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Chapter

Chronic Sinusitis: The Empiric Treatment Strikes Back: Is CRS Directly Caused by Infectious Agent(s)?

Alexander Nowicki, Natalie Nowicki, Stella Nowicki, Alfred Samet, Michal Michalik, Roger Su, James K. Fortson and Bogdan Nowicki

Abstract

Chronic sinusitis leads to unresolved infection and inflammation resulting in tissue remodeling, then further propagates the vicious cycle of deterioration and dysfunction of the sinuses' natural defense mechanisms, and yet another cycle of infection and mucosal injury. Antibiotic therapy targeting pathogens classically implicated in sinusitis could augment the risk of therapeutic failure through the natural selection of resistant and/or virulent pathogens, especially in the presence of Gram-negative *E. coli*. Our recent demonstration of highly pathogenic *E. coli,* detected through intraoperative biopsy of sinus tissue, allowed the resolution of chronic sinusitis symptoms upon *E. coli* targeted therapy. The isolated *E. coli* carried three genes, each coding biofilm formation, which may, in part, account for the chronicity of *E. coli* sinusitis. We recommend that, patients with chronic sinusitis be considered for intraoperative biopsy for unusual pathogens, therefore allowing targeted therapy. In the future, use of vaccines and biofilm inhibitors might be an effective therapeutic consideration.

Keywords: chronic sinusitis, rhinosinusitis, *E. coli*, biofilm, genotype, virulence factors, antibiotic treatment, antibiotic resistance, biopsy

1. Introduction

1.1 Is CRS directly caused by infectious agents?

Our current state of knowledge indicates that chronic rhinosinusitis (CRS) is not directly caused by infectious agents [1]. Instead, the current paradigm states that CRS is a spectrum of "self-perpetuating" non-infectious inflammatory processes. If this is the case, that would mean that repetitive, long term, systemic antibiotic therapy has little to no role in the treatment of CRS, except in the event of an acute exacerbation. Furthermore, this would suggest that clinical improvement of CRS would be more appropriately explained by the reduction of inflammatory injury as a whole, and only secondarily by the amelioration of bacterial load and the resultant removal of super-antigens.

Albeit this working theory pivots upon a non-infectious etiology it does raise many concerns in the direction of microbiology. The most paramount of which is that the misappropriate, frequent, and long term use of antibiotics actually selects for a pathological microflora, composed of microorganisms resistant to antibiotics, which may also form biofilms that may never be eradicated [1]. These biofilms may then act as the perfect stage for future acute exacerbations, functioning as a protective bunker for bacteria lying dormant within the film, and even create quasi-resistant bacteria. For example, a naturally antibiotic-sensitive bacterium contained within a biofilm may be out of reach of the action of an antibiotic, rendering it resistant-in-vivo.

This idea is closely paralleled and supported by animal models of *Pseudomonas*-biofilm formation within sinus mucosa; where, *Pseudomonas*-biofilm required 400 times the concentration of tobramycin to be eradicated. Similarly, topical antibiotics are frequently ineffective at standard doses, which is often considered clinical proof of the non-bacterial etiology of CRS [2]. However, whether or not the proposed explanations are clinically valid for a non-bacterial mechanism of CRS remains a debatable issue and should be carefully evaluated in the context of published studies.

Now, we will review these questions in a step-by-step fashion: physiology, sinus microflora, and recent discoveries on the role of punch biopsy in CRS and its detection of deep-tissue sinus infection.

2. Is a healthy sinus cavity free of bacteria?

So, now the question is, is sterility synonymous with well-being? By using microbiome technology to detect difficult to culture bacteria, it was observed that bacteria are present in both healthy and diseased sinuses [3]. However, a pilot study on CRS patients actually discovered a significantly lower taxa of bacteria than their healthy control. So, at first glance it may look like the opposite, a lower number of bacteria is correlated with a higher likelihood of CRS. Does this point to a non-infectious etiology, then?

Importantly, these microbiome studies did not only reveal a difference in absolute number of bacteria, but in the content of the bacterial flora. Further analysis revealed that the bacterial taxa of the CRS patients was largely defined by relatively high numbers of unique single species, such as *Corynebacterium tuberculostearicum*, while microbiome analysis in the healthy control group showed a relative abundance of *Lactobacillus* spp., *Enterococcus* spp., and *Pediococcus* spp., but what does all of this mean in practice? These findings suggest that the etiology of CRS may hinge upon balance and equilibrium, and not at all upon bacterial load.

To investigate this hypothesis further, a study was designed on a mouse model of inflammatory sinusitis. This study revealed something extremely interesting. Sinus infection by *C. tuberculostearicum* led to hyperplasia [3], but not by itself. This hyperplasia only occurred with the administration of antibiotics. It looks that the use of antibiotics backfired. Upon antibiotic treatment the commensal bacteria of the healthy sinus cavity were eliminated, selecting for an antibiotic resistant strain *C. tuberculostearicum,* which became opportunistically pathogenic without a commensal microflora to police its growth. But what would happen if we rebalanced our flora? Could this process be reversed?

Interestingly enough, upon the addition of the *Lactobacillus sakei* the process reversed entirely, returning the sinus cavity to its natural state. The conclusion of this intriguing study was that antibiotic treatment of acute rhinosinusitis may be a "Catch-22", and although it may rid the body of the archetypal bacteria of acute

sinusitis, it may contribute to the future development of persistent sinusitis and/or CRS. These findings spark many questions and begin to steer the medical mind toward similar situations within different specialties.

Taking these discoveries of bacterial imbalance into consideration, it may be appropriate to draw analogies across specialties, and explore the realm of microbiotic imbalance in the upper respiratory tract as it relates to the female urogenital tract. We may be able to draw important conclusions in the pathogenesis of floral-imbalance-induced-CRS through the data analysis of microbiome studies in bacterial vaginosis (BV). BV is an infection in which anaerobic bacteria overgrow vaginal mucosa as a direct result of the, often inadvertent, elimination of Lactobacillus species [4]. These species naturally secret bactericidal H_2O_2 that kills anaerobic species—protecting the delicate membranes of the vaginal mucosa. Just as CRS, BV is frequently a recurrent process. However, a very simple single treatment with Metronidazole and/or recolonization with Lactobacillus often restores the health of mucosal membranes. It may be an oversimplification of a complex disease state, but the possibility of a similar etiology and therefore similar non-invasive cost-effective treatment is tantalizing.

2.1 Alternative thesis: CRS involves direct bacterial infection

As much evidence as there may be for the noninfectious hypothesis of CRS, there is just as much supporting the opposite. So where does the truth lie? As with most things in life, most likely somewhere in the middle. Either way, here we will explore the possibility of infectious CRS, and some of the most recent discoveries and theories behind it.

The noninfectious hypothesis of CRS is certainly a tantalizing one, but it is strongly challenged by the alternative hypothesis [5]. The authors of this chapter tend to lean toward the more active process of infection as the most common etiology, and we propose that the predominant progression of CRS directly involves bacterial infection. Furthermore, we believe that most of the theories and concepts pointing toward a noninfectious etiology, have been improperly evaluated and interpreted, and when reanalyzed tend to support an infectious cause of CRS.

Many parallels can be drawn between the two main arguments, one of which is the selection of microflora and or pathogens by inadequate or improper antimicrobial treatment. Some pathogens, such as *E. coli*, are able to both actively and passively elude destruction and clearance through multiple mechanisms, and current studies are pointing toward the fact that we as clinicians are inadvertently selecting for them. Through mechanisms similar to those described in the previous sections, incomplete treatment of bacterial sinusitis looks to be inducing the escape of such organisms from the reach of the immune system as a whole, as well as antibiotics specifically, by driving these microorganisms into our body's white cells or deep within the sinus mucosa. Simultaneously, the resultant disruption of the commensal bacterial community and mucosal integrity of the sinus leads to the formation of biofilm, which in our opinion is both a strong supplementary contributor and a direct cause of subacute and chronic infectious processes.

As discussed previously, a weakened microflora may contribute to the dysfunction of the sinus mucosa and disruption of the general local immune state. This, in combination with a slew of other complex factors, creates the perfect platform for the formation of a biofilm. Once formed, biofilm contributes to the failure of the antibiotic treatment by preventing any significant antibiotic penetration. Bacteria hiding within the structure of the film, become effectively invulnerable, when in any other situation they would be easily eliminated. As an added layer to the issue, superficial swab and culture of the mucosal surface may be completely misleading.

A positive bacterial culture of the biofilm showing in vitro antibiotic sensitivity may misdirect therapy entirely. Although you've confirmed in vitro effectiveness of therapy in regard to your surface culture, the chosen antimicrobial will most likely miss any pathogen lying deep within the film, interstitium, or intracellular space, rendering the chosen treatment clinically moot when used in-vivo.

Now put yourself in the shoes of the clinician. You've swabbed properly and sent for culture and sensitivity, then treated accordingly, but there is no clinical improvement in your patient's state of health. So, what do you do next? What conclusions may you draw? Such a cycle of negligible response to antibiotic therapy may inappropriately perpetuate the idea of pathogen independent CRS, when in reality it should raise questions of drug choice, administration, and adjunct therapy.

This thought process brings one particular example to mind and into question. Recently Antunes et al. showed that a *Pseudomonas* containing biofilm required 400 times the concentration of tobramycin to be eradicated than its control counterpart. While this finding became a warning, heeded by many, against the "ineffective" antibiotic treatment of biofilm, and even further, considered by some as the disproval of a bacterial origin of CRS, this may be a grave misunderstanding. Looking back to our foundations in pharmacology we must remember that many antibiotics have near-no activity on intracellular pathogens hiding within white or epithelial cells [6]. A fantastic real-world example of this being the aminoglycosides, like tobramycin, in particular.

In the world of microbiology the classic model for establishing intracellular infection in vitro is achieved by introducing an aminoglycoside to the infected epithelial cell culture. Once introduced the aminoglycoside does in fact eliminate the extracellular bacteria, however counterintuitively it actually positively selects for the intracellular pathogens. This pharmacological model is well established in many fields of microbiology and Infectious Disease research, often exploited in many classic experimental algorithms, across many specialties—except, it seems, for those in the area of ENT and CRS [6]. Such an oversight may have immensely detrimental effects on the validity of conclusions drawn from an otherwise extremely important finding.

The current paradigm of thought, that chronic rhinosinusitis has no direct infectious etiology, is further challenged by the clinical efficacy of treatment with Mupirocin lavage in CRS patients who had positive endoscopically guided cultures for *Staphylococcus aureus* [7]. In one recent investigation of CRS, 15 of 16 patients treated with Mupirocin-saline nasal irrigation, twice daily for 3 weeks, saw significant clinical improvement followed by a negative repeat culture for *S. aureus after* treatment. A follow-up double-blinded, placebo-controlled, study on 22 patients with CRS non-responsive to surgery demonstrated infection clearance in 8 of 9 patients after 1 month of mupirocin treatment [8]. Although the clinical improvement could be explained by the resolution of an acute exacerbation or the elimination of *Staphylococcus* super-antigens, these studies clearly challenge the current dogma of noninfectious CRS, and furthermore may directly support a pathogenic etiology of chronic sinusitis.

3. Finding *E. coli* in patients chronically ill with sinusitis

There is much left to understand and discover about the pathogenesis of CRS, from both the infectious and non-infectious standpoints, and it will be many years before we have a full grasp on the matter, if ever. In the meantime, many groups are publishing some interesting studies with very exciting results, and conclusions.

Recently, we have reported on the importance of proper biopsy in chronic sinusitis, and how such data may influence treatment and outcomes [5]. Interestingly, the predominance of specific pathogens differs in congruence with the method of sample collection. For instance, with swab and culture bacterial growth is most commonly dominated by the classic Gram-positives implicated in sinusitis. However, when samples are collected intraoperatively, by punch biopsy, the script is flipped and a predominance of Gram-negatives, including *E. coli*, is found [9, 10]. Therefore, logic dictates that if antibiotic therapy targets only the classic culprits of sinusitis, with Gram-negatives present, we may be achieving an incomplete or even inappropriate eradication of microflora and pathogens. This could explain and contribute to therapeutic failure in recurrent sinusitis, its transition into chronicity, and its interpretation as noninfectious [11–19].

In general, the presence of nonclassical pathogens such as Gram-negatives, namely *E. coli*, has been poorly documented. However, more and more groups are finding *E. coli* in patients chronically ill with sinusitis, and the question remains, "Are these contaminants, or are they true pathogens?". By definition if the latter is true, and these isolated *E. coli* are pathogenic, there should be evidence of their ability to produce disease, through the demonstration of various virulence factors [20–22]. Alternatively, if they are non-pathogenic and represent random contamination or commensal properties then there should be no evidence of genetic markers of virulence. So far, the nature of *E. coli* virulence and potential for cause of CRS remains largely unknown [23–26]; and while numerous studies have explored the role of virulence genes in chronic and recurrent GI and Urinary Tract infections, no such data has been available in regard to chronic sinusitis, until recently [5, 23–25].

We recently published the first report demonstrating an association between a highly pathogenic *E. coli*, chronic sinusitis, and the resolution of symptoms upon *E. coli* targeted therapy [5]. Our findings support the theory that a non-classical pathogen may lurk below the radar in non-pharmacologically-responsive CRS and would only be detected by the use of proper techniques. When we performed intraoperative biopsy and culture on our chronic sinusitis patients, followed by genetic analysis of virulence factors, we found the presence of a clearly non-random pathogenic *E. coli*. These *E. coli* carried genes encoding multiple virulence factors, granting them the ability to produce biofilm. Upon catering our antibiotic therapy to each patient's biopsy and culture, we were able to obtain long term resolution of symptoms. These results, as a whole, lead us to believe that there very well may be genetic uniformity amongst *E. coli* isolated from patients suffering from CRS. These are not randomly occurring colonizers, or opportunistic colonizers.

3.1 Genetic analysis discover highly pathogenic *E. coli* in CRS

Generally, *E. coli* can be grouped genetically. Commonly, commensal *E. coli* are placed in phylogenetic groups A or B1, while pathogenic isolates are grouped in B2 or D [27, 28]. Upon in-depth genetic analysis of these patients, we found that 77% of isolated *E. coli* belonged to the pathogenic phylogenetic group B2, while only 23% belonged to the commensal B1 group [5]. This is concerning, not only due to shear pathogenicity, but the numerous dangerous traits associated with the bacteria in group B2. *E. coli* within this group are commonly capable of iron acquisition, granting them the ability to invade cells and multiply intracellularly and even within the blood stream. This makes members of the phylogenetic group B2 particularly toxic—contributing greatly to the inflammatory process and tissue injury of chronic infection.

Diving deeper, we find that these *E. coli* share many attributes with extraintestinal-pathogenic-*E. coli*. However, other features suggest that they might

be specifically pathogenic to sinus tissue [29, 30]. One example of this tissue specificity is the *sfa* adhesin gene, normally associated with meningitis [31]. It is no stretch of the imagination to think that two anatomical structures, in such close proximity as the sinuses and the meninges, may be invaded through similar cytophysiological pathways. Especially by multiple bacteria with a generally enigmatic local affinity, whom happen to share virulence factors. This association needs to be explored further, but for now it is exciting to think that we may be able to better explain local affinity (tropism) to the head and neck through such mechanisms.

Other highlights of this genetic analysis include the finding of both the *hly*A and *usp* genes. These genes encode for the formation of bacterial toxins and are only present in highly virulent bacterial strains. In this patient group, they were present in over 70% of the *E. coli* isolates. By the other side of the same token, isolates were found to lack *dra*/*afa* adhesins, which are implicated in chronic and recurrent UTI and gestational pyelonephritis. Such a bold distinction may further support the idea that these isolates represent a novel subset of *E. coli*, with a unique genome, and possibly even tropism for the mucosa of the paranasal sinuses [32].

Unexpectedly, there were three genes that were found in 100% of isolated *E. coli* from our patients. These genes were agn43, fimG/H, and fyuA [33–36]. All of which are associated with UTI, and play a role in biofilm formation: agn43 assists in *E. coli*-*E. coli* self-adhesion, fimG/H codes for type 1 fimbriae allowing for *E. coli* to aggregate and adhere to mannose receptors on mucosal membranes, while fyuA assists in iron scavenging and is often implicated in septicemia.

Possibly most shocking of all is that, when analyzed via a pseudo-phylogenetic tree, these genes had closely associated genetic loci, which signifies a very probable cooperation amongst them. This raises a very concerning question. Could these three genes, working together, code for some sort of "super biofilm"? This could explain how and why so many mono-therapies and empiric treatments fail to yield any improvement in patients who suffer from CRS. A biofilm of this nature would in essence be both a defensive and offensive fortification for the pathogen. A sort of moated fortress with large watch towers, never allowing antibiotics or the host immune system to penetrate it, creating an ideal environment for lingering infection and chronic inflammation.

The resolution of CRS—following FESS, intra-operative biopsy, and antibiotic therapy targeted toward the resultant culture and sensitivity—is highly suggestive of *E. coli*'s strong contribution to the disease state of this patient population. Undoubtedly, this all hinges upon the genetic makeup of these bacteria, and the fact that their genetic code is set for pathogenesis by carrying the information necessary to express virulence factors, including the production of biofilm [37, 38]. Further deductive reasoning leads us to believe that, *E. coli* is a generally undermined and undetected etiologic factor of CRS and a major contributor of inflammation in these patients. Whether or not the presence of biofilm producing *E. coli* is directly responsible for the poor therapeutic response, after FESS alone, will continue to be explored in more detail [39–42].

As with all, there are limitations to this study that should be recognized. For example, the present investigation was a study of healthcare-seeking adults; only including those that were *E. coli* positive, raising a very important question. To what extent do these results apply to the general population? Next, due to the resolution of symptoms and subsequently negative cultures, along with consideration for cost and patient comfort, we did not perform a follow-up punch biopsy and analysis.

4. Future studies

Future studies should investigate the role of important factors in human health, such as the effects of hormones, like estrogen and progesterone, on chronic sinusitis [43, 44]. Which are known to control the immune system. We must also further explore the effects of obesity and diabetes mellitus on the risk of infection, as well as the relation of anatomical structure and function on the role of bacterial colonization. All of these factors change the expression of mucosal receptors, which is often exploited by various bacterial species, easing colonization and/or infection [32, 45].

In regard to the possibility of hormonal control of the immune system of the upper respiratory tract, we speculate that the head and neck may be analogous to the female urogenital tract. Wherein sensitivity to infection rises during the secretory and proliferative phases of the menstrual cycle [44]. Exploring further in this direction, the anatomical structure of the upper respiratory system appears to resemble the urogenital tract in many ways. Within the urinary tract an ascending infection begins with the colonization of vaginal introitus, before migrating proximally [21]. Genital colonization with *E. coli* may progress to infection of the urethra, which then ascends to the bladder, and further up to the kidneys via the ureters. This is made possible through the exploitation of tissue specific receptors to which bacteria anchor via specialized adherence structures called fimbriae [46, 47]. This process of bacterial migration results in acute pyelonephritis, often followed by chronic kidney infection with even further spread to the blood stream and resultant urosepticemia [48–50]. Similarly, we implore the medical community to consider the oropharynx, nasal cavities and paranasal sinuses as another anatomical system conducive to similar ascending infections [21, 45]. Beginning with the colonization of the oral and nasal cavities, bacteria may migrate "upstream" to the maxillary and then frontal sinuses, as well as others along the way via similar receptor-ligand interaction. All of which may be complicated by anatomical variation, anomaly, and pathology, ranging from nasal polyps and turbinate hypertrophy to choanal atresia and structural issues of the sort. These problems may be caused by everything from allergy to genetic mutation—resulting in a slew of aggravating factors, expression of specialized epithelial cell types, and tissue receptors—all contributing to the risk of chronic rhinosinusitis.

5. Considerations and conclusions

All things considered, chronic sinusitis remains a bit of an enigma. However, the more we explore the better we will be able to understand the complex multifactorial etiology that's sure to be lying below the surface. That being said, we've learned and discovered so much as a medical community in recent years, we believe there is no better time than now to begin making the most of it.

Keeping in mind the most recent publications and studies, we urge physicians to consider intraoperative punch biopsy on all of their chronic sinusitis patients [5]. Biopsied samples should be homogenized, and host cells should be exposed to membrane destabilizing buffers, lysing them and releasing trapped intracellular bacteria, allowing for the most thorough culture and analysis. Considering that a direct culture of the sample on solid media may not always be fruitful, we recommend the use of liquid media which may better allow the growth and detection of bacteria, even at low numbers. Next, cultures should be tested individually for antibiotic sensitivity and a personalized therapy should be prescribed to each individual patient. Finally, we also urge you to consider sending bacterial isolates for

genotyping [35, 48, 51–57]. Through doing so we can finally stop asking of ourselves if we're fighting the right bug and know for certain that if it expresses virulence it is part of the problem.

We believe that through the use of these methods we may be able to better differentiate between specific etiologies of CRS within our patients, and through doing so we hope that we can avoid inappropriate antibiotic use, repeat surgeries, and prolonged treatment. Giving our patients their health and quality of life back faster and more effectively than ever.

In conclusion, we hope that personalized medicine may one day overshadow empiric treatment in chronic sinusitis, and all of our patients will be catered to with the utmost efficiency. With further testing and experimentation, we may be able to someday use vaccines or bacterial adhesion blockers to augment our therapies [30, 58]. Using genotyping to pick and choose what's best for our patients, we may be able to target specific virulence factors that allow such abilities as iron binding or cellular adherence, effectively rendering those bacterial invaders non-pathogenic. Through interdisciplinary exploration we may be able to adopt and adapt what other specialties have learned and use it to restore mucosal and micro-floral balance, and band together to fight bacteria and biofilm together as a medical community.

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Conflict of interest

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