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Microbiome and disease in the upper airway

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Abstract

Purpose of review—Microbiome refers to the genetic potential of resident microorganisms that inhabit a given niche. The exact role of the microbiome and its relation to chronic disease processes remains largely unknown, although various associations have been observed. We reviewed current literature investigating the microbiome of the upper airway by subsite (nasal cavity, sinus cavities, nasopharynx, and larynx) and its relation to chronic inflammatory disease processes.

Recent findings—The disruption of indigenous microbiota at a specific subsite may lead to pathogen overgrowth and increased susceptibility to infection. This has previously been demonstrated in the gastrointestinal tract and lower airways. The role of the microbiome and its relation to pathogenesis of disease in the upper airway, however, is less clearly understood. The present review discusses the recent studies that appear to link dysbiosis to upper airway chronic inflammatory diseases.

Summary—Despite mounting research, the role of microbiota in the upper airway remains poorly understood. Based on review of the current literature comparing healthy versus diseased patients with site-specific inflammatory conditions, a complex consortium of microbial communities inhabits the upper airway. Fluctuations in the baseline microbiome may contribute to disease pathogenesis, and improved understanding of the dynamics between shifting microbiota may be critical to guiding future medical therapy.

Keywords

Microbiome; bacteria; upper airway; sinus; nasal cavity; larynx; nasopharynx

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Introduction

Microbiome refers to the genetic potential of the entire cohort of resident microorganisms (commensal, symbiotic, pathogenic) that inhabit a given niche and function as an organized community.¹ Although the exact role of the microbiome and its relation to chronic disease processes remains largely unknown, we now understand that the disruption of indigenous microbiota (*dysbiosis*) may lead to pathogen overgrowth and increased susceptibility to infection. This has previously been demonstrated in the gastrointestinal tract and lower airways²⁻⁴, but has not been as thoroughly investigated in the upper airway.

The purpose of this article was to review current literature regarding the microbiome of the upper airway by subsite and its relation to chronic inflammatory disease processes. In particular, we focused on four specific subsites: the nasal cavity, paranasal sinus cavities, nasopharynx, and larynx, with the goal to identify common microbiome alterations or disease mechanisms in patients with chronic disorders at these subsites. Specifically, we examined chronic rhinitis, chronic sinusitis, chronic otitis media, and reflux laryngitis, respectively.

Methods

A systematic literature search was performed using the Medline, EMBASE, and Cochrane Review databases up to October 1, 2018, on recent studies that investigated the upper airway microbiome. Keywords used in the initial screening included “microbiome,” “microbe,” “microbial,” and “community”. A secondary search was also completed for specific classes of microbes by using the following keywords: “bacteria,” and “bacterial”. Finally, a tertiary search was conducted using keywords: “nasal cavity”, “chronic rhinitis”, “sinus”, “chronic sinusitis”, “nasopharynx”, “otitis media”, “larynx”, and “reflux laryngitis”.

References of original articles and relevant reviews were individually retrieved and perused for pertinent findings to identify those studies that specifically assessed the upper airway microbiome in healthy and unhealthy patients. In particular, we attempted to identify those articles specifically examining the role of microbiota in four upper airway sites (nasal cavity, sinus cavities, nasopharynx, and larynx) and connect these microbiota profiles to disease processes. Specifically, we sought to link dysbioses of these anatomic sites to corresponding diseases of interest: chronic rhinitis, chronic sinusitis, chronic otitis media, and reflux laryngitis, respectively.

Nasal cavity

Chronic rhinitis affects up to 20% of the population globally and consists of a heterogeneous group of suspected etiologies that results in chronic inflammation⁵⁻⁶. It can broadly be classified into allergic rhinitis (AR), infectious rhinitis, and nonallergic rhinitis (NAR). We sought to examine the role of dysbiosis of the nasal microbiome in each of these disease entities.

Hyun et al. recently performed a prospective study to characterize the microbiota of the inferior turbinate via biopsies in 20 AR patients and 20 healthy controls undergoing

septoplasty⁷. In addition, they also sought to investigate the relationship of mucosal microbiota with presence of disease, allergen number, as well as allergen-specific and total IgE levels. The results showed that alterations toward dysbiosis in the composition and predicted function of the inferior turbinate microbiota in individuals with AR was associated with high total IgE levels. Furthermore, the dominance of *Staphylococcus* in the altered microbiota suggested the importance of its role in AR development and progression. An increase in both *Staphylococcus* and a decrease in the phylum *Actinobacteria* were linked to high total IgE levels in allergic rhinitis. Thus, the authors concluded that the inferior turbinate microbiota may be impacted by collective allergic responses against sensitized allergens, and that site-specific microbial changes may contribute to disease pathophysiology.

Ramakrishnan et al. performed a prospective longitudinal study to examine the shift of microbiota in response to physician-prescribed interventions⁸. In this study, 5 subjects were serially examined over an 8-week period using pan-bacterial 16S rRNA gene sequencing. Four of these patients were administered topical mometasone furoate spray, while one subject underwent a mupirocin decolonization procedure in anticipation of orthopedic surgery. The results showed that microbial diversity was unaffected by intranasal treatment in two patients but markedly increased in the remaining 3. This was secondary to clearance of *Moraxella* and a simultaneous increase in members of the phylum *Actinobacteria*. Both of these effects persisted at least 2 weeks beyond cessation of treatment. Furthermore, there were transient changes in the relative abundance of several bacterial genera, including *Staphylococcus* and *Propionibacteria* (*Actinobacteria* phylum).

In both of these articles, two key genera--*Staphylococcus* and *Propionibacteria*--appear to be implicated in the development of chronic rhinitis.

Sinus

Chronic rhinosinusitis (CRS) represents one of the most common health care problems in the United States, with one in seven adults affected and 31 million newly diagnosed individuals each year^{9–10}. No clear etiology, however, has been identified. The pathogenesis is likely multifactorial with both host (allergy, immunodeficiency, ciliary immotility, anatomic obstruction) and environmental factors (bacterial and/or viral infections, biofilms, pollutants) believed to play a role in its development¹¹.

A recent meta-analysis conducted by Mackenzie et al. sought to examine potential differences in sinonasal bacterial community composition and to predict function between healthy and CRS patients¹². They found that the most abundant bacteria for all subjects were *Staphylococcus*, *Propionibacterium*, *Corynebacterium*, *Streptococcus*, and an unclassified lineage of *Actinobacteria*. The results from the meta-analysis suggested that in CRS patients, ecological networks promoting healthy communities become fragmented, leading to dispersion of bacterial communities, reduced bacterial diversity, and increased abundance of *Corynebacterium*. Furthermore, elevated relative abundance and diversity of members from the phylum *Actinobacteria* and genus *Propionibacterium* differentiated healthy sinuses from sinuses that were chronically inflamed. The absence of *Burkholderia* and *Propionibacterium*

phylotypes from the healthy community dataset were associated with increased network fragmentation, leading the authors to conclude that these two genera may act as gatekeepers with their presence playing a critical role in maintaining a stable sinonasal bacterial community.

Similarly, Hoggard et al. sought to differentiate bacterial communities in 94 patients with CRS undergoing endoscopic sinus surgery (ESS) and 29 controls undergoing ESS for indications other than CRS¹³. Bacterial communities underwent 16S rRNA gene amplicon sequencing and quantification with polymerase chain reaction. Control patients were primarily comprised of members of the genera *Corynebacterium* and *Staphylococcus*, with lower abundance of *Streptococcus*, *Moraxella*, and *Haemophilus*. The dysbiotic communities in CRS patients were mostly composed of members from genera *Staphylococcus*, *Streptococcus*, *Haemophilus*, *Pseudomonas*, *Moraxella*, or *Fusobacterium*.

Kuhar et al. also obtained sinus swabs during ESS for CRS patients and assessed the microbiome alterations and potential relationship to tissue histopathology¹⁴. In 51 patients, they found that a relative abundance of *Firmicutes* correlated with neutrophilic infiltration, mucosal ulceration, squamous metaplasia, and absence of Charcot-Leyden crystals. Relative abundance of *Bacteroidetes* phylum was associated with increased inflammation severity and mucosal ulceration. The authors thus concluded that the phyla *Firmicutes* and *Bacteroidetes* correspond to distinct pathologic features of CRS.

Koeller et al. compared the microbiome of healthy subjects to that of patients with chronic rhinosinusitis with nasal polyposis (CRSwNP) and chronic rhinosinusitis without nasal polyposis (CRSsNP) during ESS¹⁵. They found no clear distinction between bacterial communities in healthy versus CRSwNP patients, but found a relative abundance of *Flavobacterium*, *Pseudomonas*, *Pedobacter*, *Porphyromonas*, *Stenotrophomonas*, and *Brevundimonas* in CRSsNP versus healthy controls. These authors thus concluded that changes in the microbiome may be a more critical factor for development of CRSsNP compared to CRSwNP.

In a similar approach, Cope et al evaluated sinus brushings from CRS and control patients (59 vs 10, respectively), and assessed the microbiome compared to tissue RNA profiling and predictive metagenomics.¹⁶ The authors defined three categories of CRS, termed phylotypes, where each consisted of functionally distinct microbiomes and host immune responses. Mahdavinia and colleagues similarly utilized predictive metagenomics to identify dysregulated bacterial functional pathways computationally derived from 16S rRNA gene sequencing of middle meatal swabs from CRS versus control subjects.¹⁷ Although the identified pathways in the two studies were actually different, these are two articles that have implicated functional bacterial pathways in the chronic inflammatory disease process of CRS.

Larynx

An estimated 18 million Americans report voice problems each year¹⁸. The vocal folds are composed of stratified squamous epithelium and underlying lamina propria, and they reside

in the larynx at the junction between the respiratory and gastrointestinal tracts. In patients with chronic laryngeal inflammation, it is difficult to establish an exact etiology, but it has often been attributed to acid reflux, smoking, allergies, vocal overuse, or a combination of these factors¹⁹. The incomplete understanding we currently have of the pathophysiology of chronic laryngeal inflammation represents a barrier to adequate treatment in most patients. Frequently, patients are empirically treated with proton pump inhibitors (PPI), but this has demonstrated limited efficacy²⁰.

Only four prior studies published to date have examined the role of laryngeal microbes in disease, including chronic laryngitis, vocal fold polyps, nodules, cysts, laryngeal cancer, and Reinke's edema¹⁹. None of these studies, however, have compared microbial data of diseased versus healthy tissue.

Jette et al. is the first known study to examine the contribution of the two most commonly known mucosal irritants, cigarette smoke and reflux, to microbial community composition in the larynx¹⁹. The authors hypothesized that refluxed material from the stomach may lead to colonization of the upper respiratory tract in patients with reflux laryngitis; and therefore microbiota found in laryngeal tissue and the stomach in these patients would be similar. In this study, the authors investigated the laryngeal microbiome of 97 healthy volunteers using 16S rRNA sequencing. Similar to previous studies looking at laryngeal microbiome in healthy subjects, there was highly abundant *Cordnarnonadaceae*. In smokers, however, they found reduced microbial diversity with differences in relative abundances of *Streptococcus*, unclassified *Cordnarnonadaceae*, *Cloacibacterium*, and *Helicobacter*. Reflux status, however, did not appear to impact microbial diversity, community structure, or composition. Furthermore, when the authors examined the laryngeal microbiome of healthy patients versus those with benign vocal fold disease, they found an abundance of *Streptococcus* in the latter group.

The authors thus concluded that the diversity of the laryngeal microbiome is affected by smoking, but not by reflux. The preponderance of *Streptococcus* in both smokers and those with benign vocal fold lesions versus healthy suggests that this bacteria may contribute to the pathophysiology of laryngeal disease.

Nasopharynx

Otitis media is a very common childhood disease. It represents the leading cause of visits to the pediatrician by children, and is also the most frequent indication that children consume antibiotics or undergo surgery^{21–23}. Given its prevalence in the pediatric population, our literature search of the nasopharyngeal microbiota yielded a majority of studies conducted in this population.

In determining the relevance of the microbiota of the nasopharynx, we sought to identify changes in the host microbiota in patients with otitis media. Chonmaitree et al. assessed nasopharyngeal microbiota in infants followed from near birth to the first acute otitis media (AOM) episode or 12 months of age in order to determine how fluctuations in nasopharyngeal bacterial colonization could potentially lead to viral URI and AOM²⁴.

The authors analyzed 971 specimens collected monthly and during URI and acute otitis media episodes from 139 infants to elucidate interactions between nasopharyngeal microbial pathogens and commensals. The data were collected longitudinally during both health and disease. The highly abundant genus-level nasopharyngeal microbiota included *Moraxella*, non-typeable *Haemophilus influenzae*, and *Streptococcus* (3 otopathogen genera); *Corynebacterium*, *Dolosigranulum*, *Staphylococcus*, *Acinetobacter*, *Pseudomonas*, and *Bifidobacterium*. The authors thus concluded that the bacterial otopathogen genera *Moraxella*, *Haemophilus influenzae*, and *Streptococcus* played critical roles in development of AOM. The increasing trend in colonization of these otopathogen genera also correlated with frequencies of URI. Furthermore, *Staphylococcus*, but not the commonly used probiotic bacterium *Bifidobacterium*, appeared to counteract the deleterious effects of these otopathogens.

Interestingly, the authors found that during symptomatic viral infection, there were significant increases in the relative abundance of otopathogen genera, but no significant change in otopathogen or commensals during asymptomatic viral infection. Stability of the microbiome during asymptomatic viral infection may therefore play a role in the failure of asymptomatic viral infection to progress to AOM.

Lappan et al. performed a case-controlled study of recurrent AOM (rAOM) to identify potentially protective bacterial genera²⁵. They hypothesized that healthy children with no history of AOM harbor protective commensal bacteria that could be used as potential probiotic therapy to inhibit the cycle of re-infection. They compared nasopharyngeal swabs from both children with rAOM and healthy controls using 16S rRNA gene sequencing. In the control group, there was a significantly higher abundance of *Corynebacterium* and *Dolosigranulum*. The authors thus concluded that these two genera are characteristic of a healthy nasopharyngeal microbiome. Of note, *Alloiococcus*, *Staphylococcus*, and *Turicella* were abundant in the middle ear and ear canal of the rAOM group but uncommon in the nasopharynx of both groups. The authors believe that these three present possible novel otopathogens that could contribute to rAOM.

Conclusions

The role of microbiota in the upper airway is incompletely understood, although appears implicated in several disease processes. Healthy adults seem to harbor anatomical site-specific core microbiota that directly influence immunity and epithelial barrier function⁸. When this baseline microbiota at a particular body subsite, however, is subjected to perturbation from external stimuli (eg. bacterial, virus, pH changes, medications), this could result in at least a transient shift away from the stable core. This shift may ultimately be responsible for creating periods of increased susceptibility to disease or pathophysiology.

Based on the recent review of literature comparing healthy versus diseased patients with site-specific inflammatory conditions (Table 1), there are still many unanswered questions regarding the significance of microbiomes. While we recognize that complex microbial communities are present throughout the upper airway, further investigation is necessary to better understand how fluctuations in the baseline microbiome contribute to disease

pathogenesis. Furthermore, a better delineation of the dynamics between shifting microbiota is critical to understanding the microbial contribution to these disease processes, and guiding any potential future medical interventions.

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* of special interest

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Key points

- Microbiome refers to the genetic potential of the entire cohort of resident microorganisms that inhabit a given niche and function as an organized community.
- Dysbiosis may play a critical role in the development of chronic upper airway inflammatory diseases.
- Improved understanding of fluctuations in the baseline microbiome and its role in disease pathogenesis may help to guide future medical therapy.

Table 1.

Literature summary of findings classified by upper airway site of the key articles discussed in this review. (ESS: endoscopic sinus surgery, rAOM: recurrent acute otitis media, AOM: acute otitis media, URI: upper respiratory tract infection; CRSwNP: chronic rhinosinusitis with nasal polyposis; CRSsNP: chronic rhinosinusitis without nasal polyposis)

	No. subjects	Method	Key findings	Implicated bacteria in disease
Nasal cavity				
Hyun et al. (2018) ⁷	32 (20 with allergic rhinitis, 12 healthy controls)	Inferior turbinate biopsies	Dysbiosis of the inferior turbinate mucosa microbiota linked to high total IgE levels in allergic rhinitis	<i>Staphylococcus</i> , <i>Actinobacteria</i>
Ramakrishnan et al. (2018) ⁸	5 patients with chronic rhinitis	Nasal swabs collected longitudinally over 8 weeks	Administration of topical nasal therapy resulted in shifts in microbial diversity	<i>Staphylococcus</i> , <i>Actinobacteria</i>
Sinus				
Mackenzie et al. (2017) ¹²	11 studies (472 total samples)	Meta-analysis	<i>Burkholderia</i> and <i>Propionibacterium</i> may play gatekeeper role, with their presence maintaining a stable sinonasal bacterial community.	<i>Corynebacterium</i>
Hoggard et al. (2017) ¹³	123 (94 extensive bilateral CRS undergoing ESS, 29 controls undergoing ESS not for CRS)	Sinus sampling during ESS	Controls dominated by <i>Corynebacterium</i> and <i>Staphylococcus</i> with lower abundance of several other genera including <i>Streptococcus</i> , <i>Moraxella</i> , and <i>Haemophilus</i> .	<i>Staphylococcus</i> , <i>Streptococcus</i> , <i>Haemophilus</i> , <i>Pseudomonas</i> , <i>Moraxella</i> , <i>Fusobacterium</i>
Cope et al. (2017) ¹⁶	59 CRS patients undergoing ESS, 10 controls	Sinus brushings during ESS	CRS patients clustered into distinct sub-groups dominated by a pathogenic family: <i>Streptococcaceae</i> , <i>Pseudomonadaceae</i> , <i>Corynebacteriaceae</i> , <i>Staphylococcaceae</i>	<i>Streptococcaceae</i> , <i>Pseudomonadaceae</i> , <i>Corynebacteriaceae</i> , <i>Staphylococcaceae</i>
Mahdavinia et al. (2018) ¹⁷	111 CRS patients. 21 controls	Middle meatal swabs	No significant differences in alpha-diversity. CRS with significantly lower <i>Corynebacterium</i> and <i>Petioniphilus</i>	<i>Corynebacterium</i> and <i>Petioniphilus</i> reduced in CRS
Kuhar et al. (2018) ¹⁴	51 CRS patients undergoing ESS	Sinus swabs during ESS	<i>Firmicutes</i> and <i>Bacteroidetes</i> are associated with increased neutrophilic infiltrate, mucosal ulceration, inflammation.	<i>Firmicutes</i> and <i>Bacteroidetes</i>
Koeller et al. (2018) ¹⁵	18 (5 CRSwNP, 5 CRSsNP, 5 unilateral purulent maxillary CRS, 3 healthy controls)	Middle meatus swabs during ESS	Alterations of the bacterial community might be a more crucial factor for the development of	Relative abundance of <i>Flavobacterium</i> , <i>Pseudomonas</i> , <i>Pedobacter</i> , <i>Porphyromonas</i> , <i>Stenotrophomonas</i> , and <i>Brevundimonas</i> in CRSsNP only.

	No. subjects	Method	Key findings	Implicated bacteria in disease
			CRSsNP compared to CRSwNP	
Larynx				
Jette et al. (2016) ¹⁹	97 healthy volunteers	Vocal fold biopsies	Diversity of the laryngeal microbiome is affected by smoking, but not reflux.	Relative abundance of <i>Streptococcus</i> in smokers and in benign vocal fold lesions.
Nasopharynx				
Chonmaitree et al. (2017) ²⁴	139 infants	971 specimens collected monthly and during URI and AOM episodes	Otopathogen genera played key roles in URI and AOM occurrences. <i>Staphylococcus</i> counteracts otopathogens and thus may be beneficial.	<i>Moraxella</i> , <i>Haemophilus influenzae</i> , and <i>Streptococcus</i>
Lappan et al. (2018) ²⁵	196 children (93 rAOM and 103 controls)	Nasopharyngeal swabs from rAOM children	<i>Corynebacterium</i> and <i>Dolosigranulum</i> are characteristic of a healthy nasopharyngeal microbiome	<i>Alloiococcus</i> , <i>Staphylococcus</i> and <i>Turicella</i> are potential otopathogens