sinusitis

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Article

Contemporary Update on the Microbiology of Paranasal Sinusitis

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Abstract: Background: Sinusitis, whether acute or chronic, is likely due at least in part to disruptions in the microbiota of the paranasal sinuses. Sinus cultures are often employed to guide medical treatment. Objective: To quantify the contemporary microbiology of the paranasal sinuses and better understand the utility of paranasal sinus cultures. Methods: We identified patients from 2018 to 2019 with sinus cultures taken by an otolaryngologist in the outpatient setting in our healthcare system with a concurrent diagnosis of acute or chronic rhinosinusitis. These cultures were analyzed based on their culture type and result. The most commonly isolated bacteria were further analyzed by species; *Staphylococcus* resistance patterns were analyzed as well. Results: A total of 2302 culture samples were collected: 2012 (87%) bacterial, 287 (13%) fungal, and 3 (0.1%) mycobacterial cultures. The results of more than half (1142, 57%) of these bacterial cultures were positive for a named genus, while those of 592 (29%) were positive for normal sinus flora and 16 (0.8%) for normal oral flora, and those of 183 (9%) showed no growth. The results of another 79 (4%) bacterial cultures were positive for unnamed bacteria, which were not further classified (e.g., Gram-negative rods). Of the positive bacterial cultures with named genera, the most common genera identified was *Staphylococcus* (383, 34%). Of these, the most common species of *Staphylococcus* was *S. aureus* (311, 81%), 42 of which (14%) showed methicillin resistance (MRSA). Of the fungal cultures, 265 (92%) resulted in no growth, and all three mycobacterial cultures showed no growth. Conclusions: In contrast to fungal cultures, the majority (57%) of sinus bacterial cultures showed positive results, with the identification of a named genus, highlighting the potential utility of this assay in guiding medical therapy.

Keywords: sinusitis; rhinosinusitis; chronic rhinosinusitis; medical therapy of chronic rhinosinusitis; acute sinusitis; *Staphylococcus aureus*; MRSA; sinus culture; *Propionibacterium*; *Haemophilus*

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1. Introduction

Rhinosinusitis, whether acute, recurrent, or chronic, is thought to be at least in part characterized by the disruption of the microbiological landscape of the nasal and sinus cavities. This landscape consists of the natural microbiota of the sinuses and its interactions with the surrounding immune system. The types of disruptions that occur can vary widely and may have implications for treatment approach. For example, in the case of acute sinusitis, there are often changes within the microflora composition through new bacterial or viral pathogens or through an imbalance of naturally occurring sinus flora [1]. This latter process, where naturally occurring bacteria may become more pro-inflammatory or invasive, has been termed dysbiosis, and presents a more nuanced picture in patients presenting with acute on chronic changes in symptoms [1,2]. Moreover, patients with unresolving sinus symptoms after 12 weeks that suffer from chronic rhinosinusitis (CRS) may also have underlying immune system disruptions in addition to—or even triggered by—sinus dysbiosis [1]. This is evidenced by studies demonstrating that nasal lavage samples from patients with CRS stimulate IL-5 activation in peripheral leukocytes from healthy controls [3,4].

While many classes of disruptions (e.g., bacterial, immunological, etc.) have been described, there is currently a poor understanding of the relationship that exists between these disruptions and a clinical presentation of rhinosinusitis [5]. To that end, characterizing nasal microbiology is an essential step to understand the clinical significance of nasal bacterial composition. Furthermore, understanding this relationship may shed light on the utility of sinus nasal cultures and subsequent antibiotic treatment for rhinosinusitis.

Previous studies have described the microbiology of the paranasal sinuses of both healthy patients and patients with CRS: paranasal sinus cultures from both groups of patients most commonly grow *Staphylococcus*, *Propiononibacterium*, *Corynebacterium*, and *Streptococcus* species [6–9]. Studies comparing healthy controls versus patients with CRS note variations in both certain types of bacteria present on sinus cultures between the two groups—like higher rates of *Haemophilus* and *Escherichia coli* [10] as well as *Staphylococcus* [11] in patients with CRS vs. healthy controls—as well as reduced bacterial diversity in patients with CRS [12]. However, among patients with CRS, there still is significant bacterial diversity, especially between patients of certain phenotypes, like those with CRS with purulence or CRS with asthma [13].

Most studies, however, are limited by their sample size and are confined to a single institution [7,8,13], limiting their generalizability. We sought to analyze a large microbiological dataset corresponding to sinusitis in a large metropolitan healthcare system among otolaryngologists practicing in multiple different institutions to obtain a contemporary update on the microbiology of sinusitis. Such data would offer insight into the current microbiological landscape as well as provide information on the utility of sinus culture data in the management of acute and chronic sinusitis.

2. Materials and Methods

We conducted a retrospective analysis of paranasal sinus cultures collected during calendar years 2018 through 2019 within our healthcare system. This study was approved by the Committee on Clinical Investigations of our institution (Mass General Brigham). All sinus culture specimens collected at an outpatient otolaryngology visit corresponding to a visit diagnosis of acute or chronic sinusitis were extracted from our clinical patient data registry. Cultures were processed in CLIA-certified laboratories across our hospital system and processed via standard institutional protocols.

All bacterial, fungal, and mycobacterial paranasal sinus cultures collected during this time frame were included in analysis. Cultures were analyzed based on their culture type (bacterial, fungal, mycobacterial) and culture result (no growth vs. named bacteria or fungal/mycobacterial genera). The most common bacteria were then analyzed at the species level as well.

Additional subgroup analyses were conducted for *Staphylococcal* species and in particular for *Staphylococcus aureus*. All *Staphylococcus aureus* cultures were sent for sensitivity testing. In the interest of brevity, we excluded in our tables all bacteria constituting less than 0.5% of the subset (e.g., less than 0.5% of cultures resulting in a named bacterial genera).

3. Results

A total of 2302 cultures were collected during this time period. Of these, 2012 (87.4%) were submitted as bacterial cultures, 287 (12.5%) were submitted as fungal cultures, and 3 (0.1%) were submitted as mycobacterial cultures (Table 1). As noted in Table 1, 61% of bacterial cultures were positive for bacterial growth, whereas 39% exhibited no growth or normal flora.

Table 1. Sinus cultures by type and associated positivity rates.

Type of Culture and Isolate Type	Cultures Results (n)	Percentage of Culture Type
Bacterial (N = 2012)		
Named bacteria identified (positive cultures)	1142	56.8%
Unnamed bacteria identified *	79	3.9%
No growth	183	9.1%
Normal sinus flora	592	29.4%
Normal oral flora	16	0.8%
Fungal (N = 287)		
No growth	265	92.3%
Growth without genus result	19	6.6%
Growth with genus result	3	1.1%
Mycobacterial (N = 3)		
No growth	3	100.0%

Description: Number of paranasal sinus cultures by media type and associated positivity rates. * Unnamed includes Gram-negative rods, Gram-positive rods, etc.

Of the fungal cultures, 92% had no growth; of the fungal cultures with growth, genus results were available for three (one each of *Candida*, *Penicullum*, and *Scedosporium*). All three mycobacterial cultures were negative.

Of the positive bacterial cultures, there was a mix of cultures from bacteria that were aerobic bacteria vs. facultative or obligate anaerobic bacteria: about half were aerobic (533, 47%), a third facultatively anaerobic (378, 33%), and then the remaining 231 (20%) obligate anaerobes. These bacteria cultures consisted of slightly more Gram-positive bacteria than Gram-negative (644 cultures of Gram-positive [56%] versus 498 Gram-negative [44%] bacteria), and spanned 32 genera, as shown in Table 2.

Table 2. Frequency of genera of bacteria among positive cultures.

Bacteria Genus	Number of Cultures	Percentage
Staphylococcus	383	33.5% *
Propionibacterium	145	12.7%
Haemophilus	101	8.8%
Pseudomonas	94	8.2%
Streptococcus	83	7.3%
Klebsiella	45	3.9%
Prevotella	41	3.6%
Escherichia	35	3.1%
Moraxella	31	2.7%
Serratia	29	2.5%
Fusobacterium	26	2.3%
Enterobacter	24	2.1%
Stenotrophomonas	17	1.5%
Peptoniphilus/Peptostreptococcus	15	1.3%
Proteus	15	1.3%
Citrobacter	9	0.8%
Corynebacterium	8	0.8%
Acinetobacter	6	0.5%
Enterococcus	6	0.5%

Description: Number of paranasal sinus cultures of each bacterial genus. * Note these percentages use the total number of cultures resulting in named bacteria genera (1142) as denominator.

Of the *Staphylococcus* cultures, 325 (85%) had speciated results, the vast majority of which were *Staphylococcus aureus* (311 cultures, 96%), and only a minority of which (42, [11%]) showed methicillin resistance (Table 3). Many of the other commonly found bacteria (*Propionbacterium*, *Haemophilus*, *Pseudomonas*, *Streptococcus*, *Klebsiella*, *Prevotella*) did have speciation results available and are shown in Table 4.

Table 3. Frequency of *Staphylococcus* species within cultures (n = 383).

***Staphylococcus* Species**	**Number of Cultures**	**Percentage**
Staphylococcus aureus—MSSA	311	81.2%
Staphylococcus aureus—MRSA	42	11.0%
Staphylococcus epidermidis	6	1.6%
Staphylococcus lugdenesis	3	0.8%
Staphylococcus intermedius	3	0.8%
Staphylococcus cohnii	1	0.3%
Staphylococcus saprophyticus	1	0.3%
Staphylococcus, not speciated	58	15.1%

Description: *Staphylococcus* sinus cultures of each species as well as those demonstrating methicillin resistance. MSSA: methicillin-sensitive *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*.

Table 4. Frequency of species within common non-*Staphylococcus* bacteria within cultures.

Bacteria Genus and Species	**Number of Cultures**	**Percentage within Genus**
Propionibacterium	145	
Propionibacterium acnes	132	91.0%
Propionibacterium granulosum	13	9.0%
Haemophilus	101	
Haemophilus influenzae	88	87.1%
Haemophilus, not speciated	13	12.8%
Pseudomonas	94	
Pseudomonas aeruginosa	92	97.8%
Pseudomonas stutzeri	1	1.1%
Pseudomonas, not speciated	1	1.1%
Streptococcus	83	
Streptococcus pneumoniae	46	55.4%
Streptococcus intermedius	2	2.2%
Streptococcus pyogenes	1	1.2%
Streptococcus, not speciated	35	42.2%
Klebsiella	45	
Klebsiella oxytoca	22	48.9%
Klebsiella pneumonaie	21	46.7%
Klebsiella ozaenae	1	2.2%
Prevotella	41	
Prevotella oralis	10	24.3%
Prevotella melaninogenica	7	17.1%
Prevotella loescheii	5	12.2%
Prevotella intermedia	4	9.8%
Prevotella oris	4	9.8%
Prevotella denticola	3	7.3%
Prevotella bivia	3	7.3%
Prevotella buccae	2	4.9%
Prevotella, not speciated	3	7.3%

Description: Number of paranasal sinus cultures of non-*Staphylococcus* named genera.

4. Discussion

Our study provides a contemporary detailed analysis of the sinus microbiology in a broad population of patients across our healthcare system. The large majority of cultures taken were bacterial (2012 of 2302, 87%), and importantly, more than half (57%) of these bacterial cultures were positive, identifying a named genus as a target for potential medical therapy and thus supporting the utility of paranasal sinus cultures as a means to guide antibiosis. The use of antibiosis in CRS, however, is controversial: while prior guidelines did recommend culture-directed antibiotic treatment for CRS exacerbations [14,15], newer guidelines have taken a more nuanced approach, recommending antibiotics only in certain circumstances, like the acute presentations of rhinosinusitis or chronic symptoms in a patient with immunodeficiency [16]. Additionally, in patients who have undergone surgery, infections after endoscopic sinus surgery have been shown to arise not from colonizing

bacteria but instead from de novo bacteria, necessitating cultures to guide antibiosis [17]. In fact, there is evidence of improved patient quality of life after endoscopic surgery with antibiosis directed by intraoperative cultures [18], although another study suggested these cultures may not be cost effective, requiring a cost of USD 4300 for one culture to change management for a patient [19].

The use of sinus cultures to guide antibiosis assumes a pathogen that can be targeted medically can be identified with this assay. However, given that acute or chronic sinusitis can in part be characterized not just by the introduction of external pathogens but also the overgrowth of naturally occurring pathogens, in conjunction with possible immune dysregulation, the interpretation of sinus culture results can be difficult, as these alone do not holistically describe a patient's sinus microbiological environment. Our data demonstrate this diagnostic challenge: the most common bacteria identified—*Staphylococcus* (34% of positive cultures), *Propionibacterium* (13%), and *Haemophilus* (9%), and *Streptococcus* (4%)—can all inhabit the sinuses of healthy, asymptomatic individuals [6–9]. Unfortunately, there currently are no readily available clinical diagnostic tools to determine if a patient's symptoms stem directly from the overgrowth of this one genus versus a more nuanced disruption of this patient's microbiota. In addition, even in cultures that exhibited bacteria non-native to the sinuses, this assay does not differentiate between colonization versus active infection, a critical nuance for patients with results of *Pseudomonas* [20] (8%) or methicillin-resistant *Staphylococcus aureus* [21] (4%). There may be a role for more advanced culture assays, such as DNA sequencing analysis (DNAsa) [22,23]. This method, in contrast to standard cultures, does identify more organisms, and may be of utility in more complex patients with recurrent or polymicrobial infections, or to predict response to surgical interventions [13,24]; however, the cost-effectiveness of these more advanced techniques is yet to be investigated. Our study did not utilize these molecular biological techniques for our analysis given that our aim was to collect as many cultures as possible for a broader understanding of paranasal sinus microbiology; however, for the analysis of a smaller cohort of patients, these may provide a higher diagnostic yield.

Our study, on the other hand, does seem to negate the utility of fungal cultures, given that the large majority (92%) resulted in no growth. Other studies have shown higher positivity rates for fungal cultures, which likely vary with geography [25,26]. Otherwise, our study largely echoes the microbiological findings of other studies in terms of the most common bacteria found in the paranasal sinuses (see Table 3) [1,11], especially with the finding of *S. aureus* being the most frequent bacteria found among *Staphylococcus* cultures, although our study does find in particular a dominant presence of *S. aureus* versus coagulase-negative *Staphylococcus* compared to other studies (see Table 4). Like other studies, we found *Staphylococcus* and *Propionibacterium* to be the most common genera [11]. Given the size of our study, it is the first to provide a breakdown of this size at the species level for multiple bacteria in the sinuses (*Propionibacterium*, *Haemophilis*, *Pseudomonas*, *Prevotella*, etc.) and shows a broad range of bacteria, both in terms of genera identified in Table 3, as well as across aerobic vs. anaerobic bacteria (see Table 2). The lack of positivity in mycobacterial cultures is consistent with other studies given the rarity of this type of infection in the sinuses [27].

Our study certainly has several limitations given it was performed in a single-hospital system, and we did not include data that could have clarified the extent of symptoms that the patients were experiencing at the time of culture collection as well as prior or during antibiotic use. However, our goal was to broadly describe the contemporary microbiology of the paranasal sinuses, and not to compare the flora of patients with certain diagnoses or symptoms with that of controls. We also did not differentiate patients into those with acute or chronic sinusitis—again to more broadly comment on paranasal sinus microbiology; investigating these patient subsets individually may more specifically identify short- versus long-term microbiological disruptions and should be the focus of future studies. Moreover, some patients in our dataset may have more than one culture and thus be over-represented, and there may be heterogeneity in culture collection techniques across providers. We did

not investigate the specific indication for different types of cultures (e.g., mycobacterial). We also did not examine antibiotic resistance among bacteria outside of MRSA versus MSSA species. We are pursuing an additional study to assess time-dependent changes in microbial resistance in CRS. Additionally, these data were collected before the COVID-19 pandemic, which may have changed the microbiology of some patients' sinuses both acutely as well as in the long term [28].

5. Conclusions

Our study analyzed over 2000 sinus cultures collected across a healthcare system in a calendar year. The large majority of these were bacterial cultures, over half of which showed positive results, identifying a named bacterial genus that could be targeted with antibiosis. The most commonly identified bacteria in the cultures were *Staphylococcus*, *Propionbacterium*, *Haemophilus*, *Pseudomonas*, and *Streptococcus*. The most common species of *Staphylococcus* bacteria was *S. aureus*, with only a small portion (11%) of the cultures showing methicillin resistance. The large majority of fungal cultures resulted in no growth, suggesting their lack of utility. While our study shows that sinus cultures can identify bacterial genera, it is controversial whether antibiosis directed at these bacteria leads to the symptomatic improvement or restoration of microbiological homeostasis in the paranasal sinuses.

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Informed Consent Statement: Written consent was not required nor obtained given deidentified patient data was utilized for the study.

Data Availability Statement: The data used in the study is not publicly available given associated with our institution.

Conflicts of Interest: The authors declare no conflicts of interest.

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