processes (including CHES and AERD), each requiring its distinct treatment approach. As we have highlighted, even to the extent that bacteria are important in exacerbating these diseases, these bacteria reside in biofilms where they can not be eradicated with antibiotics at the typical doses, even when local irrigation is considered. Biofilms create an inhospitable environment for antibiotic potency by down-regulating the metabolic activity of “core” bacteria and creating a metabolic milieu conducive for antibiotic resistance. Despite the relative metabolic dormancy of these bacteria, they remain an important source of superantigens and other immunogenic products that may exacerbate these diseases and, when targeted, this may contribute to the temporary improvements observed with antibiotic interventions. Ultimately, if antibiotics are considered, they should be endoscopic culture directed and with an appropriate length of therapy.

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