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Chronic Rhinosinusitis: Endotypes, Biomarkers and Treatment Response

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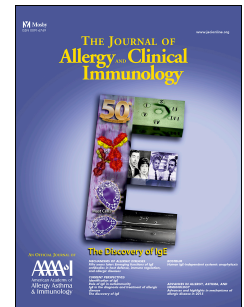
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Chronic Rhinosinusitis:**Endotypes, Biomarkers and Treatment Response**Jose Gurrola, II, MD^{1,*}Larry Borish, MD^{2,ψ}¹Department of Otolaryngology-Head and Neck Surgery

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24 **Key words**

25 Chronic Rhinosinusitis; Endotypes; biomarkers

26

27 **Abbreviations**

28 CRS chronic rhinosinusitis

29 CU chronic urticaria

30 E eosinophilic

31 ECP eosinophil cationic protein

32 GCS glucocorticoids

33 IFN interferon

34 IL interleukin

35 N neutrophilic

36 NP nasal polyps

37 Th2 type 2 T helper lymphocyte

38

Abstract

It is increasingly recognized that chronic rhinosinusitis (CRS) comprises a spectrum of different diseases with distinct clinical presentations and pathogenic mechanisms. Defining the distinct phenotypes and endotypes of CRS impacts prognosis and most importantly is necessary as the basis for making therapeutic decisions. The need for individualized defining of pathogenic mechanisms prior to initiating therapy extends to virtually all therapeutic considerations. This is clearly crucial with antibiotics where, barring an influence from their off-target anti-inflammatory pharmacological effects, an understanding of the role of individual biome predicts likelihood of therapeutic benefit. But this need for identifying individual phenotypes and endotypes also extends to the agent that is currently considered the mainstay of treatment of CRS, specifically glucocorticoids (GCS). As with asthma, it is recognized that a large minority of CRS patients have a steroid-resistant phenotype, identification of which will preclude use of these agents with their potential side effects. Identification of endotypes is also becoming increasingly imperative as targeted biotherapeutic agents, such as anti-IgE and anti-cytokine antibodies are becoming available. These agents are likely to benefit patients in whom the targeted mediator is not only expressed but demonstrably driving a central mechanism in that individual. In summary, the treatment of CRS is at an exciting crossroad. On the positive side, numerous therapeutics are in development that seem likely to positively impact our patients who suffer from this condition. The challenge is that these therapies will require targeted individualized treatments based upon identifying subjects with the relevant endotype.

Introduction

Historically, chronic rhinosinusitis (CRS) was defined as any inflammatory condition of the paranasal sinuses and associated nasal mucosa that persisted for >12 weeks.¹⁻² However, it is increasingly recognized that CRS comprises a spectrum of conditions with distinct clinical presentations and pathogenic mechanisms.³⁻⁵ Defining these distinct endotypes is more than an academic exercise as properly distinguish different presentations of CRS impacts prognosis and forms the basis for making therapeutic decisions. This latter consideration is becoming increasingly imperative as targeted biotherapeutic agents, such as anti-IgE and anti-cytokine antibodies are becoming increasingly available. These agents are most likely to benefit patients in whom the targeted mediator is not only expressed but demonstrably driving a central mechanism in that individual.

While this concept may seem self-evident with biologics, the need for individualized defining of pathogenic mechanisms prior to initiating therapy likely extends to virtually all therapeutic considerations. For example, this is also crucial with antibiotics where, barring an influence from their off-target pharmacological effects, an understanding of the role of individual biome is certain to predict likelihood of therapeutic benefit. But this need for identifying individual phenotypes and endotypes also extends to the agent that is currently considered the mainstay of treatment of CRS, specifically corticosteroids (GCS).^{1, 2}

Phenotypes of CRS

Epithelial Phenotypes of CRS. The loss of epithelial barrier function plays an essential role in the pathogenesis of CRS with the loss of tight junctions permitting access to the sinus stromal tissue of allergens, bacteria, bacteria-derived antigens and other pathogen-associated molecular patterns, and other pro-inflammatory compounds that contribute to the presence and severity of

inflammation present. Loss of epithelial barrier function reflects numerous inflammatory processes including most importantly the metaplastic transformation of epithelial cells into goblet cells, a process mediated especially by IL-13 as well as the recently recognized importance of epithelial mesenchymal transition (EMT), a process driven by numerous mediators, but especially ascribed to amphiregulin and oncostatin M.⁶

Nasal polyposis. While the need for defining individualized disease pathogenic mechanisms (i.e., endotypes) seems apparent, what is less apparent is recognition of unambiguous, validated, and reasonably accessible biomarkers to define these disease types. Current recommendations phenotype CRS based upon the presence (CRSwNPs) or absence (CRSSNP) of nasal polyps.^{1,2} This was based on the observation that NP disease is more likely to be associated with an eosinophil-mediated Th2^{high} (IL-4^{high}/IL-5^{high}/IL-13^{high}) cytokine profile. In contrast, CRSSNP was thought to present as a non-eosinophilic disease. This phenotyping approach remains valid primarily based upon the relative ease of endoscopically-defining polyp status. More recently, however, it has been recognized that NP status alone, while helpful, can often be inadequate for defining a Th2^{high}IL-5^{high} state. There are numerous exceptions to this concept and these can become quite profound especially based upon regional differences.⁷ In this latter study, it was recognized that CRSwNPs can be Th2^{low} in between 15-80% of patients (figure 1) and similarly anywhere from 20-75% of these subjects did not express a robust eosinophilia profile. And, in contrast, a significant subset (5-40%) of the CRSSNP subjects displayed a Th^{high}/eosinophil^{high} profile. This increasing recognition that NPs alone cannot be used to distinguish an eosinophilic from a non-eosinophilic presentation of CRS has more recently been confirmed.⁸ These studies do confirm both higher concentrations of IL-5 within the sinus mucosa of CRSwNP compared to

CRSsNP subjects, however, there is remarkable degree of overlap in the expression of these molecules between the two cohorts.

This problem of using NPs alone to define immune status becomes apparent when considering the endotype of cystic fibrosis. The term endotype can be appropriately used for this disease as it is defined by the presence of mutations in a specific gene, CFTR. Yet when the *phenotype* of CF sinus disease is considered, it is recognized that these patients develop polyps that run the spectrum of being paucigranulocytic, neutrophilic, eosinophilic, or mixed granulocytic.⁹ This raises the intriguing question as to how any inflammatory insult in the sinuses – such as that generated by CF – can variously and seemingly randomly lead to “switching” on of a Th2/eosinophilic process or not. Similar variable pathological outcomes are also observed with other distinct CRS endotypes such as those driven by common variable immune deficiency and primary ciliary dyskinesia.

This concept that a single genetic endotype can elicit numerous phenotypes could likely extend to all presentations of CRS and this identifies yet another obstacle to defining endotypes.¹⁰ And, to make this even more daunting, these observations raise the intriguing question as to whether any given phenotype is “fixed” or, as seems equally plausible, that any given phenotype (such as eosinophilia) can evolve and resolve over time. Or, as an alternative example, whether a polyp might start with Th1 inflammation and then evolve through Th2 to a Th17 processes (with mixing in between).

Inflammatory Cell Profile (Neutrophilic (N)- and Eosinophilic (E)-CRS). As NP can only at best approximate acting as a surrogate for assessing eosinophil status, an alternative approach is to specifically evaluate sinus tissue and quantify eosinophil expression. In the study by Tan et al.,⁸ however, not only was the presence of NPs inadequate in distinguishing a Th2^{high} state,

neither was the presence of eosinophilia. Thus, using tissue concentrations of eosinophil cationic protein (ECP) as a surrogate marker for tissue eosinophilia, as with IL-5, although significantly higher in CRSwNP, there was extensive overlap in ECP concentrations between subjects with and without NP.⁸ It should be appreciated that, at least in part, the poor ability of ECP to distinguish CRS phenotypes may reflect its lack of complete specificity to the eosinophils including its secretion by PMNs and basophils.

Microbiome Phenotypes of CRS

The evaluation of the microbiome is of particular interest in CRS in that characterization of the microbial environment that gives rise to the disease process would seemingly allow for directed anti-*microbial* treatment measures. Multiple studies have now demonstrated that CRS involves dysbiosis of the microbiome, suggesting asymmetric diversity rather than overexpression of a predominant species as the culprit.¹¹⁻¹² Advances in bacterial detection with next-generation sequencing allow diagnostic methods that advance beyond current swab and culture techniques, although the ideal method by which to examine the microbiota of a given patient remains unclear.^{13,14} ~~Abreu et al. demonstrated both a decrease in diversity among their CRS patients and results that suggested a novel pathogen.~~⁶ Other works have evaluated potential harmful changes that occur with antibiotic and anti-inflammatory treatments, paradoxically treatments that are generally considered primary components in the medical treatment of CRS.¹⁵ Collectively, these microbiome studies allow for consideration of new schema by which to approach CRS patients, similar to the re-evaluations based upon endotypes and immunologic profiles. Hoggard et al., recently demonstrated that microbiota dysbiosis was more likely to be observed between groups when patients were broken into the clinic variants (i.e., with or without asthma), rather than a predominant association between a specific pathogen and an associated phenotype or endotype.¹²

Specifically, asthma and CF patients more strongly demonstrated decreased bacteria diversity and an overall increased bacterial load than patients without these comorbidities. Cope et al. suggested distinct microbiota classifications that demonstrate or correlate with unique immunologic responses, functional attributes and related risk of phenotypes such as presence or absence of polyps.¹⁶ As more is learned about the immunologic and the inflammatory profiles of CRS, it seems certain that the interwoven impact of the microbiome will be further elucidated.

Endotyping of CRS

Theoretically, it may be possible in the future to make clinically available the means of defining the inflammatory endotype based upon microarray-based studies with detailed analyses of individual transcriptomic, proteomic, or one of the vast number of other “omic” signatures. At present, initial steps towards such approaches have been taken with detailed analyses of cytokine signatures associated with Th1, Th2, and Th17 inflammation. As discussed, CRSwNP was originally proposed as a distinct phenotype based upon the likelihood that it would define a distinct Th2^{high} and, more specifically, an IL-5^{high} endotype. Despite regional differences, up to 85% of NPs can be defined as demonstrating high concentrations of IL-5 (in many, but not all, regions in the world).⁷ This gets even more complicated with consideration of other cytokines, as NPs can also display mixed patterns of expression of IL-5 with concomitant expression of Th17 (IL-17)- and Th1 (IFN- γ)-associated cytokines. Adding more confusion to these concepts, the concentrations of IL-5 extend across a broad continuum in all of these studies with vast overlap in sinus tissue from those with and without NPs. This promiscuous expression of IL-5 in CRS was further demonstrated when inflammatory endotypes of CRS were studied by unbiased cluster analyses, where moderate or high IL-5 expression could be observed in clusters that included or excluded NPs.¹⁰ Finally, it should be emphasized that while early studies suggested

that CRSsNP was likely to be a disease with a Th1 signature, subsequent work demonstrates this tissue is fully capable of expressing profiles associated with Th1, Th2, and Th17 signatures alone or in combination (albeit with comparatively lower levels of the Th2 cytokines).⁷ However, the most common profile is probably that of an innate inflammatory process.¹⁷

All of these observations force consideration that the very concept of their being “distinct” endotypes in CRS is misguided. That is, instead of their being distinct phenotypes or endotypes defined by the absolute presence or absence of eosinophils, of a given cytokine, or of any other specific marker, that CRS properly needs to be approached as a continuum of inflammatory processes highly and variably expressing immune and inflammatory markers. Thus, in the case of eosinophilia, in our recently published studies,¹⁸ while it was possible to define a cohort of non-eosinophilic NPs (≤ 3 eosinophils in 10 distinct 400x high-powered fields and similarly, we could define “hyper-eosinophilic” NPs (≥ 25 eosinophils), the majority of subjects fell within a continuum of intermediate expression (figure 2) without any distinct cutoff that would unambiguously separate an “eosinophilic” from a non-eosinophilic” process. These data argue that any attempt to define a distinct cutoff distinguishing eosinophilic from non-eosinophilic polyps would be at best arbitrary. This concept is further demonstrated by the Wang et al.⁷ study where the investigators distinguished “high” from “low” IL-5 CRS using a tissue concentration of 1189.10 $\mu\text{g/L}$ (suggesting that 1189.09 would not be an IL-5-driven disease whereas a tissue concentration of 1189.11 $\mu\text{g/L}$ would – and thereby only at that threshold would consideration of using IL-5 antagonists be entertained). While accepting the arbitrariness of any specific cutoff being used to define an endotype, it remains reasonable to speculate that more robust expression of any of these markers can serve as an aid for guiding therapeutic decisions. Finally, it is perhaps also important to recognize that in the absence of unambiguous overarching evidence

diagnostic of a specific endotype (e.g., the rare CF polyp with too many eosinophils to count) none of these markers has proved superior (and certainly not easier to identify) than distinguishing the presence and absence of NPs.

A completely distinct and intriguing endotype of CRS has recently been described based upon expression of bitter taste receptors. Studies have described the presence of taste receptors in the airway and more specifically also in the sinonasal mucosa.¹⁹⁻²¹ A specific bitter taste receptor, T2R38, localized to the motile cilia, was found to be capable of responding to specific “quorum sensing molecules” produced by gram-negative bacteria such as *Pseudomonas*. In vivo studies show human sinonasal differentiated cells with normal T2R38 respond to stimulation with increased nitrous oxide production and increased ciliary beat frequency. ~~The development of the capacity of the immune system to detect these molecules has been postulated to be a potential type of surveillance system to drive innate antimicrobial responses to bacteria.~~^{16,18} Several studies report an increased rate of “non-tasters” in the CRS population,^{22, 23} while others have noted these patients are at increased risk of failed medical treatment of CRS and have a predicted increased need for surgical intervention.²⁴

Interestingly, Carey et al. showed that *Staphylococcus Aureus* conditioned medium lead to an increase in nitrous oxide production in human sinonasal cells through a bitter taste receptor-independent mechanism.²⁵ Determination of this specific mechanism of action and the *S. aureus* specific agonist hold promise for additional areas of study into CRS development. Taken together with potential role of taste receptors in CRS, both areas of study offer the potential yield of novel therapeutic targets independent of antibiotics or corticosteroids.

Current Medical Treatments of CRS (Table II)

Nasal Saline irrigation. Although saline irrigations are not typically utilized as an isolated treatment for CRS, their utility and benefits both pre- and post-operatively is well reported in practice and medical literature.²⁶⁻²⁸ In addition to the mechanical clearance of debris and post-operative packing, benefits noted include improved medication delivery, improved healing outcomes and improved mucociliary clearance.²⁹⁻³¹ Ongoing areas of research include attempts at quantifying the impact of saline irrigation on nasal secretions and determination of the optimal composition and pH of irrigations.³²⁻³³ Generally speaking, the benefits, cost, and ease of irrigating the sinus allow for this treatment method to be recommended across the collective umbrella of the CRS population both as an initial adjunct and as a post-operative treatment measure.

Corticosteroids. Both oral and topical GCS are recognized as effective therapies for CRS and are widely utilized in most patients.^{2, 34-36} However, the CRS response rate to GCS reportedly varies from 50-80%³⁶⁻³⁸ with few detailed analyses having been performed to identify the distinguishing features of responders and non-responders.^{39, 40} That a large cohort of CRS patients is likely to be non-responders to GCS is best evinced from the asthma literature, where it is recognized that up to 1/3rd of asthmatics do not respond to these agents. In asthma, this was already recognized in the late 1950s with a publication that the presence of induced sputum eosinophils was essential for defining a cohort in whom systemic steroids would be effective.⁴¹ These observations presumably reflect the therapeutic benefits derived from the ability of corticosteroids to induce eosinophilic apoptosis. And, more recently, this observation has been consistently confirmed with the understanding that a high eosinophil type 2 T-helper lymphocyte (Th2) signature (IL-5^{high}/IL-13^{high}) is a prerequisite for steroids to provide clinical benefit.^{42,43} It seems likely that this observation will extend to CRS and, as with this asthma experience,

defining individual endotype will be required to determine the appropriateness of recommending GCS.

Systemic Antibiotics. Microbial resistance to antibiotics continues to increase at alarming rates.⁴⁴⁻⁴⁶ Despite routine administration from health care providers, the actual evidence for oral antibiotics in the treatment of CRS remains sparse. Quality double-blind prospective studies are limited and those that have been performed often involve significant heterogeneity of the patient groups and inconsistent outcomes measures.^{47,48} Soler et al. examined the literature involving evidence for antibiotic treatment for CRS, including separation of non-macrolide from macrolide treatment.⁴⁹ The authors suggested that short courses, but not courses longer than 3 weeks, of non-macrolide treatment remained an option, with the caveat noted that the evidence was sparse and randomized control trials should be a research priority. They noted several studies in which macrolide treatment resulted in a reduction of IL-8 levels, with one study demonstrating a significant effect on patients with low IgE levels.⁵⁰ While further investigation into the mechanism of macrolide effect is recommended they conclude that prolonged macrolide therapy could be considered an optional treatment in CRS, specifically in patients with low IgE levels. A recent Cochrane review by Head et al. noted the dearth of evidence of benefit in the literature for oral antibiotic treatments in CRS.⁵¹ The authors concluded there was sparse quality evidence in support of oral antibiotics in the treatment of CRS, although they similarly did acknowledge the limited potential for extended macrolide therapy on quality-of-life outcomes. Van Zele et al., in a study incorporated by the reviews listed above, previously compared the effectiveness of either methylprednisolone or doxycycline to placebo in patients with significant or recurrent nasal polyposis, demonstrating similar impact of both treatment arms on decreased polyp size.⁵² More recently, the senior authors of that group compared two groups of post-

operative, recurrent CRSwNP patient groups.⁵³ Treatment with doxycycline for 12 weeks in combination with nasal steroids and saline irrigations demonstrated improved validated symptom and CT scan scores compared to treatment with nasal steroids and saline alone. In an interesting take on the role of antibiotic treatment in CRS, Günel et al. recently examined the impact of amoxicillin/clavulanic acid, as a *non*-anti-inflammatory antibiotic, in the treatment of eosinophilic CRS.⁵⁴ In patients with non-eosinophilic CRS, the authors noted improvement in both symptom and CT scores, although there was no change in endoscopic appearance. Interestingly, the eosinophilic CRS group demonstrated improvement in the CT scores, but no significant improvement in either the symptom score or endoscopy. The authors suggested the findings warrant altering the treatment paradigm, and reconsideration of role of antibiotics in appropriately phenotyped CRS populations. As the role of microbial *infection* in CRS becomes further elucidated, the appropriate role of antibiotics in the treatment of the disease will need to be thoroughly re-examined. Well executed studies that examine the antimicrobial versus the anti-inflammatory impact of antibiotics on appropriate CRS subgroups are also needed to determine which patients are appropriate for treatment with a given antibiotic regimen.

Topical antibiotics. The role of topical antibiotics in the recalcitrant population also continues to be an area of controversy. Conceptually, in the post-operative period, the sinus cavities are ideally patent, with the removal of diseased tissue allowing for increased delivery of medication to the sinonasal mucosa. Despite the best efforts of medical and surgical treatment, some patients may experience return of inflamed mucosa and purulent drainage. Several studies have examined the utility of mupirocin rinses in the treatment of CRS, showing variable results.⁵⁵⁻⁵⁸ In general, treatment-associated negative cultures and improvements in endoscopy or quality-of-life scores appear to be short-lived. The lack of robust studies with appropriate follow up and the variability

of the treatment groups have lead multiple systemic reviews and guideline groups to not recommend this intervention as either first-line or as an appropriate prolonged therapy.⁵⁹⁻⁶³ As both the inflammatory pathways and microbiome data are further delineated, however, the ability to individualize topical antibiotic and/or anti-inflammatory therapies may warrant reevaluating their utility.

Surfactants. Given the refractory nature of CRS, other treatments beyond normal saline have been examined. Surfactants are amphiphilic organic compounds that can reduce the surface tension, which in the case of CRS is thought to enable treatment and potential prevention of biofilm formation. Chiu et al. found post-operative utilization of 1% baby shampoo in a post-operative population lead to overall improvement in sinus symptom scores, with specific subjective improvements noted with decreased mucus accumulation and decreased post-nasal drip.⁶⁴ In addition, the experimental group demonstrated improved olfactory scores and endoscopic exams when compared to normal saline-using control patients. Desrosiers et al. demonstrated *in vitro* potential of decreasing biofilms with a citric acid/zwitterion surfactant combined with a hydrodebrider.⁶⁵ Of concern, however, Valentine et al. subsequently demonstrated worsened cilial morphology in sheep models with zwitterion usage as compared to when only saline was used.⁶⁶ Farag et al. compared the postoperative impact of hypertonic saline to surfactant irrigations, demonstrating no significant difference in CRS symptoms.⁶⁷ Interestingly, both patient groups reported increased quality-of-life and olfactory function during the post-operative period, but 20% of the patients reported poor toleration and cessation of the surfactant irrigations in this study. Although currently not recommended as a first line treatment, as CRS populations are better described and profiled, and as newer, more tolerable products are

developed, it may be found that there is a specific patient population that benefits from use of surfactants.

Manuka Honey and Other Non-Antibiotic Approaches to Dysbiosis in CRS. Given the potential side effects of antibiotic use and the potential for bacterial resistance, non-antibiotic treatments that address dysbiosis remain enticing. Investigations with various probiotics are early but do show promise. While the therapeutic and medicinal applications of honey were known in antiquity, it has more recently been considered for use in the treatment of skin wounds and ulcers.^{68,69} Noted therapeutic properties of honey that could mediate antimicrobial effects include a low pH and high osmotic pressure.⁷⁰ In addition, the glucose oxidase in honey produces hydrogen peroxide at levels that are not damaging to tissues but can impact bacterial loads.⁷¹ Manuka honey specifically has been found to contain increased levels of methylglyoxal, a bioactive compound that correlates with its bactericidal properties.⁷² Kwakman et al. demonstrated in a stepwise neutralization experiment that the antimicrobial properties of honey were related to the production of hydrogen peroxide and methylglyoxal, as well as bee defensin-1.⁷³ Although several studies have attempted to assess the potential role of honey in the treatment of CRS with variable results, they highlight the potential that exists for examination of alternative and naturally occurring therapies that may ultimately provide significant benefit.⁷⁴⁻⁷⁶

Future Treatments of CRS

The most intriguing advances in our approach to patients suffering from CRS is being derived from the development of targeted biotherapeutics. Recent studies suggest the potential benefit of biologics in appropriately identified patients with CRS. Of particular interest is the potential use of biologics directed against Th2 inflammation-associated mediators including those that target IgE, IL-4/IL-13, and IL-5.

Anti-IgE. Omalizumab is currently FDA approved for the treatment of treatment-resistant allergen-exacerbated asthma and for chronic urticaria (CU). The role of aeroallergen sensitization (specifically allergic rhinitis) in the pathogenesis of CRS is somewhat controversial and beyond the scope of this paper.⁷⁷ This controversy is driven in part by the recognition that aeroallergens are unlikely to access the sinus cavities. Furthermore, the concept that anatomical obstruction of the sinus ostia – secondary to allergic rhinitis or for any other reason – has an etiological role in the pathogenesis of CRS is increasingly questioned. However, the recognition that there is a high prevalence of CRS subjects with elevations in their total serum IgE and with allergic sensitization led to speculation that IgE-targeting therapies might prove efficacious. If not driven by aeroallergen sensitization, this may reflect IgE sensitization to other antigens, staphylococcus-derived exotoxins,^{10,78} for example, or the concept that this therapy has efficacy in other conditions not associated with aeroallergen sensitization, such as intrinsic asthma and CU. In one study, this agent was demonstrated to reduce NP size and improve sinus CT scores while also restoring sense of smell⁷⁹ although this was not confirmed in another, underpowered, study⁸⁰

Anti-Interleukin-5/IL-5R. Recently, antibodies that target IL-5 have been approved in the US for the treatment of refractory asthma and in the near future it is expected that an anti-IL-5R antibody will become available. Initial studies with IL-5 antagonists in asthma produced surprisingly disappointing results until it was demonstrated that it was necessary to first identify only those asthmatics with a Th2^{high}/eosinophil^{high} phenotype.⁸¹⁻⁸³ An interesting observation is that one of the better biomarkers predictive of a response to IL-5 antagonism in asthma was the concomitant presence of NPs, pointing to the relative ability of NPs to identify a (systemic) Th2^{high}/eosinophil^{high} inflammatory state.⁸⁴ Subsequently IL-5 antagonists have been

demonstrated to reduce frequency of asthma exacerbations, improve lung function and quality of life, and reduce need for systemic corticosteroids. While not as well studied as asthma, trials of IL-5 antagonism in CRS have demonstrated reductions in NP size and reduced need for revision surgery.^{85,86} It is important to note that in at least one trial of an IL-5 antagonist in CRS, the investigators confirmed the need to demonstrate the presence of an IL-5^{high} endotype to predict efficacy.⁸⁷

Anti-IL-4/IL-13. Because of their shared use of the IL-4R α chain, antibodies to IL-4R α antagonize binding and the biological activity of both IL-4 and IL-13. The anti-IL-4R α antibody dupilumab recently received FDA approval for use in refractory atopic dermatitis. This agent is also being studied in asthma and, as with the IL-5 antagonists, is demonstrated to reduce frequency of exacerbations and improve lung function in asthmatics with a Th2^{high} phenotype.⁸⁸ Not surprising, IL-13 antagonists may be particularly useful in asthmatics with an IL-13^{high} inflammatory signature again pointing to the need to identify appropriate patients for these targeted therapies.^{89,90} As with IL-5 antagonists, anti-IL-4R α therapy also shows promise in Th2^{high}/eosinophil^{high} CRS, having been shown to reduce NP size and sinus CT score while also improving sinus symptoms and restoring sense of smell.⁹¹

Other biotherapeutics in CRS. Given the similarity of CRS, especially eosinophilic CRS to (eosinophilic) asthma, it is reasonable to speculate that, as with topical GCS and currently available biologics, newer agents being developed for asthma may prove to have efficacy in eosinophilic CRS. Current studies emphasize the importance of airway epithelial cells in having a primary pathogenic role in driving Th2 immune deviation. In particular, the cytokines TSLP, IL-25, and IL-33 are recognized for their ability to interact with T helper lymphocytes (IL-25 and IL-33) or dendritic cells (TSLP) to create a milieu in which naïve T helper lymphocytes will

differentiate into Th2 effector cells. Such a role for epithelial-derived IL-33 in driving a type 2 cytokine signature in CRS is increasingly recognized⁹² Perhaps even more important than their role in Th2 immune deviation is the ability of these cytokines to drive type 2 cytokine production from many other cell types including mast cells, innate lymphoid cells, resident memory T cells, eosinophils, and others. Biologics targeting these cytokines are currently under investigation in eosinophilic asthma and atopic dermatitis and, as such, show potential promise in E-CRS. Addressing the upstream Th2 cytokine inducing transcription factor, GATA3, has shown promise in decreasing early and late phase asthmatic response in patients, which may be of potential use in the Th2 patient population.⁹³

Conclusion.

Treatment of CRS is currently at a potentially exciting crossroad. On the positive side, numerous therapeutics are in development that seem likely to positively impact our patients who suffer from this condition. The challenge is that these therapies will certainly require targeted individualized treatments based upon identifying subjects with the relevant endotype. However, given their expense and the unreasonable expectation that a serial “trial and error” approach with these costly reagents is plausible, this will require development of practical, efficient, and cost-effective means of identifying and connecting the right patient to the right agent. This may prove even more daunting than developing the drugs, as challenging as drug development is. Ultimately, our ability to define appropriate treatment involves appropriate workup, disease classification and validating consistent outcome measures.

400 Table I: What is Unknown in CRS?

Appropriate endotype classification schema for CRS
Appropriate biomarkers–endotype correlation
Role of the microbiome in CRS
Microarray assessment of microbiome vs. endoscopic culture
Relationship of pathogen expression to endotype/phenotype
Role of bitter taste receptors in CRS; potential as treatment target
Role of non-anti-inflammatory antibiotics
Appropriate patient population and dosing of anti-inflammatory antibiotics
Endotype-specific role of corticosteroids in treatment for CRS
Endotype-specific appropriateness of topical treatments (topical steroids, antibiotics, homeopathic, surfactant, etc.) for CRS
(Re)Define maximal medical treatment of CRS and endotype variations of MMT
Biologic treatments of CRS: defining appropriate patient populations
Understand inflammatory/immunologic pathogenic pathways of CRS to target with novel therapeutics

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402

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Table II

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(separate file)

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Figure Legends

- Figure 1: Patterns of TH1/TH2/TH17 cytokine expression in samples from patients with CRSwNP: Benelux (A), Berlin (B), Adelaide (C), Beijing (D), Chendu (E), and Tochigi (F). Reproduced with permission from: Wang, X, Zhang, N, Bo M, Holtappels, G, Zheng M, Lou H, Wang H, Zhang L, and Bachert C. 2016. Diversity of TH cytokine profiles in patients with chronic rhinosinusitis: A multicenter study in Europe, Asia, and Oceania. *J Allergy Clin Immunol.* 138:1344-53).
- Figure 2: Tissue eosinophil distribution in nasal polyp samples. Eosinophils were counted in ten 400x high-powered fields. These figures display the range of distribution of the eosinophils enumerated in nasal polyps as a function of average (A) and peak (B) expression. For the distribution of eosinophil numbers, [indicates inclusion of that number and) indicates < than that number. Reproduced with permission from: Steinke, J.W, A Smith, D Carpenter, J Patrie, S Payne, L Borish. 2017. Lack of efficacy of symptoms and medical history in distinguishing eosinophilic from non-eosinophilic chronic rhinosinusitis. *J Allergy Clin Immunol: In Practice* (Published on line: May 10, 2017).

References:

1. Slavin RG, Spector SL, Bernstein IL, Kaliner MA, Kennedy DW, Virant FS, et al. The diagnosis and management of sinusitis: A practice parameter update. *J Allergy Clin Immunol* 2005; 116:S13-S47.
2. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology* 2012; 50:1-12.
3. Bachert C, Akdis CA. Phenotypes and Emerging Endotypes of Chronic Rhinosinusitis. *J Allergy Clin Immunol Pract*. 2016 Jul-Aug;4(4):621-8. doi: 10.1016/j.jaip.2016.05.004. PubMed PMID: 27393777.
4. Akdis CA, Bachert C, Cingi C, Dykewicz MS, Hellings PW, Naclerio RM, Schleimer RP, Ledford D. Akdis CA, Bachert C, Cingi C, Dykewicz MS, Hellings PW, Naclerio RM, Schleimer RP, Ledford D. Endotypes and phenotypes of chronic rhinosinusitis: a PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol*. 2013 Jun;131(6):1479-90. doi: 10.1016/j.jaci.2013.02.036. Epub 2013 Apr 12. PubMed PMID: 23587334; PubMed Central PMCID: PMC4161279.
5. De Greve G, Hellings PW, Fokkens WJ, Pugin B, Steelant B, Seys SF. Endotype-driven treatment in chronic upper airway diseases. *Clin Transl Allergy*. 2017 Jul 12;7:22. doi: 10.1186/s13601-017-0157-8. eCollection 2017. Review. PubMed PMID: 28706720; PubMed Central PMCID: PMC5506670.
6. Pothoven KL, Schleimer RP. The barrier hypothesis and Oncostatin M: Restoration of epithelial barrier function as a novel therapeutic strategy for the treatment of type 2

inflammatory disease. *Tissue Barriers*. 2017 Jul 3;5(3):e1341367. doi:

10.1080/21688370.2017.1341367. Epub 2017 Jun 13. PubMed PMID: 28665760

7. Wang X, Zhang N, Bo M, Holtappels G, Zheng M, Lou H, et al. Diversity of TH cytokine profiles in patients with chronic rhinosinusitis: A multicenter study in Europe, Asia, and Oceania. *J Allergy Clin Immunol* 2016; 138:1344-53.
8. Tan BK, Klingler AI, Poposki JA, Stevens WW, Peters AT, Suh LA, Norton J, Carter RG, Hulse KE, Harris KE, Grammer LC, Schleimer RP, Welch KC, Smith SS, Conley DB, Kern RC, Kato A. Heterogeneous inflammatory patterns in chronic rhinosinusitis without nasal polyps in Chicago, Illinois. *J Allergy Clin Immunol*. 2017 Feb;139(2):699-703.e7. doi: 10.1016/j.jaci.2016.06.063. Epub 2016 Sep 14. PubMed PMID: 27639939; PubMed Central PMCID: PMC5303134.
9. Steinke, J.W., S.C. Payne, P.G. Chen, J. Negri, E.B. Stelow, and L. Borish. 2012. Etiology of nasal polyps in cystic fibrosis: Not a unimodal disease. *Annals of Otolaryngology & Laryngology*. 121(9): 579-86
10. Tomassen P, Vandeplas G, Van Zele T, Cardell LO, Arebro J, Olze H, Förster-Ruhrmann U, Kowalski ML, Olszewska-Zięber A, Holtappels G, De Ruyck N, Wang X, Van Drunen C, Mullol J, Hellings P, Hox V, Toskala E, Scadding G, Lund V, Zhang L, Fokkens W, Bachert C. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. *J Allergy Clin Immunol*. 2016 May;137(5):1449-1456.e4. doi: 10.1016/j.jaci.2015.12.1324. Epub 2016 Mar 4. PubMed PMID: 26949058.
11. Boase S, Foreman A, Cleland E, et al. The microbiome of chronic rhinosinusitis: culture, molecular diagnostics and biofilm detection. *BMC Infectious Diseases*. May 2013:1-9.

12. Hoggard M, Biswas K, Zoing M, Wagner Mackenzie B, Taylor MW, Douglas RG. Evidence of microbiota dysbiosis in chronic rhinosinusitis. *Int Forum Allergy Rhinol.* 2016;XX:1–10.
13. Ramakrishnan VR, Hauser LJ, Feazel LM, Ir D, Robertson CE, Frank DN. Sinus microbiota varies among chronic rhinosinusitis phenotypes and predicts surgical outcome. *J Allergy Clin Immunol.* 2015 Aug;136(2):334-42.e1. doi: 10.1016/j.jaci.2015.02.008. Epub 2015 Mar 26. PubMed PMID: 25819063.
14. Hauser LJ, Feazel LM, Ir D, Fang R, Wagner BD, Robertson CE, Frank DN, Ramakrishnan VR. Sinus culture poorly predicts resident microbiota. *Int Forum Allergy Rhinol.* 2015 Jan;5(1):3-9. doi: 10.1002/alr.21428. Epub 2014 Oct 2. PubMed PMID: 25278448.
15. Liu CM, Soldanova K, Nordstrom L, et al. Medical therapy reduces microbiota diversity and evenness in surgically recalcitrant chronic rhinosinusitis. *Int Forum Allergy Rhinol.* 2013;3(10):775-781. doi:10.1002/alr.21195.
16. Cope EK, Goldberg AN, Pletcher SD, Lynch SV. Compositionally and functionally distinct sinus microbiota in chronic rhinosinusitis patients have immunological and clinically divergent consequences. *Microbiome.* 2017 May 12;5(1):53. doi: 10.1186/s40168-017-0266-6. PubMed PMID: 28494786; PubMed Central PMCID: PMC5427582.
17. Stevens W, CJ Ocampo, S Berdnikovs, et al. 2015. Cytokines in chronic rhinosinusitis. Role in eosinophilia and aspirin-exacerbated respiratory disease. *Am. J Respir Crit Care Med* 192(6):682-94.
18. Steinke, JW, A Smith, D Carpenter, J Patrie, S Payne, L Borish. 2017. Lack of efficacy of symptoms and medical history in distinguishing eosinophilic from non-eosinophilic chronic rhinosinusitis. *J Allergy Clin Immunol: In Practice* (Published on line: May 10, 2017).

19. Shah AS, Ben-Shahar Y, Moninger TO, Kline JN, Welsh MJ. Motile cilia of human airway epithelia are chemosensory. *Science* 2009;325:1131–1134.
20. Lee RJ, Xiong G, Kofonow JM, et al. T2R38 taste receptor polymorphisms underlie susceptibility to upper respiratory infection. *J Clin Invest* 2012; 122:4145–4159.
21. Lee RJ, Kofonow JM, Rosen PL, et al. Bitter and sweet taste receptors regulate human upper respiratory innate immunity. *J Clin Invest* 2014; 124:1393–1405. doi: 10.1172/JCI72094.
22. Adappa ND, Howland TJ, Palmer JN, Kennedy DW, Doghramji L, Lysenko A, Reed DR, Lee RJ, Cohen NA. Genetics of the taste receptor T2R38 correlates with chronic rhinosinusitis necessitating surgical intervention. *Int Forum Allergy Rhinol.* 2013 Mar;3(3):184-7. doi: 10.1002/alr.21140. Epub 2013 Jan 16. PubMed PMID: 23322450.
23. Rom DI, Christensen JM, Alvarado R, Sacks R, Harvey RJ. The impact of bitter taste receptor genetics on culturable bacteria in chronic rhinosinusitis. *Rhinology.* 2017 Mar 1;55(1):90-94. doi: 10.4193/Rhin16.181. PubMed PMID: 28214914.
24. Carey RM, Workman AD, Chen B, Adappa ND, Palmer JN, Kennedy DW, Lee RJ, Cohen NA. *Staphylococcus aureus* triggers nitric oxide production in human upper airway epithelium. *Int Forum Allergy Rhinol.* 2015 Sep;5(9):808-13. doi: 10.1002/alr.21568. Epub 2015 Jun 22. PubMed PMID: 26097237; PubMed Central PMCID: PMC4829394.
25. Adappa ND, Zhang Z, Palmer JN, Kennedy DW, Doghramji L, Lysenko A, Reed DR, Scott T, Zhao NW, Owens D, Lee RJ, Cohen NA. The bitter taste receptor T2R38 is an independent risk factor for chronic rhinosinusitis requiring sinus surgery. *Int Forum Allergy Rhinol.* 2014 Jan;4(1):3-7. doi: 10.1002/alr.21253. Epub 2013 Dec 2. PubMed PMID: 24302675; PubMed Central PMCID: PMC4082560.

26. Rabago D, Zgierska A, Mundt M, Barrett B, Bobula J, Maberry R. Efficacy of daily hypertonic saline nasal irrigation among patients with sinusitis: a randomized controlled trial. *Journal of Family Practice* 2002;51(12): 1049–55
27. Bachmann G, Hommel G, Michel O. Effect of irrigation of the nose with isotonic salt solution on adult patients with chronic paranasal sinus disease. *European Archives of Oto-Rhino-Laryngology* 2000;257(10):537–41.
28. Talbot AR, Herr TM, Parsons DS. Mucociliary clearance and buffered hypertonic saline solution. *Laryngoscope* 1997; 107(4):500–3.
29. Pynnonen MA, Mukerji SS, Kim HM, Adams ME, Terrell JE. Nasal saline for chronic sinonasal symptoms: a randomized controlled trial. *Archives of Otolaryngology--Head & Neck Surgery* 2007;133(11):1115–20.
30. Huang A, Govindaraj S. Topical therapy in the management of chronic rhinosinusitis. *Curr Opin Otolaryngol Head Neck Surg.* 2013 Feb;21(1):31-8. doi: 10.1097/MOO.0b013e32835bc4ab. Review. PubMed PMID: 23277167.
31. Hauptman G, Ryan MW. The effect of saline solutions on nasal patency and mucociliary clearance in rhinosinusitis patients. *Otolaryngol Head Neck Surg.* 2007 Nov;137(5):815-21. PubMed PMID: 17967652.
32. Woods CM, Tan S, Ullah S, Frauenfelder C, Ooi EH, Carney AS. The effect of nasal irrigation formulation on the antimicrobial activity of nasal secretions. *Int Forum Allergy Rhinol.* 2015;5:1104–1110.
33. Low TH, Woods CM, Ullah S, Carney AS. A double-blind randomized controlled trial of normal saline, lactated Ringer's, and hypertonic saline nasal irrigation solution after

endoscopic sinus surgery. *Am J Rhinol Allergy*. 2014 May-Jun;28(3):225-31. doi:
10.2500/ajra.2014.28.4031. Epub 2014 Jan 16. PubMed PMID: 24598116.

34. Hartwig S, Linden M, Laurent C, Vargo AK, Lindqvist N. Budesonide nasal spray as prophylactic treatment after polypectomy (a double blind clinical trial). *J Laryngol Otol* 1988; 102:148-51.
35. Steinke JW, Payne SC, Tessier E, Borish L, Han JK, Borish L. Pilot study of budesonide inhalent suspension irrigations for chronic eosinophilic sinusitis. *J Allergy Clin Immunol* 2009; 124:1352-4.
36. Vaidyanathan S, Barnes M, Williamson P, Hopkinson P, Donnan PT, Lipworth B. Treatment of chronic rhinosinusitis with nasal polyposis with oral steroids followed by topical steroids: a randomized trial. *Ann Intern Med* 2011; 154:293-302.
37. Tuncer U, Soylu L, Aydogan B, Karakus F, Akcali C. The effectiveness of steroid treatment in nasal polyposis. *Auris Nasus Larynx* 2003; 30:263-8.
38. Hissaria P, Smith W, Wormald PJ, Taylor J, Vadas M, Gillis D, et al. Short course of systemic corticosteroids in sinonasal polyposis: a double-blind, randomized, placebo-controlled trial with evaluation of outcome measures. *J Allergy Clin Immunol* 2006; 118:128-33.
39. Milara J, Peiro T, Armengot M, Frias S, Morell A, Serrano A, et al. Mucin 1 downregulation associates with corticosteroid resistance in chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol* 2015; 135:470-6.
40. Wen W, Liu W, Zhang L, Bai J, Fan Y, Xia W, et al. Increased neutrophilia in nasal polyps reduces the response to oral corticosteroid therapy. *J Allergy Clin Immunol* 2012; 129:1522-8.

41. Brown HM. Treatment of chronic asthma with prednisolone; significance of eosinophils in the sputum. *Lancet* 1958; 2:1245-7.
42. Woodruff PG, Boushey HA, Dolganov GM, Barker CS, Yang YH, Donnelly S, et al. Genome-wide profiling identifies epithelial cell genes associated with asthma and with treatment response to corticosteroids. *Proc Natl Acad Sci U S A* 2007; 104:15858-63.
43. Cowan DC, Cowan JO, Palmay R, Williamson A, Taylor DR. Effects of steroid therapy on inflammatory cell subtypes in asthma. *Thorax* 2010; 65:384-90.
44. [No authors listed.] Tackling drug-resistant infections globally: final report and recommendations (review on antimicrobial resistance, 2016). *AMR Review* https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf (2016).
45. Andersson DI, Hughes D. Antibiotic resistance and its cost: is it possible to reverse resistance? *Nat Rev Microbiol.* 2010 Apr;8(4):260-71. doi: 10.1038/nrmicro2319. Epub 2010 Mar 8. Review. PubMed PMID: 20208551.
46. Andersson DI, Hughes D. Microbiological effects of sublethal levels of antibiotics. *Nat Rev Microbiol.* 2014 Jul;12(7):465-78. doi: 10.1038/nrmicro3270. Epub 2014 May 27. Review. PubMed PMID: 24861036.
47. Huck W, Reed BD, Nielsen RW, et al. Cefaclor vs amoxicillin in the treatment of acute, recurrent, and chronic sinusitis. *Arch Fam Med.* 1993;2:497–503.
48. Legent F, Bordure P, Beauvillain C, Berche P. A double-blind comparison of ciprofloxacin and amoxycillin/clavulanic acid in the treatment of chronic sinusitis. *Chemotherapy.* 1994;40 Suppl 1:8-15. PubMed PMID: 7805431.
49. Soler ZM, Oyer SL, Kern RC, et al. Antimicrobials and chronic rhinosinusitis with or without polyposis in adults: an evidenced-based review with recommendations. *Int Forum*

Allergy Rhinol, 2013; 3:31–47.

50. Wallwork B, Coman W, Mackay-Sim A, Greiff L, Cervin A. A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. *Laryngoscope*. 2006 Feb;116(2):189-93. PubMed PMID: 16467702.
51. Head K, Chong LY, Piromchai P, Hopkins C, Philpott C, Schilder AG, Burton MJ. Systemic and topical antibiotics for chronic rhinosinusitis. *Cochrane Database Syst Rev*. 2016 Apr 26;4:CD011994. doi: 10.1002/14651858.CD011994.pub2. Review. PubMed PMID: 27113482.
52. Van Zele T, Gevaert P, Holtappels G, Beule A, Wormald PJ, Mayr S, Hens G, Hellings P, Ebbens FA, Fokkens W, Van Cauwenberge P, Bachert C. Oral steroids and doxycycline: two different approaches to treat nasal polyps. *J Allergy Clin Immunol*. 2010 May;125(5):1069-1076.e4. doi: 10.1016/j.jaci.2010.02.020. PubMed PMID: 20451040.
53. Pinto Bezerra Soter AC, Bezerra TF, Pezato R, Teles Abdo TR, Pilan RM, Pinna FR, Gevaert P, van Zele T, Bachert C, Voegels RL. Prospective open-label evaluation of long-term low-dose doxycycline for difficult-to-treat chronic rhinosinusitis with nasal polyps. *Rhinology*. 2017 Jun 1;55(2):175-180. doi: 10.4193/Rhin15.291. PubMed PMID: 28434014.
54. Günel C, Bleier BS, Meteoglu I. Antibiotics in eosinophilic chronic rhinosinusitis: Rethinking maximal antimicrobial medical therapy. *Laryngoscope*. 2017 Apr;127(4):794-796. doi: 10.1002/lary.26415. Epub 2016 Nov 26. PubMed PMID: 27888519.
55. Solares CA, Batra PS, Hall GS, et al. Treatment of chronic rhinosinusitis exacerbations due to methicillin-resistant *Staphylococcus aureus* with mupirocin irrigations. *Am J Otolaryngol* 2006;27(3):161–5.

56. Uren B, Psaltis A, Wormald PJ. Nasal lavage with mupirocin for the treatment of surgically
recalcitrant chronic rhinosinusitis. *Laryngoscope*. 2008;118:1677–1680.
57. Jervis-Bardy J, Wormald PJ. Microbiological outcomes following mupirocin nasal washes
for symptomatic, *Staphylococcus aureus*-positive chronic rhinosinusitis following endoscopic
sinus surgery. *Int Forum Allergy Rhinol*. 2012;2:111–115.
58. Desrosiers M, Bendouah Z, Barbeau J. Effectiveness of topical antibiotics on *Staphylococcus*
aureus biofilm in vitro. *Am J Rhinol* 2007;21(2):149–53.
59. Kim JS, Kwon SH. Mupirocin in the Treatment of Staphylococcal Infections in Chronic
Rhinosinusitis: A Meta-Analysis. *PLoS One*. 2016 Dec 1;11(12):e0167369. doi:
10.1371/journal.pone.0167369. eCollection 2016. PubMed PMID: 27907108; PubMed
Central PMCID: PMC5132234.
60. Lim M, Citardi MJ, Leong JL. Topical antimicrobials in the management of chronic
rhinosinusitis: a systematic review. *Am J Rhinol*. 2008 Jul-Aug;22(4):381-9. doi:
10.2500/ajr.2008.22.3189. Review. PubMed PMID: 18702902.
61. Lee JT, Chiu AG. Topical anti-infective sinonasal irrigations: update and literature review.
Am J Rhinol Allergy. 2014 Jan-Feb;28(1):29-38. doi: 10.2500/ajra.2014.28.3988. Review.
PubMed PMID: 24717876.
62. Huang A, Govindaraj S. Topical therapy in the management of chronic rhinosinusitis. *Curr*
Opin Otolaryngol Head Neck Surg. 2013 Feb;21(1):31-8. doi:
10.1097/MOO.0b013e32835bc4ab. Review. PubMed PMID: 23277167.
63. Rudmik L, Hoy M, Schlosser RJ, Harvey RJ, Welch KC, Lund V, Smith TL. Topical
therapies in the management of chronic rhinosinusitis: an evidence-based review with

recommendations. *Int Forum Allergy Rhinol*. 2013 Apr;3(4):281-98. doi: 10.1002/alr.21096.

Epub 2012 Oct 8. Review. PubMed PMID: 23044832.

64. Chiu AG, Palmer JN, Woodworth BA, et al. Baby shampoo nasal irrigations for the symptomatic post-functional endoscopic sinus surgery patient. *Am J Rhinol* 2008;22(1):34–7.

65. Desrosiers M, Myntti M, James G. Methods for removing bacterial biofilms: in vitro study using clinical chronic rhinosinusitis specimens. *Am J Rhinol* 2007;21(5): 527–32.

66. Valentine R, Jervis-Bardy J, Psaltis A, Tan LW, Wormald PJ. Efficacy of using a hydrodebrider and of citric acid/zwitterionic surfactant on a *Staphylococcus aureus* bacterial biofilm in the sheep model of rhinosinusitis. *Am J Rhinol Allergy*. 2011 Sep-Oct;25(5):323-6. doi: 10.2500/ajra.2011.25.3659. PubMed PMID: 22186246

67. Farag AA , Deal AM , McKinney KA , et al. Single-blind randomized controlled trial of surfactant vs hypertonic saline irrigation following endoscopic endonasal surgery. *Int Forum Allergy Rhinol*, 2013; 3:276–280.

68. Dunford C, Cooper R, Molan P, White R. The use of honey in wound management. *Nurs Stand*. 2000 Nov 29-Dec 5;15(11):63-8. PubMed PMID: 11971572.

69. Lusby PE, Coombes A, Wilkinson JM. Honey—a potent agent for wound healing? *J Wound Ostomy Continence Nurs* 2002;29:295–300.

70. Moore OA, Smith LA, Campbell F, et al. Systematic review of the use of honey as a wound dressing. *BMC Complement Altern Med* 2001;1:2.

71. Lusby PE, Coombes AL, Wilkinson JM. Bactericidal activity of different honeys against pathogenic bacteria. *Arch Med Res*. 2005 Sep-Oct;36(5):464-7. PubMed PMID: 16099322.

72. Mavric E, Wittmann S, Barth G, Henle T. Identification and quantification of methylglyoxal as the dominant antibacterial constituent of Manuka (*Leptospermum scoparium*) honeys from New Zealand. *Mol Nutr Food Res*. 2008 Apr;52(4):483-9. doi: 10.1002/mnfr.200700282. PubMed PMID: 18210383.
73. Kwakman PH, te Velde AA, de Boer L, Speijer D, Vandenbroucke-Grauls CM, Zaat SA. How honey kills bacteria. *FASEB J*. 2010 Jul;24(7):2576-82. doi: 10.1096/fj.09-150789. Epub 2010 Mar 12. PubMed PMID: 20228250.
74. Alandejani T, Marsan J, Ferris W, et al. Effectiveness of honey on *Staphylococcus aureus* and *Pseudomonas aeruginosa* biofilms. *Otolaryngol Head Neck Surg* 2009;141(1):114–8.
75. Thamboo A, Thamboo A, Philpott C, Javer A, Clark A. Single-blind study of manuka honey in allergic fungal rhinosinusitis. *J Otolaryngol Head Neck Surg*. 2011 Jun;40(3):238-43. PubMed PMID: 21518647
76. Lee VS, Humphreys IM, Purcell PL, Davis GE. Manuka honey sinus irrigation for the treatment of chronic rhinos-inusitis: a randomized controlled trial. *Int Forum Allergy Rhinol*. 2017;7:365–372.
77. Steinke, J.W. and L. Borish. 2016. Chronic rhinosinusitis phenotypes *Annals of Allergy, Asthma, and Immunol*. 117(3):234-40. PMCID: PMC5018302.
78. Van Zele T, Gevaert P, Watelet JB, Claeys G, Holtappels G, Claeys C, van Cauwenberge P, Bachert C. *Staphylococcus aureus* colonization and IgE antibody formation to enterotoxins is increased in nasal polyposis. *J Allergy Clin Immunol*. 2004 Oct;114(4):981-3. PubMed PMID: 15480349.
79. Gevaert P, Calus L, Van Zele T, Blomme K, De Ruyck N, Bauters W, Hellings P, Brusselle G, De Bacquer D, van Cauwenberge P, Bachert C. Omalizumab is effective in allergic and

- nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol*. 2013 Jan;131(1):110-6.e1. doi: 10.1016/j.jaci.2012.07.047. Epub 2012 Sep 27. PubMed PMID: 23021878.
80. Pinto JM, Mehta N, DiTineo M, Wang J, Baroody FM, Naclerio RM. A randomized, double-blind, placebo-controlled trial of anti-IgE for chronic rhinosinusitis. *Rhinology*. 2010 Sep;48(3):318-24. doi: 10.4193/Rhin09.144. PubMed PMID: 21038023.
81. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014; 371:1198-207.
82. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015; 3:355-66.
83. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016; 388:2128-41.
84. Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, Wilkins HJ, Henkel T, Nair P; Res-5-0010 Study Group.. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med*. 2011 Nov 15;184(10):1125-32. doi: 10.1164/rccm.201103-0396OC. Epub 2011 Aug 18. PubMed PMID: 21852542.

85. Gevaert P, Van Bruaene N, Cattaert T, Van Steen K, Van Zele T, Acke F, et al.
Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis.
J Allergy Clin Immunol 2011; 128:989-95 e1-8.
86. Bachert C, Sousa AR, Lund VJ, Scadding GK, Gevaert P, Nasser S, Durham SR, Cornet ME,
Kariyawasam HH, Gilbert J, Austin D, Maxwell AC, Marshall RP, Fokkens WJ. Reduced
need for surgery in severe nasal polyposis with mepolizumab: Randomized trial. J Allergy
Clin Immunol. 2017 Jul 4. pii: S0091-6749(17)31081-3. doi: 10.1016/j.jaci.2017.05.044.
[Epub ahead of print] PubMed PMID: 2868723
87. Gevaert P, Lang-Loidolt D, Lackner A, Stammberger H, Staudinger H, Van Zele T,
Holtappels G, Tavernier J, van Cauwenberge P, Bachert C. Nasal IL-5 levels determine the
response to anti-IL-5 treatment in patients with nasal polyps. J Allergy Clin Immunol. 2006
Nov;118(5):1133-41. Epub 2006 Sep 26. PubMed PMID: 17088140.
88. Wenzel S, Castro M, Corren J, Maspero J, Wang L, Zhang B, Pirozzi G, Sutherland ER,
Evans RR, Joish VN, Eckert L, Graham NM, Stahl N, Yancopoulos GD, Louis-Tisserand M,
Teper A. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite
use of medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist: a
randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. Lancet.
2016 Jul 2;388(10039):31-44. doi: 10.1016/S0140-6736(16)30307-5. Epub 2016 Apr 27.
PubMed PMID: 27130691.
89. Corren J, Lemanske RF, Hanania NA, Korenblat PE, Parsey MV, Arron JR, et al.
Lebrikizumab treatment in adults with asthma. N Engl J Med 2011; 365:1088-98.

90. Hanania NA, Noonan M, Corren J, Korenblat P, Zheng Y, Fischer SK, et al. Lebrikizumab in moderate-to-severe asthma: pooled data from two randomised placebo-controlled studies. *Thorax* 2015; 70:748-56.
91. Bachert C, Mannent L, Naclerio RM, Mullol J, Ferguson BJ, Gevaert P, Hellings P, Jiao L, Wang L, Evans RR, Pirozzi G, Graham NM, Swanson B, Hamilton JD, Radin A, Gandhi NA, Stahl N, Yancopoulos GD, Sutherland ER. Effect of Subcutaneous Dupilumab on Nasal Polyp Burden in Patients With Chronic Sinusitis and Nasal Polyposis: A Randomized Clinical Trial. *JAMA*. 2016 Feb 2;315(5):469-79. doi: 10.1001/jama.2015.19330. PubMed PMID: 26836729.
92. Soyka MB, Holzmann D, Basinski TM, Wawrzyniak M, Bannert C, Bürgler S, Akkoc T, Treis A, Rückert B, Akdis M, Akdis CA, Eiwegger T. The Induction of IL-33 in the Sinus Epithelium and Its Influence on T-Helper Cell Responses. *PLoS One*. 2015 May 1;10(5):e0123163. doi: 10.1371/journal.pone.0123163. eCollection 2015. PubMed PMID: 25932636; PubMed Central PMCID: PMC4416791.
93. Bachert C, Holtappels G. Pathophysiology of chronic rhinosinusitis, pharmaceutical therapy options. *GMS Current Topics in Otorhinolaryngology, Head and Neck Surgery*. 2015;14:Doc09. doi:10.3205/cto000124.

Table II: Medical Treatments of Chronic Sinusitis

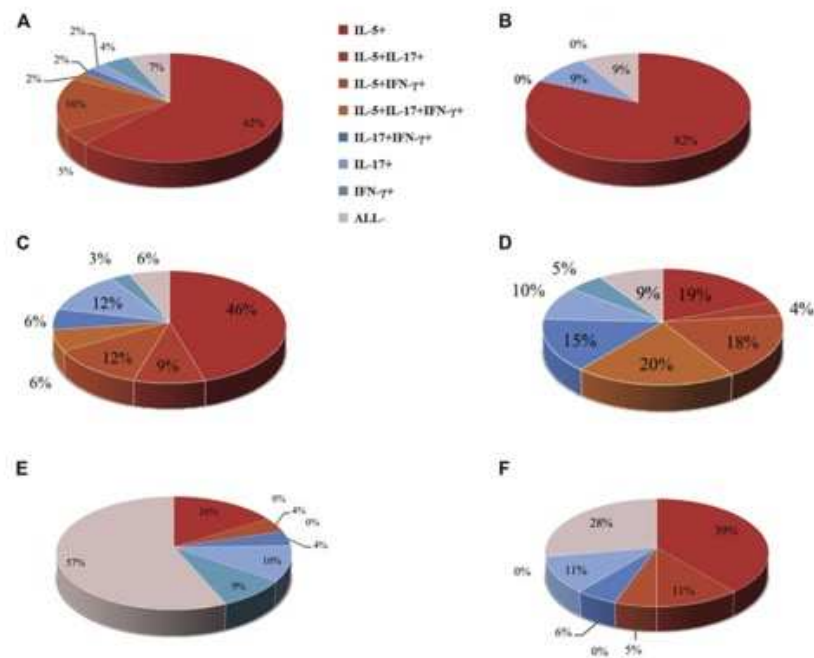
Topical				
<u>Treatment</u>	<u>CRS Endotype</u>	<u>Advantages</u>	<u>Disadvantages</u>	<u>Comments</u>
Saline Sprays and/or Irrigations	CRSwNP, CRSsNP	Inexpensive, readily available, easy to use	Discomfort, only mechanical clearance	Hygiene and mechanical impact in CRS with and without polyps; high adjunctive and post-operative utility
Topical Steroid Sprays	CRSwNP, CRSsNP	Widely available, easy to use	Newer formulations expensive, lack of equal medication distribution, potential for epistaxis	First line treatment
Topical Steroid Irrigations	Th2 ^{high} CRS, CRSwNP	Increased delivery to pre- and post-surgical sinuses (vs. sprays), improved mechanical clearance	Discomfort, cost, further diagnostic techniques needed to identify ideal population.	Off label use
Topical Antibiotics	Undetermined	Not currently recommended. Theoretical local (non-systemic) treatment of bacterial infection	Results appear short-lived, unclear benefits vs. placebo	Effects short-lived; Potential for improved directed treatment as ability to diagnose and identify impact of specific pathogens evolves
Surfactants	Undetermined	Non-antibiotic treatment of biofilm vs. possible biofilm prevention	Discomfort, uncertain optimal surfactant formula; rare temporary anosmia with shampoos	Ideal surfactant and role in treatment of specific endotypes to be determined
Manuka Honey and other homeopathic treatments (e.g. colloidal silver, xylitol, etc.)	Undetermined	Potential non-antibiotic mediated antimicrobial vs. anti-inflammatory effects; role to be determined	Further basic science and clinical studies required to identify/validate respective mechanisms of action and ideal patient population for	Potential role in primary and more likely adjunctive role in specific CRS endotypes to be determined.

			treatment	
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Oral				
<u>Treatment</u>	<u>CRS Endotype</u>	<u>Advantages</u>	<u>Disadvantages</u>	<u>Comments</u>
Oral Glucocorticoids	CRSwNP, unclear role in CRSsNP	Anti-inflammatory effect, potential multisystem improvement of symptoms	Generally limited duration of benefit, significant systemic side effects (weight gain, endocrine system, osteopenia, mania, etc.)	Th2 ^{high} with short lived response; significant side effects.
Oral Antibiotics (non-macrolide)	Directed antimicrobial potential in acute exacerbations.	Potential resolution/decrease of active infection	Bacterial resistance, GI Distress, <i>C. diff</i> , anaphylaxis	Potential role for doxycycline in CRSwNP.
Oral Antibiotics (macrolide)	Non-eosinophilic/low IgE CRS	Potential anti-inflammatory effect	GI distress with long-term treatment	Potential role in low IgE CRS patients; cystic fibrosis

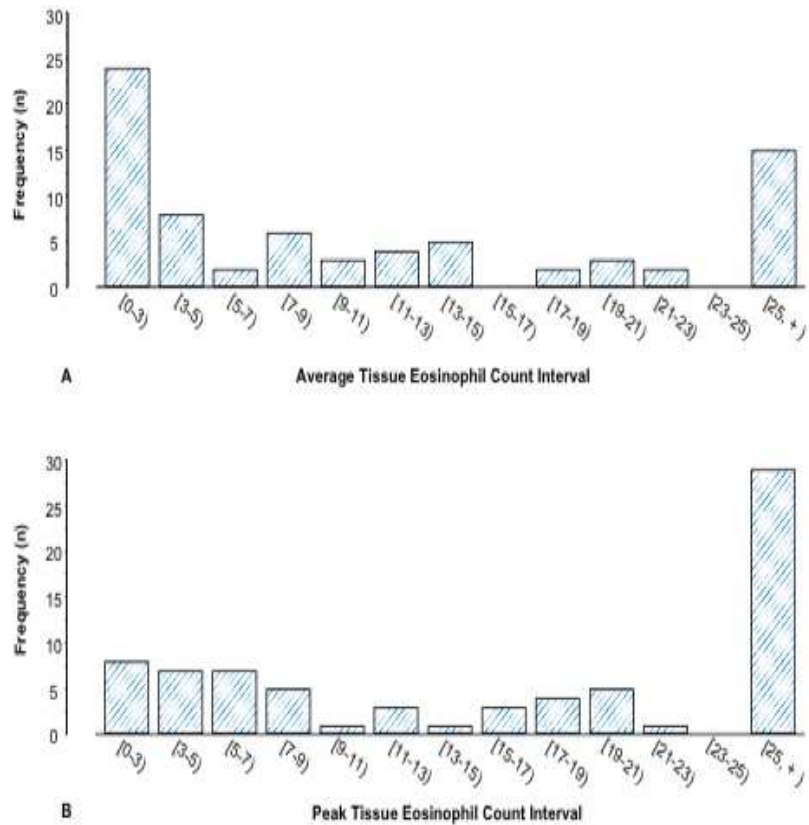
Biotherapeutics				
<u>Treatment</u>	<u>CRS Endotype</u>	<u>Advantages</u>	<u>Disadvantages</u>	<u>Comments</u>
Anti-IgE	Elevated IgE, atopic; with comorbid asthma	Targeted at systemic cause of disease, potential decreased need for surgery, potential decreased need for oral or topical steroids	Expense/Cost prohibitive; potential off-label use in CRS, need for further clinical studies	Ideal endotypes and comorbid conditions for applications under investigation.
Anti-IL-5/IL-5R	Potential role in IL-5 ^{high} CRS			
GATA-3 DNzyme	CRS role undetermined, likely use in Th2 ^{high} CRS	Induces decreased GATA-3 (Th2 immune deviation) and IL-5 expression		

Figure 1



ACCEPTED MANUSCRIPT

1 Figure 2:



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