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Microbiome of the Aerodigestive Tract in Health and Esophageal Disease

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Abstract

The diverse human gut microbiome is comprised of approximately 40 trillion microorganisms representing up to 1000 different bacterial species. The human microbiome plays a critical role in gut epithelial health and disease susceptibility. While the interaction between gut microbiome and gastrointestinal pathology is increasingly understood, less is known about the interaction between the microbiome and the aerodigestive tract. This review of the microbiome of the aerodigestive tract in health, and alterations in microbiome across esophageal pathologies highlights important findings and areas for future research. First, microbiome profiles are distinct along the aerodigestive tract, spanning the oral cavity to the stomach. In patients with reflux-related disease such as gastro-esophageal reflux disease, Barrett's esophagus, and esophageal adenocarcinoma, investigators have observed an overall increase in gram negative bacteria in the esophageal microbiome compared to healthy individuals. However, whether differences in microbiome promote disease development, or if these shifts are a consequence of disease remains unknown. Interestingly, use of proton pump inhibitor therapy is also associated with shifts in the microbiome, with distinct shifts and patterns along the aerodigestive tract. The relationship between the human gut microbiome and esophageal pathology is a ripe area for investigation, and further understanding of these pathways may promote development of novel targets in prevention and therapy for esophageal diseases.

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Introduction

The human microbiome plays a critical role in gut epithelial health and disease susceptibility, and over the past decade interest in the human microbiome, particularly the gut microbiome, has rapidly grown. The human gut microbiome has approximately 40 trillion microorganisms, mostly compromised of about 500 to1000 different bacterial species.[1] Within the gastrointestinal tract, the oral cavity, esophagus, stomach, and intestines contain diverse and host-specific microbiomes. The microbiome benefits their human host in a variety of ways including digestion, immune system responses, metabolism, and vitamin production.[2–4] Emphasis has grown on studying the relation of the microbiome to the pathogenesis of gastrointestinal disorders, as alterations in the human microbiome can play a crucial role in disease susceptibility. The gut microbiome consists of many tightly connected epithelial cells, which limits interactions between the immune system and microbiome. In healthy individuals, a homeostasis exists between these systems. In disease states, the homeostasis is disrupted leading to inflammation or dysbiosis.[5] For example, the gut microbiome is known to modulate disease processes such as peptic ulcer disease, gastric cancer, inflammatory bowel disease, to name a few. Furthermore, gastrointestinal diseases are often responsive to microbiome directed therapy.

However, less is currently known about the microbiome in the aerodigestive tract. The aerodigestive tract is defined as the airway (pharynx and larynx), pulmonary tract (trachea, bronchi, and lungs), and upper digestive tract (esophagus).[6] As, the upper respiratory system and foregut are closely situated, and up to 30% of the population experiences gastro-esophageal reflux symptoms, understanding the microbiome of the aero-digestive GI tract is novel and relevant to modern medicine. Studies on microbiota are possible due to the development of culture-independent molecular techniques. This article will be a review of the microbiome of the aerodigestive tract in health, and associations between alterations in microbiome and disease pathogenesis of the aerodigestive tract, with a primary focus on its relation to esophageal disorders.

Microbiome of the Aerodigestive Tract in Healthy Individuals (Figure 1)

Oral Cavity

There is an abundance of microorganisms in the human oral cavity. Approximately 96% of the microbiome in a healthy human oral cavity can be divided into six phyla: Firmicutes, Actinobacteria, Proteobacteria, Fusobacteria, Bacteroidetes and Spirochaetes with *Actinomyces, Atopobium, Corynebacterium, Rothia, Bergeyella, Capnocytophaga, Prevotella, Granulicatella,* Streptococcus*, Veillonella, Campylobacter, Cardiobacterium, Haemophilus, Neisseria, TM7,* and *Fusobacteria* forming the core of the oral microbiome.[7,8] Of those, Streptococcus, *Veillonella*, and *Prevotella* are the predominant genera. The oral cavity has many different areas of colonization, with a particular preference for the palates, gingival surfaces, teeth, lips, cheeks, and tonsils.[9]

Esophagus

Despite close proximity to the oral cavity, the esophageal microbiome is quite different. Initially, the esophagus was thought to be lacking its own microbiome and that it had transient translocation from the oral cavity or stomach. However, a pivotal study by Mannell and colleagues in 1983 demonstrated that the esophagus has its own, unique microbiome, with predominance of *Streptococcus viridans, H. influenzae, Neisseria catarrhalis,* Group B Streptococcus *and Klebsiella pneumonia*.[10] Esophageal secretions of study participants were aspirated using a sterile catheter and were placed in aerobic and anaerobic cultures. Further studies examining the esophageal microbiome in healthy individuals have shown a prevalence of six phyla: Firmicutes, Bacteroides, Actinobacteria, Proteobacteria, Fusobacteria, and TM7, with predominance of Streptococcus, *Prevotella*, and *Veilonella* genera.[11] Additional studies have also demonstrated predominance of *Streptococcus* species in the esophagus, along with Prevotella, and Veillonella, *Neisseria* and *Hemophilus* species.[12]

There are many similarities between the microbiome in the oral cavity and the esophagus. *Streptococcus* species (*S. salivarius*, *S. sanguinis*, *S. oralis*, and *S. mutans)* form the majority of the microbiome in both locations, suggesting the esophageal microbiome is derived from an oral origin[10]. This is not surprising given *Streptococcus* ability to adhere to epithelial surfaces.[13] One notable difference was the presence of *Spirochaetes,* which was found to be more prevalent in the oral cavity compared to the esophagus.[14]

Stomach

Similar to the esophagus, the gastric microbiome was thought to be non-existent due to the acidic nature of the stomach and presence of proteolytic enzymes.[15] However, many studies have refuted those beliefs, showing the stomach has its own unique microbiome, quite different than the oral cavity and esophageal microbiome. At the phyla level, multiple studies show the presence of Actinobacteria, Bacteroidetes, Firmicutes, and Proteobacteria in the gastric mucosa of healthy individuals.[15] Studies differed at the genus level, with multiple showing an abundance of *Neisseria, Prevotella*, and *Streptococcus*, though some had increased presence of *Porphyromonas* and *Haemophilius,* while others showed *Halomona, Rhodococcus,* and *Brevundimona*.[16]

Helicobacter pylori is worth briefly mentioning, as it is another dominant species present, playing a significant role in determining the entire microbial landscape of the gastric flora. Given the major role *Helicobacter pylori* plays, as it inhabits in a commensal fashion, there is a rich diversity constituted by other dominant genera such as *Streptococcus, Prevotella, Veillonella,* and *Rothia*.[17,18] Numerous studies have found that the predominant location of *H. pylori* was in the corpus and antrum of the stomach.[19,20]

Lungs

The gastrointestinal and respiratory systems are closely connected via the aerodigestive tract, and not surprisingly there have been some associations between the microbiome of both systems. For instance, the bronchi and lung tissue are composed of Bacteroidetes and

Firmicutes.[21] Both phyla also comprise the hypopharynx, in addition to *Proteobacteria*, as well as the stomach and esophagus as previously mentioned.

Modulators of Microbiome in Health

Among healthy individuals, certain factors such as age, culture, and geographic differences have shown variations in different parts of the microbiome.[15,22] For example, one study has shown the presence of halophilic bacteria and soil bacteria, attributed to the consumption of salted or fermented food unique to a culture.[16] Diet has also been shown to be an important modulator of the gut microbiota.[23] A study examining children raised in a rural setting were found to have unique microbiome changes compared to children of the same ethnicity but raised in a more urban setting.[24] High fiber, low fat diets were found to create an environment that promoted proper digestion, nutrient uptake, and healthy metabolism.[21] Healthy habits and good hygiene help maintain an equilibrium in our microbiome.[25–27] Disruptions such as dietary changes, poor hygiene, medications, and toxin ingestion such as tobacco and alcohol, can disrupt the equilibrium and increase susceptibility to different diseases.[27–29] These imbalances lead to pH changes or alter the inflammatory response, increasing likelihood of non-commensal microbial colonization.

In addition to modifiable factors, certain diseases lead to alterations in the human microbiome. In particular, inflammatory processes are associated with increased presence of certain bacteria, not otherwise found in healthy individuals.[30] Knowledge of these differences can be used to detect biomarkers or develop directed therapy towards these diseases.

Microbial Shifts Related to Esophageal Conditions (Table 1)

Gastro-esophageal reflux disease

Several gastro-esophageal reflux conditions, including gastroesophageal reflux disease (GERD), Barrett's Esophagus (BE), and esophageal adenocarcinoma (EAC), have demonstrated changes in gut microbiota in otherwise previously healthy individuals.

Many studies have investigated the role of oral microbiota and the changes associated with these diseases. Peters et al. found an association between oral microbiota composition and EAC, in which the genus *Neisseria* and species *Streptococcus pneumoniae* were associated with increased EAC risk.[31] In a study by Gall and colleagues, saliva samples from 12 participants of the Seattle Barrett's Esophagus Research Program suggested that the upper GI tract is seeded, in part, by oral communities. They did not detect substantial difference in microbial diversity between squamous and columnar esophageal lining in BE.[32]

Blacket and colleagues compared bacterial alterations in 154 subjects, and observed a shift in the esophageal microbiota from the predominant Streptococci to an increase in Gram-negative species in patients with GERD and BE when compared to controls.[33] Similar findings were confirmed in another study that detected reduction in Streptococcus species, and an increase in gram negative and anaerobic species such as *Prevotella, Veillonella, Haemophilus, Neisseria,* and *Rothia* in patients with BE.[34] This was further observed in a study which found that patients with BE and reflux esophagitis had an increased relative

abundance of Gram-negative bacteria, including *Fusobacterium, Neisseria, Campylobacter, Bacteroides, Proteobacteria*, and *Veilonella*, and a relative decrease in *Streptococcus* in reflux-related conditions.[35]

Interestingly, previous studies demonstrate a link between increased risk of BE and EAC and obesity, or more specifically central adiposity.[36–40] Many proposed mechanisms for this link exist including increased abdominal pressure and gastric compression, inflammatory cytokine release, and diet.[41–43] One notable proposed mechanism includes alterations in gut microbiome associated with inflammation.[44] As discussed above, alterations in the ratio of Streptococcus species to gram negative species is associated with reflux-related conditions. In the study by Gall et al, central adiposity and hiatal hernia length was also associated with similar alterations in the ratio, which may further explain the link between obesity and disease states.[45]

Achalasia

Few studies have reviewed the esophageal microbiome in patients with achalasia, a primary motility disorder. Different bacterial, protozoal, and viral organisms such as *Trypanosoma cruzi, Mycobacterium gondii*, and human immunodeficiency virus have been associated with achalasia, however it is unclear if and how this leads to alterations in the esophageal microbiome.[46,47]

Eosinophilic Esophagitis

Eosinophilic Esophagitis (EOE) is another disease process which has been shown to have alternations in the esophageal microbiome. EOE is an antigen mediated disorder triggered by different environmental allergens such as food, leading to an eosinophilic infiltration of the esophageal mucosa. In a pediatric study conducted by Benitez et al, they found that children with EOE had an increase in *Neisseria* and *Corynebacterium* and a decrease in *Streptococcus* and *Atopobium* compared to children without EOE.[48] In an additional study conducted by Harris et al, they found an increase in *Haemophilus* in patients with active EOE compared to healthy controls. Additionally, they found an increase in bacterial load in EOE patients and not bacterial diversity. Interestingly, patients with *Helicobacter pylori* were found to have a decreased risk of developing EOE.[49] An additional study performed by Kashyap et al also showed reduced microbial diversity in patients with EOE and decreased *Clodistria* and *Clostriadles* compared to healthy controls.[50]

Changes in the Microbiome with PPI Use (Table 2)

Proton pump inhibitors (PPI) therapy is a mainstay treatment for GERD, BE, and commonly used for EOE. Numerous studies demonstrate that PPI use is associated with composition changes of gut microbiomes and decreased microbiome diversity throughout the GI tract (Table 1).[16,51,52] PPIs act directly on the proton pumps in the stomach, leading to changes in the acidic environment, which may adversely affect the natural microenvironments of commensal bacteria. While the mechanism of alterations in gut microbiomes associated with PPI use has not been extensively studied, it has been repeatedly demonstrated that the

inhibition of gastric acid secretion induces a dysbiosis of microbiota, while also impacting intestinal microbiota.[53]

There is limited data regarding the impact of PPI use on the oral microbiome. A study conducted in 10 healthy volunteers examining the effects of PPI usage on oral and gut microbiota observed an increase of *Fusobacterium* and *Leptotrichia* in the periodontal pocket, and a decrease of *Neisseria* and *Veillonella* in saliva after four weeks of PPI use.[54]

PPI use has also been shown to affect the esophageal microbiome. PPI use was associated with an increase in *Micrococcocacae, Actinomycetaceae,* and *Clostridiaceae* and a decrease in *Comamonadaceae*.[35] Another has shown an increase in Firmicutes and a decrease in the abundance of Bacteroidetes and Proteobacteria.[55] In addition to the esophageal microbiome, there has also been associations with the gastric microbiome, with an increase in *Streptococcaceae* and decrease in *Prevotellaceae*. It is thought that the high gastric pH gives rise to a significant increase in oral bacteria in the stomach, such as such as *Pepto-streptococcus stomatis, Streptococcus anginosus, Parvimonas micra, Slackia exigua* and *Dialister pneumosintes*.[56] A separate study in 2019 by Yi-Chao Shi et al examined the association between PPI use and microbiota in GERD patients versus healthy controls and found that PPI use in GERD patients had lowered relative bacterial diversity of gastric microbiota.[16] They reported higher abundances of *Planococcaceae*, *Oxalobacteraceae*, and *Sphingomonadaceae* in the gastric microbiota with PPI use in GERD patients, and decreased abundance of *Desulfuromonadaceae* and *Shewanellaceae* compared to non-PPI users.

Association Between GERD and Microbiome

Whether the alterations in microbiome promote the development of GERD, or chronic GERD leads to microbiome shifts remains a point of debate. One study suggested that the microbiota dysbiosis is a potential side effect of the acidic environment caused by GERD.[55] However, another study suggests that the bacterial shift towards Gram-negative bacteria could be an indication that dysbiosis is the cause of various GI disorders.[57] In addition, chronic inflammation has been demonstrated to play a role in the development of various GI disorders such as BE and EAC.[22,58–60] One proposed mechanism suggests that chronic inflammation induced alterations in gut microbiota further contribute to disease development.[21,61] A review by Corning and colleagues highlighted that GERD consistently produces a shift in the microbiome and demonstrates an increasing number of Gram-negative and anaerobic bacteria.[14] It has been proposed that bacterial antigens specific to Gram-negative bacteria, including lipopolysaccharide (LPS), may promote tissue inflammation via induced expression of NF-κβ, a signaling pathway involved in inflammation.[62,63] Activation of NF-κβ has been demonstrated to induce production of cytokines such as IL-1β, IL-2, IL-8 and tumor necrosis factor-α (TNF-α). Another study from 2019 comparing mouse models showed germ free mice fed a high fat diet had an increased risk of progression of BE to EAC via upregulation of IL8/CXCL1 inflammatory markers, again suggesting a mechanistic link to the influence of the microbiome on progression of disease.[60] Also of note, studies have shown that LPS may relax the lower esophageal sphincter and delay gastric emptying, which may further contribute to the

development of GERD.[64,65] The limited and conflicting data shows there is still limited understanding in the relation of gut microbiota to GERD.

Even less well understood is the association between microbiome and extra-esophageal reflux, the reflux of gastric contents proximal to the upper esophageal sphincter.[66] It is postulated that chronic and repetitive exposure of noxious chemical stimuli at the laryngeal mucosa results in inflammation, and potentially laryngeal cancer.[67] Further, it is known that regurgitation of gastric and esophageal contents can result in micro- or macro-aspiration into the lungs and result in pneumonia. Certainly, alterations in the microbiome along the aerodigestive tract may explain chronic inflammation observed outside of the gastrointestinal tract.

Future Direction

Microbiome research in the aerodigestive tract is a ripe area for investigation with potential to uncover mechanisms of inflammation and nociception, as well as to explore potential therapeutic targets. Of interest is whether alterations in gut microbiota are consistently observed in GERD, and specifically whether changes occur before or after development of disease as well as its relationship with obesity. It is important to understand the progression of GERD and its relation, as GERD is the precursor to BE and EAC. Further understanding shifts in the oral microbiome in relation to GERD may help identify diagnostic biomarkers, and better understand disease pathways. With a greater understanding on mechanism of progression of GERD and its relation to gut microbiome, future novel targets targeting these pathways may be developed in potential prevention and therapy for GERD. In addition, microbiome research can potentially also help with other disease processes such as EOE and achalasia.

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Abbreviations:

BE	Barret Esophagus
EAC	Esophageal Adenocarcimoma
GERD	Gastroesophageal Reflux Disease
PPI	Proton Pump Inhibitor
EOE	Eosinophilic Esophagitis

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HIGHLIGHTS

- Human microbiome plays a critical role in gut epithelial health and disease susceptibility
- In healthy individuals, each part of the aerodigestive tract has its own unique microbiome
- Individuals with known esophageal disorders (reflux related disease) have been shown to have differences in their microbiome compared to healthy individuals
- Use of proton pump inhibitors is also associated with changes in the different parts of the aerodigestive tract

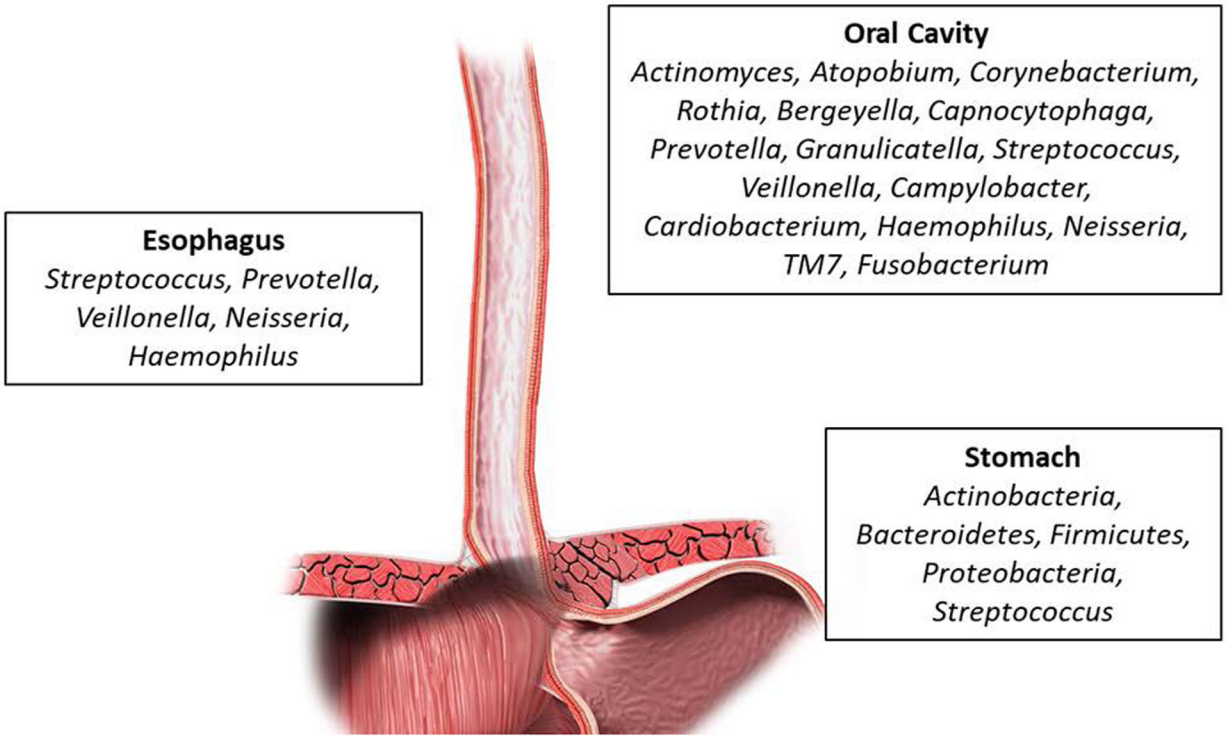

FIGURE 1.
MICROBIOME OF THE AERODIGESTIVE TRACT IN HEALTH

TABLE 1.

SHIFTS IN ESOPHAGEAL MICROBIOME IN ESOPHAGEAL DISEASE

Esophageal Disease	Gram Positive	Gram Negative
Gastro-esophageal Reflux Disease/Barrett's Esophagus	Reduced *Streptococcus* species	Increased *Neisseria, Proteobacteria, Veillonella, Fusobacterium*
Eosinophilic Esophagitis	Incresed *Cornebacterium*	Increased *Neisseria, Haemophilus;* Reduced *Helicobacter*

TABLE 2.

SHIFTS IN MICROBIOME WITH PPI USE ALONG THE AERODIGESTIVE TRACT

Microbiome Location	Increase with PPI use	Decrease with PPI use
Oral	*Fusobacerium* and *Leptotricha*	*Neisseria* and *Veilonella*
Esophagus	*Micrococcocacae*, *Actinomycetaceae*, *Clostridiaceae*, and *Firmicutes*	*Bacteoidetes*, *Comamonadaceae*, and *Proteobacteria*
Stomach	*Streptococcaceae*, *Petop-streptococcusa stomatis, Parvimonas micra, Slackia exigua,* and *Dialister pneumosintes*	*Prevotellaceae*