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The sinonasal bacterial microbiome in health and disease

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Abstract

Purpose of review—The development of culture-independent bacterial DNA sequencing techniques and integration into research practice has led to a burgeoning interest in the microbiome and its relevance to human health and disease. Introduction into the study of chronic rhinosinusitis in the past few years has shaped current thinking on the role of bacteria in the disease process.

Recent findings—Rich and diverse populations of bacteria inhabit the sinonasal cavity at all times. Decreased bacterial richness and diversity may be associated with disease state and outcomes.

Summary—Although there is much to be explored, the sinus microbiome appears to have potentially promising roles in many aspects of sinus health and disease.

Keywords

bacteria; chronic rhinosinusitis; culture-independent microbiology; microbiome; sinusitis

INTRODUCTION

Chronic rhinosinusitis (CRS) is a common, chronic inflammatory disorder of the paranasal sinuses. Multiple host and environmental factors have been implicated in the development of CRS; however, understanding the role of microbes has become increasingly important. The simple concept of a host interacting with a single pathogen has been replaced by a more complex combination of relationships between communities of microbes among themselves and the host. The microbiome is the potentially diverse community of microbiota existing in a delicate symbiotic relationship within a human microenvironment. As the anatomic region responsible for initially filtering the inspired external environment, the warm and moist sinonasal cavity is, not surprisingly, colonized by a high burden of microbes. Our understanding of this complex human–microbial community relationship in the sinuses has

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Conflicts of interest

There are no conflicts of interest.

grown significantly in recent years. Paralleling groundbreaking research in the gastrointestinal tract, the native microbial community of the paranasal sinuses likely contributes to maintaining a healthy state of the sinonasal mucosa, whereas dysbiosis – disruption of this balance – may contribute to inflammation through any number of mechanisms [1, 2]. However, much investigation is still needed in this area to understand the composite role of bacteria and other microorganisms in health and disease states, prior to initiation of a carefully prepared and rational treatment aimed at microbiome manipulation. This article aims to review our current understanding of the bacterial communities inhabiting the paranasal sinuses in both healthy and diseased states, and to explore the many challenges to studying these microbiota.

The important causal effect of microbial community dysbiosis in local and systemic inflammatory processes has been illustrated through extensive study of the gut epithelium in allergic and inflammatory disorders. Commensal gut microbiota promote immunologic development and maturation, direct immune homeostasis, and influence susceptibility to inflammatory and/or allergic disease [3–5]. A stable, diverse microbiome contributes to fortification of the epithelial barrier, development of innate and adaptive immune properties including immunoglobulin production [6, 7], induction of regulatory T cells [8], nutrient metabolism [9], and can stimulate formation of the mucus blanket [10]. Hence, maintenance of a diverse, healthy consortium of commensal organisms promotes many beneficial functions for the sinus, as well as serving the critical function of pathogen exclusion. Commensal microbes can compete with pathogens by acting as simple niche fillers or through active direct competitive inhibition. For example, a negative correlation between *Staphylococcus epidermidis* and *S. aureus* has been observed in the nasal cavity [11], possibly because certain strains of *S. epidermidis* produce a serine protease that directly inhibits *S. aureus* biofilm formation [12]. Recently, Yan *et al*. [13▪] identified *Corynebacterium pseudodiphtheriticum* as a negative predictor of *S. aureus* in the sinonasal cavity and demonstrated an antagonistic effect *in vitro* using a bacterial coculture assay. Similarly, Bessesen *et al*. [14], observed negative associations between methicillin-resistant *S. aureus* and a variety of microorganisms, including *Streptococcus mitis*, in the anterior nares of hospitalized patients.

These concepts logically lead to the potential therapeutic value of prebiotic or probiotic therapy. Well tolerated and therapeutically effective provision of beneficial microbes to a patient first requires a thorough understanding of the patient-specific pathophysiologic process to appropriately select directed therapy to achieve a beneficial change. Blind introduction of ‘good bacteria’ could result in any number of possible effects, given the myriad, largely uncharted, relationships between bacterial products and human physiological, metabolic, and immunological processes. In a heterogeneous disease process such as CRS, this is likely to result in a type II error (failure to reject a false null hypothesis), as has been the case in prior study for allergic rhinitis [15]. Interestingly, it has become recently apparent that early and/or frequent antibiotic administration results in deleterious effects even in a much delayed fashion, beyond the initial microbiome disturbance known to occur [16–19, 20▪].

CURRENT SINUS MICROBIOME LITERATURE REVIEW

The prior notion that the paranasal sinuses were sterile in the healthy state has been largely abandoned, as the presence of viable bacteria in healthy sinuses is now well documented. Early studies utilizing culture-based microbial detection have now been replaced in the research setting with detection and identification of microbes using nucleic acid-based methods, which appear to be less biased and more sensitive than traditional culture [21, 22▪]. Using these molecular methods, numerous studies in recent years have described the rich and complex bacterial communities present in the paranasal sinuses of healthy adults, and documented a surprising preponderance of anaerobic organisms [23–25, 26▪, 27▪]. Also of note, the total amount of bacteria present in healthy and diseased sinuses appears to be similar, meaning that it is likely not the case that chronically diseased sinuses simply harbor more bacteria [28, 29▪].

Yan *et al*. [13▪] recently examined the sinonasal microbiome of 12 healthy adults, surveying the anterior nasal cavity, middle meatus, and sphenoethmoid recess over 3 weeks. The authors noted a temporally stable, highly individualized baseline microbiome, with some differences in microbiota between the anterior nares and deeper anatomic subsites. Although a thorough comparison among individual sinuses has yet to be published, these findings highlight two points: in healthy study participants, the sinonasal microbiome is relatively stable, as has been noted in previous study of the anterior nares [11], and the microbiome is highly individualized even in health. Recent large-scale studies of the human microbiome have discovered that many microbial community structures may promote health, despite the significant interpersonal variability, indicating that community function may be more important than the individual community members [30▪]. Another study that examined middle meatus swabs from 28 healthy study participants found that many harbored respiratory pathogens at low abundance, suggesting that pathogenic bacteria may be transient or permanent members of the healthy microbiome at relatively low amounts, when kept in check by a diverse healthy microbial community [27▪]. This finding suggests that an initial perturbation of the microbiome is required to remove the community check on a pathogen and allow for a ‘bloom’ that initiates a cascade of processes resulting in disease.

Recent review articles have thoroughly summarized the literature on microbial communities present in healthy and chronically diseased sinuses [31, 32]. There is no current consensus on the most common bacteria present in the healthy or diseased state, and there is no clear ‘causative’ or ‘protective’ single organism. The bacterial communities identified in prior studies have varied, likely because of the heterogeneous nature of the disease and different patient populations, but also because of variations in sampling techniques, laboratory protocols, bacterial primer selection, sequencing methods, and data analysis pipelines, making cross-study comparisons extremely difficult. Even so, a few patterns do emerge. *Propionibacterium acnes, S. epidermidis, S. aureus,* and *Corynebacterium* spp. have been frequently identified as prevalent and abundant species in healthy controls [23, 25, 26▪, 27▪]. Organisms such as *S. aureus* and coagulase negative staphylococci may behave in a commensal or pathogenic fashion based on strain, bacterial gene expression, environmental conditions, and perhaps based on surrounding microbial interactions.

Just as in the healthy state, there is not a universally accepted composition of the microbiome in CRS. However, some commonalities have been identified in multiple study findings. Although hundreds of bacterial species have been identified in CRS, anaerobes and *S. aureus* are often found to be significantly more prevalent and abundant in CRS versus healthy controls [23, 25, 26▪, 27▪, 33▪]. As mentioned earlier, despite this increased abundance of pathogenic bacteria, several groups have reported no difference in the overall quantity of bacteria present in CRS patients versus healthy patients [24, 27▪, 33▪]. Not surprisingly, reduced species richness and diversity is often found in CRS [23, 24, 33▪], further supporting the hypothesis that a shift in the bacterial community, rather than an influx of pathogenic bacteria, is associated with CRS. Conceptualizing these communities from a metagenomics and metatranscriptomics perspective, it may be that the function of the microbial community as a whole is the relevant determinant for health or disease.

As detailed study of the sinus microbiome is in its infancy, longitudinal studies of individual host and environmental influences have not yet been performed. However, cross-sectional analysis of cohorts of diseased patients have identified the presence of asthma and purulence [29▪], or a history of tobacco use [34], as factors that are associated with statistically different bacterial communities. Interestingly, in the first study, a number of patient-specific factors were examined, and the use of topical saline or topical intranasal steroids, or the presence of nasal polyps was not a predictor of altered microbiome composition. Similar findings were noted in a cross-sectional cohort of postoperative CRS with polyp patients, where the use of saline irrigations with or without budesonide was not found to influence the sinus microbiome [35]. To date, properly designed studies to evaluate for the effect of topical therapies on the microbiome have not been performed, so no real conclusions can be made. The effect of cigarette smoke and airway irritants, such as pollution, on bacteria has been studied in other contexts and it is not surprising that smokers appear to have unique bacterial signatures within the sinuses. A preliminary cross-sectional examination found that ‘ever-smokers’ – those with a history of either current or former smoking – differed from nonsmokers, indicating that the effect of cigarette smoking may result in long-lasting changes to the airway microbiome [34]. This interesting finding requires follow-up investigation, as well as expansion to those exposed to secondhand smoke.

Mounting evidence in humans suggests that a more diverse microbiome is associated with improved health outcomes and less disease burden across a broad range of abnormalities [36, 37]. For example, studies of the gut microbiome suggest that antibiotic administration can result in decreased diversity, which in some patients may be prolonged [16, 18, 38]; these patients are at increased risk of potentially life-threatening *Clostridium difficile* infections [39–41]. Similarly, a recent study has reported that patients with more diverse sinonasal microbiomes have better postsurgical outcomes [29▪], establishing that the microbiome can serve at least as a disease modulator. In this study, the authors found that greater baseline microbial diversity in the middle meatus, which was characterized by a higher abundance of corynebacteria, was associated with more favorable postsurgical endoscopy scores and less need for antibiotics or procedural intervention at 6 months of follow-up. Early evidence has also shown that treatment interventions including surgery, antibiotics, and sinus rinses have the ability to alter the bacterial community and even

ultimately increase diversity after an initial drop in the complexity of the microbiome [20▪, 42▪]. In summary, a diverse assemblage of microorganisms colonizes the sinonasal cavities in the healthy state and perturbations in the types and quantities of microorganisms making up these communities have been described in multiple studies of CRS. It is likely that the magnitude and quality of the dysbiosis that arises in an individual's sinonasal cavities can directly impact their disease severity and outcomes.

CHALLENGES

Bacteria have been the most studied of the microbes in relation to human health and disease; however, there is growing evidence that fungi, viruses, and bacteriophages may also contribute to the 'metaorganism.' Many studies have shown no difference in fungal prevalence between CRS and controls, and although findings have differed, the fungal microbiome may be more important for CRS with nasal polyps or other phenotypes of CRS than for CRS without nasal polyps [26▪]. Although no studies to date have thoroughly profiled the viral or bacteriophage populations present in the paranasal sinuses, evidence suggests that upper airway rhinovirus infection can alter the nasopharyngeal microbiome [43]. The relative absence of fungal and viral study is likely a lag behind the bacterial microbiome research explosion, as the initial microbial detection techniques focused primarily on the numerically dominant bacteria. As methods for designing reliable primers and comprehensive sequence databases are now being validated for study of fungi and viruses, we expect that a more robust understanding of the microbial diversity of the sinonasal cavities will emerge.

Sampling technique is also somewhat variable between studies, making cross-study meta-analyses a challenge. It appears that the anterior nasal cavity microbiome differs from the middle meatus and sphenoethmoid recess [13▪], but the optimal site of sampling has yet to be agreed upon. The middle meatus is frequently used as a representative sampling site for the deeper sinuses, given its high agreement in culture comparison studies with the maxillary sinus [44], likely resulting from its position within the anterior ethmoid drainage pathway of the maxillary, anterior ethmoid, and frontal sinuses [45]. Owing to its relative ease of access in the clinical and research setting, and presumed similarity to deeper sinuses, this area has been used for sampling in numerous studies to date. Furthermore, surface bacteria far outweigh intramucosal bacteria, which have recently been documented to occur in sinus disease states at a low relative amount. It is unclear if biopsies of tissue are required to provide a more nuanced means of sampling microbes or if aggressive surface swabbing is sufficient [46▪, 47].

An additional complication of microbiome studies is the reliance on identification of bacterial DNA and PCR assay, because PCR amplification of bacterial DNA may be from inactive or dead bacteria, or cells in the process of phagocytosis and DNA digestion. We initially assessed bacterial DNA obtained from surface swabs of the middle meatus in parallel using quantitative PCR and culture in nonspecific media and found that DNA counts amplified with panbacterial primers used in bacterial microbiome study correlated with colony counts obtained by culture (Fig. 1 [48]). This suggests that much of the bacterial DNA identified by surface swab using culture-independent methods is live and functional.

Although primer sets, sequencing technology, sequence databases, and tools for sequence alignment and statistical analysis vary, some common concepts can be examined. Specifically, it appears that richness (i.e., number of species present) and diversity (i.e., broad and even distribution of numerous organisms) are relevant measures.

Although bacteria are certainly easier to study at this time, this does not necessarily make them more important in disease pathogenesis. Current technology has allowed us to define bacterial populations with DNA-based detection methods such as 16S ribosomal RNA (rRNA) gene sequencing; however, enumerating the bacterial DNA and genes present is only the initial step, as we ultimately desire to understand activity and function. The real question is not simply what microbes are there, but ‘what are they doing there?’ Thus, addressing microbial community functionality through other Omic technologies such as metagenomics, metatranscriptomics, metaproteomics, or metabolomics, is critical as there are likely many ‘normal’ communities of microbes that can achieve the same healthy symbiosis with the host. Associations between bacterial communities and disease or subject metadata can be found, but are these changes an active part of the disease process, or simply a by-product? It remains a challenge to determine whether microbiome alterations initiate or propagate disease, can modulate the efficacy of therapeutic intervention, or are a by-product of the disease process or medications commonly administered to these patients [2]. And, if they are an active part of sinus physiology, how do they function, and how can we benefit from this understanding?

CONCLUSION

Although we acknowledge the high interpersonal variability in the makeup of the sinonasal microbiome and that host and external factors may influence bacterial community structure and function, it is very possible that the microbiome can influence both the natural history of a disease and its therapeutic outcomes. Many challenges remain in determining the optimal manner for research examination; however, the initial studies suggest potential for value in the nascent field and consideration for relevance in global epithelial function.

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KEY POINTS

- Rich and diverse populations of bacteria are present in the sinonasal cavities, even in the healthy state.
- Culture-independent detection has led to an appreciation of the abundance of anaerobic organisms in the sinuses.
- Bacterial richness and diversity may play a role in the maintenance of health, development of disease, and determination of treatment outcome.
- Future study will include the potential for fungi, viruses, and bacteriophages to influence the functional activity of the microbiome.

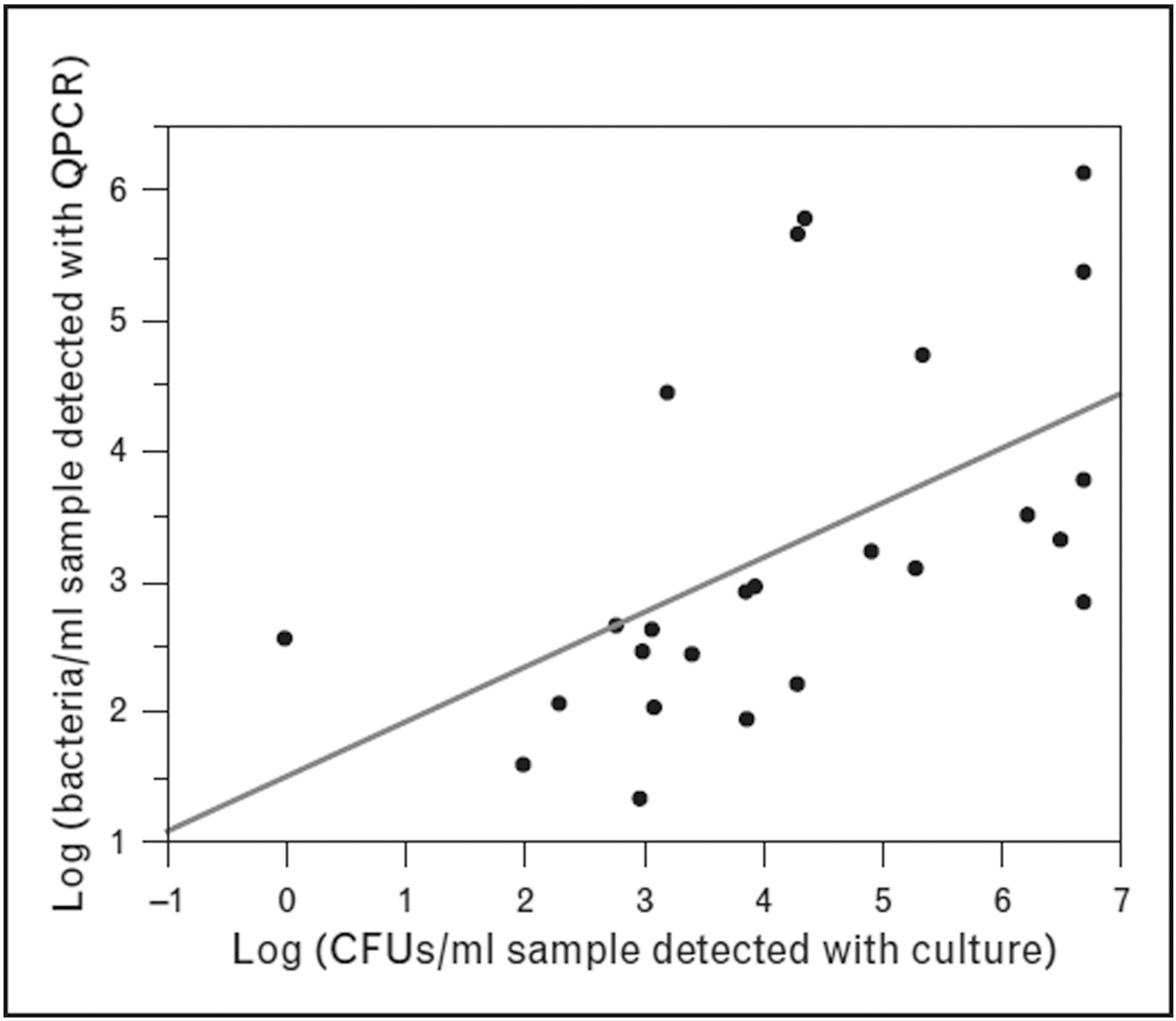

FIGURE 1.

Total bacteria/ml in each of 25 sample swabs obtained from 14 CRS patients and nine healthy control study participants, as determined by counting colonies grown with traditional culture using Amies media (BD Diagnostic Systems, Franklin Lakes, New Jersey), and with culture-independent [48] QPCR (line of fit $r^2 = 0.292$, $P = 0.0053$ using paired *t*-test and multivariate linear regression). Each point represents an average of colonies grown in duplicate culture and DNA amplified with triplicate QPCR. QPCR, quantitative PCR.