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Review Article

Gastroesophageal Reflux Disease: A Potentially Infectious Disease?

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Abstract

The gastrointestinal microbiome remains an explosively increasing topic of study, assessing the potentially pivotal roles of the microbiome in maintaining health or causality in disease pathogenesis. Gastroesophageal reflux disease (GERD) has long been understood to be a result of direct acidic injury. However, emerging evidence suggests that GERD could also be caused by alterations in the esophageal microbiome, causing an induction of a submucosal inflammatory cytokine cascade, that has a retrograde effect on the luminal mucosa. This concept of a microbial shift/dysbiosis in the causality of GERD is clearly a paradigm shift and has led to possible treatment strategies beyond the traditional approach of acid-suppressive therapies. This review focuses on the current evidence surrounding GERD and the rationale for possible esophageal microbiome-directed treatment strategies.

Introduction

Gastroesophageal reflux disease (GERD) has been traditionally described as a chronic gastrointestinal (GI) disorder in which gastric contents reflux retrograde into the esophagus. This can result in clinically significant symptoms and may progress to complications such as erosive esophagitis, eosinophilic esophagitis (EoE), Barrett's esophagus (BE), and esophageal adenocarcinoma. It has been estimated that GERD is among the most prevalent GI diseases worldwide. The prevalence of GERD ranges from 18.1% to 27.8% in the United States, resulting in substantial direct and indirect economic costs.[1–3] The pathogenesis of GERD is influenced by a number of factors, characterized by an imbalance between harmful factors (reflux frequency, acidity of refluxate, esophageal mucosal contact time) and protective factors (esophageal acid clearance, mucosal integrity, lower esophageal sphincter pressure, anti-reflux barrier).[4] Recent studies suggest that this multifactorial process is influenced by the esophageal microbiome, which can induce an immune response that eventually triggers inflammation and subsequent GERD.[5,6]

The microbiome is a collection of microorganisms, primarily bacteria, fungi (mostly yeasts), archaea, and viruses, that live in specific environments, such as the skin, mouth, respiratory tract, and GI tract.[7,8] A collection of microbes is called the microbiota, whereas a collection of genes is called the microbiome.[7] In addition to regulating the immune system, synthesis of nutrients, and protection against harmful pathogens, the microbiome plays an invaluable role in promoting health and well-being.[9,10] Microbial dysbiosis can result in tissue damage and contribute to inflammatory, autoimmune, metabolic, and neoplastic diseases.[9,11–13] Focus has been placed on understanding how changes within the microbiota may contribute to disease manifestations, a process that can now be accomplished through the development of molecular tools and techniques (metagenomic, metabolomic, lipidomic, meta-transcriptomic).[14–17] Clarifying and elucidating mechanisms by which the microbiota interacts with the underlying human physiology in the GI tract will enable the development of novel therapies and optimize clinical practices. Advances in medical science are evolv-

Keywords: Gastrointestinal microbiome; Gastrointestinal reflux disease; Dysbiosis; Cytokines; Probiotics; Prebiotics.

Abbreviations: BE, Barrett's esophagus; CGRP, calcitonin gene-related peptide; CI, confidence interval; COX-2, cyclooxygenase-2; DIS, dilated epithelial intercellular spaces; EoE, eosinophilic esophagitis; FMT, fecal microbiota transplantation; GERD, gastroesophageal reflux disease; GI, gastrointestinal; *H. pylori*, *Helicobacter pylori*; HIF, hypoxia-inducible factors; IL, interleukin; LPS, lipopolysaccharide; MIMO, maltosyl-isomaltooligosaccharides; NERD, non-erosive reflux disease; NF-κB, nuclear factor-kappa B; PPI, proton-pump inhibitors; SCFA, short-chain fatty acids; TLR, toll-like-receptor; TNF-α, tumor necrosis factor-alpha; WMT, washed microbiota transplantation.

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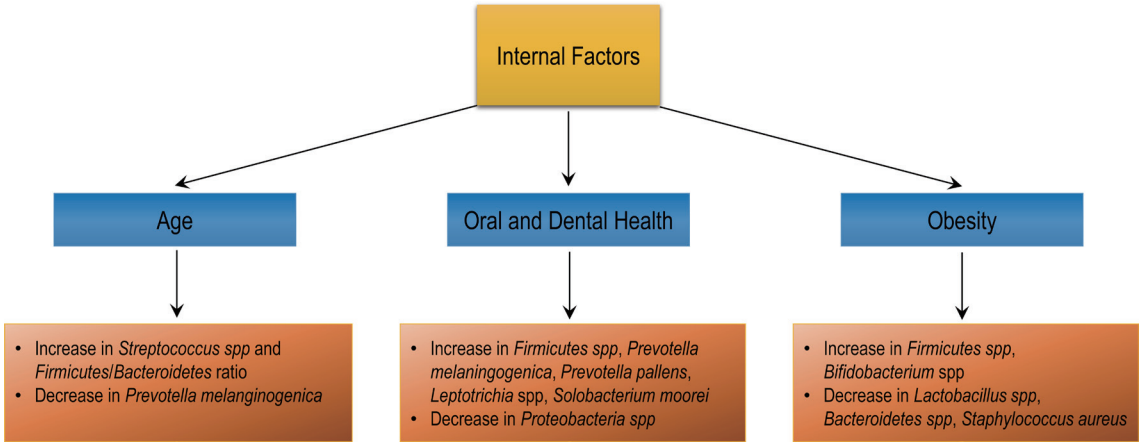

Fig. 1. Internal factors that influence esophageal disease.[24]

ing towards the ideal goal of individualizing disease management to provide more personalized directed treatment of each patient, to improve clinical outcomes.[18,19] Although the intestinal (colonic) microbiome has been extensively studied, the microbiome of the esophagus and oropharynx and its relation to GERD has not been studied to the same extent.[20] An overview of the role of the esophageal microbiome in GERD, cytokine expression, and possible mitigation strategies will be presented in this article.

GERD and cytokine expression

GERD has long been described as the result of direct esophageal mucosal inflammation/damage secondary to the reflux of gastric acid and/or duodenal bile salts.[21] It was previously thought that the refluxed acid led to direct chemical contact damage to the esophageal mucosa, and therefore a linear relationship between mucosal damage and the pH of reflux. However, many patients with clinical symptoms of GERD do not have objective mucosal evidence (erosions) of reflux.[6]

An alternative pathophysiology to the direct acid contact and disruption of the esophageal mucosal barrier involves cytokine expression and subsequent submucosal directed inflammatory damage back to the mucosa. Lipopolysaccharide (LPS) is a cell wall constituent of gram-negative bacteria and is vital for bacterial cell integrity, viability, and defense against environmental stress.[22] The toll-like-receptor (TLR)-4 protein site found on human cells is best characterized as a sensing receptor that mediates LPS-induced signal transduction.[23] Various internal and external factors can affect the oropharyngeal and esophageal microbiome, in particular altering the proportion of gram-positive to LPS-containing, gram-negative microbes (Figs. 1 and 2).[24] This leads to increased LPS-TLR-4 binding and activates production of interleukin (IL)-18, which induces a cascading inflammatory response (Fig. 3).[6] Further TLR-based signaling promotes transcription of pro-inflammatory chemokines, including IL-1, IL-6, IL-8, and tumor necrosis factor-alpha (TNF-α), and mediators such as nitric oxide synthase. The result of this cascade is a retrograde inflammatory disruption from the submucosa back to the luminal esophageal barrier, as well as possible adverse relaxation of the lower esophageal sphincter and decreased esophageal motility. The resulting disruptions at

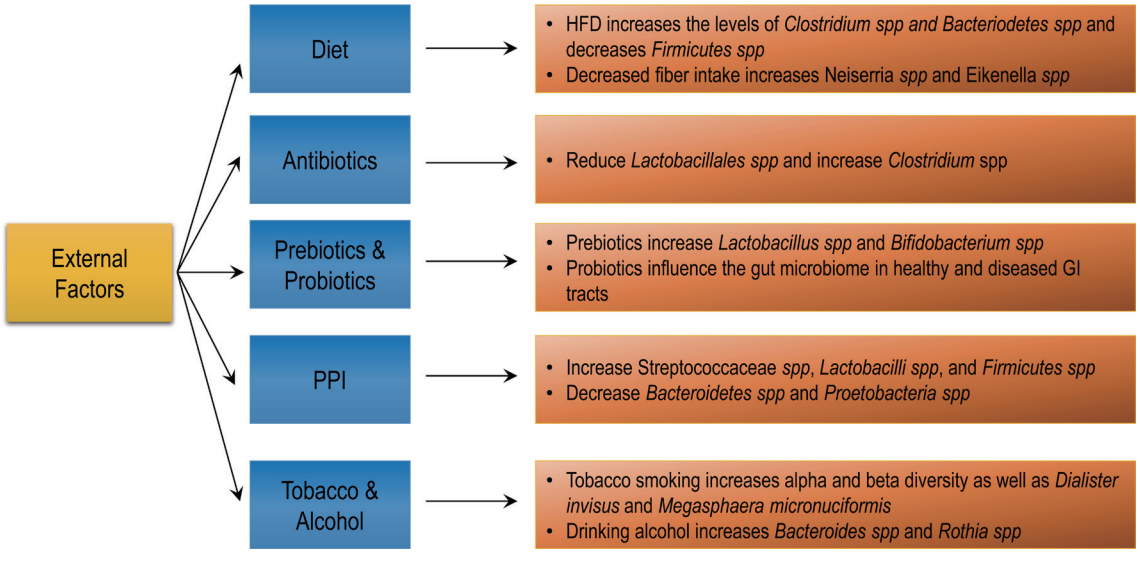

Fig. 2. External factors that influence esophageal microbiome.[24]

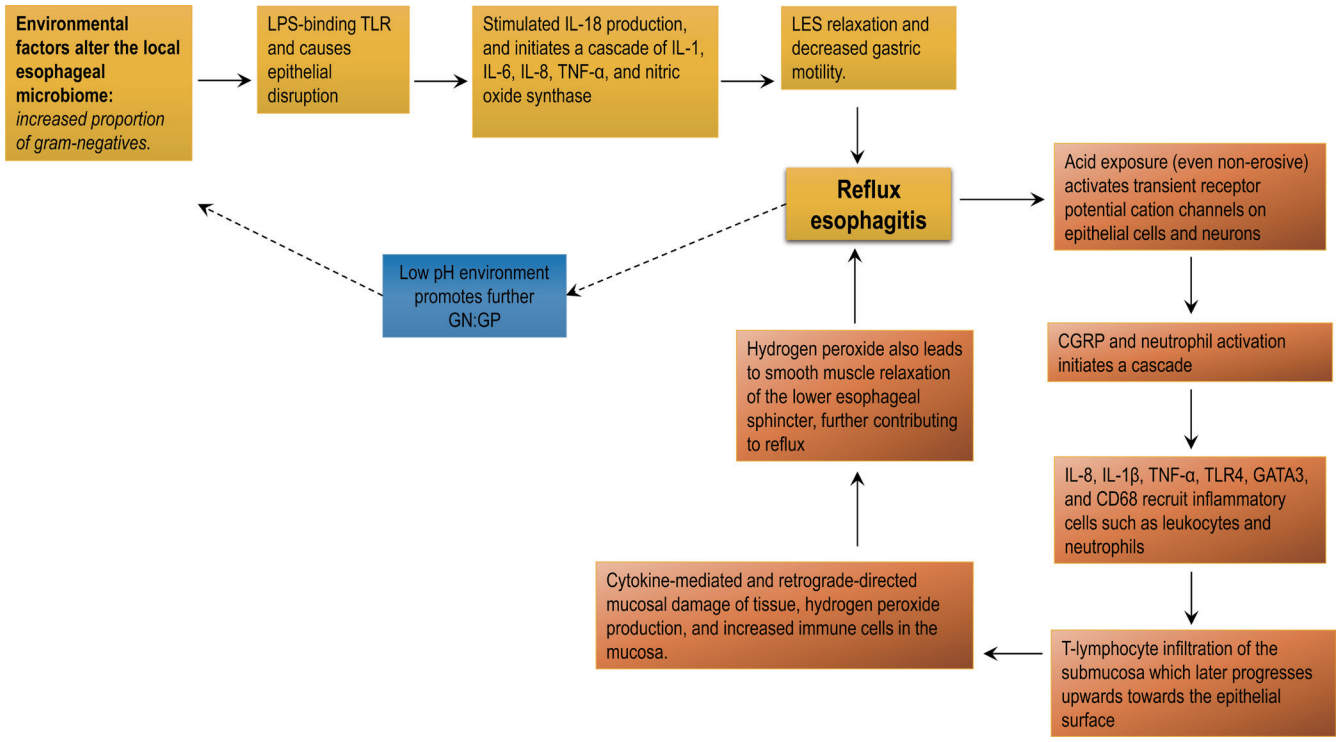

Fig. 3. Proposed mechanism of microbiome-influenced erosive disease.

the luminal esophageal mucosal barrier can subsequently result in propagation of the cytokine cascade, direct entry of acid through the mucosal barrier as well as possible further changes to the biome, and worsening of the clinical symptoms of GERD.

A pivotal and seminal study examined the mechanisms of damage from acid reflux and found that reflux esophagitis does not develop as a chemical injury at the epithelial surface as one would expect with reflux acid-induced mucosal damage.[25] Twelve patients with reflux esophagitis were treated with proton pump inhibitors (PPIs) to resolution of symptoms. Endoscopic evaluations at 1- and 2-weeks post-PPI interruption revealed that all patients had redeveloped reflux esophagitis. With traditional GERD etiology, the refluxed acid would be expected to break down the junctional proteins of esophageal epithelial cells and permeate across the basolateral membrane and lead to cell death. Over time, continued acid reflux would penetrate deeper into the lamina propria and submucosa. Following cell death, hyperplasia of basal progenitor cells and elongated and hyperplastic papillae would be expected. Instead, biopsies revealed that the damage begins with T-lymphocyte infiltration of the submucosa, followed by migration upwards towards the epithelial surface. Hyperplasia of basal progenitor cells was observed, however only in areas without surface erosion.[25] Following this study, the same investigators examined an alternate GERD etiology hypothesis involving hypoxia-inducible factor (HIF) mediated inflammation.[26] When exposed to hypoxic stress or reactive oxygen species, the lack of oxygen inhibits prolyl hydroxylases in the cytoplasm from signaling the degradation of HIF-α by proteasomes. These HIFs are then translocated to the nucleus and signal the transcription of pro-inflammatory cytokines. These investigators re-examined the biopsies from their previous study. Specifically, they immunostained for HIF-1α, HIF-2α, and phospho-p65 and measured mRNA levels of pro-inflammatory mediators. They also studied HIFs in the setting of acidic bile salts. They found that there was an increase in HIF-2α, phosphorylated nuclear factor-kappa B (NF-κB) subunit p65, and mRNA expression of IL-8, IL-1β, and TNF-α in the biopsies with redeveloped reflux esophagitis. Additionally, they observed that exposure to acidic bile salts stabilized HIF-2α in esophageal epithelial cells, assisting in the development of the subsequent pro-inflammatory state.[27]

The association between reflux-induced expression of HIF-2α and its effects on increasing pro-inflammatory cytokines further strengthens the argument that GERD-related esophageal luminal barrier disruptions are the result of more than just direct acid caustic damage.[27] Additional studies on human esophageal squamous cell lines found similar results; noting that reflux stimulated epithelial cells and led to subepithelial cytokine-mediated and retrograde-directed mucosal damage of tissue.[28]

Clearly, there is increasing evidence that GERD involves, in at least some patients, cytokine-mediated pathophysiology. The main cytokines involved in the esophageal pathophysiological cascade of the esophagus are pro-inflammatory cytokines interleukin IL-8 and IL-1β, which recruit inflammatory cells such as leukocytes and neutrophils.[6] This is primarily affected through calcitonin gene-related peptide (CGRP) and substance P expression via activation of transient receptor potential cation channel subfamily V member 1 on epithelial cells and neurons. CGRP and neutrophil activation initiate a cascade of cytokine expression, resulting in local submucosal inflammation, hydrogen peroxide production, and increased immune cells infiltration in the mucosa. In addition to mucosal damage, hydrogen peroxide can lead to smooth muscle relaxation of the lower esophageal sphincter, further contributing to reflux.[6] This theory was further supported by a recent study that examined the relationship between acid exposure and inflammatory cy-

Table 1. Esophageal microbiome compared to diseased states[6,24,41–44]

Disease state	Esophageal Microbiome
Gastrointestinal reflux disease	*Non-erosive reflux disease*: Increased *Proteobacteria* (*Neisseria oralis*, *Moraxella* spp.) and *Bacteroidetes* (*Bacteroides uniformis*, *Capnocytophaga* spp., and *Prevotella pallens*; Decreased *Fusobactereia* (*Leptotrichia*) and *Actinobacteria* (*Rothia spp*). *Reflux esophagitis*: Decreased *Firmicutes* (*Mogibacterium* spp., *Streptococcus infantis*, *Solobacterium moorei*); Increased *Fusobacteria* (*Leptotrichia* spp.) and *Proteobacteria* (*Marivita* spp., *Nisaea* spp., *Mesorhizobium* spp.)
Barrett's esophagus	Increased *Fusobacteria* and *Proteobacteria* (*Neisseria spp*, *Campylobacter spp*.); Decreased alpha diversity as well as *Bacteroidetes* and *Prevotella*
Esophageal adenocarcinoma	Increased abundance of *Proteobacteria*; Decreased *Firmicutes*; relatively unchanged *Streptococci* abundance
Eosinophilic esophagitis	Increased *Proteobacteria* (*Neisseria* and *Haemophiles*) and *Corynebacterium*; Decrease in *Clostridia spp.*
Squamous cell cancer (of the esophagus)	Increased *Fusobacterium* and *Bacteroidetes*; Decrease in relative abundance of *Firmicutes*; Consistently associated with *Porphyromonas gingivalis* and *Fusobacterium nucleatum*
Laryngopharyngeal reflux	*Prevotella ssp*. was more common; *Fusobacterium ssp*. and *Porphyromonas ssp*. were less common

tokines in the esophageal mucosa.[29] Acid exposure time, defined as the time with pH < 4.0 per day at 5 cm above the upper border of the GI junction, was associated with increased gene expression of the inflammatory cytokines IL-1β and TNF-α. Expression of these cytokines, as well as TLR4, GATA3, and CD68, inversely correlated with mean pH values in the distal esophagus.[30]

Microbiome effects on motility

The microbiome also plays a role in gut motility, thereby possibly contributing to the pathogenesis of GERD. Local LPS–TLR4 activation results in inducible nitric oxide synthase and cyclooxygenase-2 (COX-2) expression, which results in the aforementioned inflammatory cascade. In addition, this process also affects local motility within the esophagus and stomach. Nitric oxide expression results in relaxation of the lower esophageal sphincter as well as decreased esophageal motility.[31] COX-2 expression results in delayed gastric emptying.[32] Inhibitors of both enzymes have demonstrated to reversal of the respective effects, offering a mechanism with therapeutic potential.

Recognizably, PPIs provide relief for symptomatic GERD. While previously thought to provide treatment solely via decreased gastric acid production, a new study suggests an anti-inflammatory effect.[27] One study showed that when esophageal squamous cells were exposed to an acidic bile salt medium with or without PPIs, there was an increase in IL-8 mRNA levels in group that did not receive PPIs. Additionally, an acidic bile salt medium led to an increase in IL-8 via NF-κB and AP-1 DNA binding sites. However, PPIs blocked AP-1 and NF-κB subunits and immune cell migration in cells exposed to an acidic bile salt medium.[31] These therapeutic effects, independent of their role on gastric acid, further support cytokine-mediated pathophysiology in GERD.[33,34]

Colonic flora may also play a role in gastric motility. Short chain fatty acids (SCFAs) are produced as the result of fermentation of undigested carbohydrates by colonic bacteria. The associated increased SCFA production has been shown to cause decreased gastric motility.[35] One study investigating gastric emptying in healthy volunteers after oral lactulose intake found a transient decrease in gastric motility after intake.[36] This result has been reproduced through investigations of intracolonic infusions of carbohydrates (lactose) and SCFAs. Both infusions also demonstrated that SCFAs and local colonic fermentation of carbohydrates into SCFAs are associated with decreased gastric tone through an increase in peptide YY and oxyntomodulin.[35,36] These associated changes in gastric motility and tone may also reduce acid clearance and/or promote transient esophageal sphincter relaxations that are associated with GERD.[37,38]

GI microbiome in relation to GERD

The GI microbiome includes various organisms across segments of the GI tract depending on their function and is subject to changes, as mentioned previously, to intrinsic and extrinsic influences. The gastroesophageal microbiome comprises six major phyla: *Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria,* and *Saccharibacteria*.[11] The "normal" (non-disease) esophageal microbiome demonstrates an abundant number of gram-positive organisms, with the most common genus being *Streptococcus ssp*, and this is referred to as a type I microbiome.[39,40] The abnormal microbiome, type II microbiome, consists of more gram-negative organisms. Different disease states have been reported to influence the esophageal microbiota as a results of a multitude of factors (Table 1).[6,24,41–44] For example, in GERD the increased acidic environment can reduce *Prevotella ssp*, *Helicobacter ssp*, and *Moraxella ssp* in the distal esophageal microbiome leading to dysbiosis.[45] Normally, more gram-positive organisms are found in the proximal and mid-proximal esophagus, with increasing rates of gram-negative bacteria going more distal towards the stomach.[46] This likely could be due to gram-negative bacteria possessing LPS, which allows for survivability in lower pH environments.

The presence of a bacterial biofilm can allow some bacteria, those not typically accustomed to increased pH, to thrive in certain locations. A biofilm is composed of an extracellular polymeric substance that encases microorganisms.[47] These substances can withstand the extremes of certain environments, which allows microorganisms that typically do not reside within a specific area to grow and expand. Interestingly *Helicobacter pylori* (*H. pylori)*, within the past decade, has been found within biofilms.[48,49] This, along with other properties such as urease, could have allowed *H. pylori* to colonize other aspects of the GI tract.

H. pylori has been known for decades to modify gastric acid secretion, but the link to GERD had not been fully elucidated. More recently, it has been shown that there is an inverse relationship between *H. pylori* and risk of GERD. A meta-analysis concluded that

Table 2. Potential Mitigation strategies for esophageal dysbiosis and GERD

Modality	Positive outcome	No clear benefit
Prebiotics	Selling *et al*[64] in a case series reported a study of 24 patients with GERD that were given food-grade maltosyl-isomaltooligosaccharides (MIMO) soluble fiber supplements had improvement in symptoms after weeks of daily consumption.	More studies needed to discern efficacy
Probiotics	Gomi *et al*[67] enacted a double-blind, randomized, placebo-controlled trial with 100 healthy Japanese adults that were randomly assigned to a YIT10347 group or placebo group and consumed 100 mL of YIT10347-fermented milk or placebo fermented milk, respectively, every day for 4 wk. The YIT10347 group had significantly higher relief rates of overall gastrointestinal symptoms, upper gastrointestinal symptoms, flatus, and diarrhea than the placebo group. Cheng *et al*[66] in a systematic review analyzes the efficacy of probiotics in GERD. They found 13 prospective studies published in 12 articles and concluded probiotic use can be beneficial for GERD symptoms such as regurgitation and heartburn.	Ostlund-Lagerstrom[69] studied 290 older adults and failed to show any improvement in digestive health after daily intake of a probiotic supplement containing L. reuteri. Qing-Hua *et al*[65] studied the effects of probiotic capsule supplement and found no significant change in reflux diagnostic questionnaire (RDQ) or GI symptom rating scale (GSRS)
Fecal microbiome transplantation	Zheng *et al*[68] utilized a form of FMT called washed microbiota transplantation. They enrolled 27 adults and divided into WNT vs PPI groups, with outcomes showing WMT showed better GERDQ scores, which correlated with better improvement in symptoms of heartburn, acid regurgitation, chest pain, and sleep disturbances than the PPI group.	More studies needed to discern efficacy

there was an increased risk of GERD following *H. pylori* eradication.[50] *H. pylori* can reduce gastric acid secretion.[50] It requires a mucus layer in order to survive in an acidic environment, which can explain why there is a lack of *H. pylori* in the luminal mucosa of the esophagus.[51] Additionally, *H. pylori* can affect GERD by modulating hormones, such as gastrin, ghrelin, and leptin, that play a role in metabolism.[52] Studies have demonstrated that individuals with non-erosive reflux disease (NERD) have a higher prevalence of *H. pylori* compared to those with erosive reflux disease.[52,53] These findings suggest that the *H. pylori* found in NERD may prevent esophageal-gastric mucosal erosion.

Another study evaluated the esophageal microbiota in GERD as well as related complications of BE and esophageal adenocarcinoma.[51] It was also found that *Campylobacter spp.*, a common gram-negative bacteria found in the mouth, but not typically within a normal esophagus, was significantly increased in patients with GERD and BE compared to healthy individuals and those with carcinoma.[49] Due to the presence of reflux, there may be changes in the mucosal lining that allow the growth of *Campylobacter spp*. These results suggest a strong relationship of *Campylobacter spp,* with diseases involving reflux in the esophagus.

EoE is another disease state that has recently been associated with alterations in the esophageal microbiome.[41] EoE is characterized by chronic eosinophilic infiltration of the mucosa leading to mucosal barrier breakdown due to triggers such as genetic risk factors, environmental shifts, allergens, and even microbiota changes. In pediatric patients with EoE, genera *Corynebacterium spp.* and *Neisseria spp.* were increased compared to non-EoE patients.[54] An overall elevation in gram-negative organisms correlated with increased inflammation, as evidenced by histopathologic abnormalities upon endoscopic biopsy. A principal component analysis showed that EoE patients were generally characterized by larger amounts of *Haemophilus, Pasteurella, Fusobacterium*, and *Aggregatibacter spp.* and smaller amounts of *Actinomyces, Veillonella,* and *Rothia spp*. The analysis further showed a significant increase in *Haemophilus spp.*, which then normalized once EoE was treated.[55] A systematic review and meta-analysis demonstrated that PPIs have been efficacious in leading to histological remission (defined as <15 eos/hpf) in 50.5% (confidence interval (CI) = 42–58.7%) and symptomatic improvement in 60.8% (CI = 48–72%) of patients.[56–58] The likely mechanisms for these effects may involve downregulated expression of pro-inflammatory cytokines such as IL-5 and IL-3, similar to corticosteroids, and acid suppression leading to growth of additional gram-negative organisms in lower pH environments.[59]

Oral hygiene can influence the esophageal microbiome with downstream effects.[6] Good oral hygiene is associated with a higher proportion of gram-positive cocci and rods, mostly comprised of *Streptococcus spp*., which contrasts with poor oral hygiene, which is associated with shifts to a higher proportion of anaerobic gram-negative bacteria such as *Prevotella spp*.[60] The oral microbiome shift to a more gram-negative dominant flora may have distal effects of LPS-inducing TLRs and activation of an inflammatory cascade in the esophagus. A study analyzing the differences in bacteria taxa levels in untreated GERD patients found that there may be benefit in the oral cavity microbiome in patients with GERD who take PPI. This may be a result of a pH change and a subsequent effect on oral conditions.[45] Further research and randomized controlled studies can help elicit the direct effect of the oral cavity on the distal esophageal microbiome.

Mitigation strategies for esophageal dysbiosis and GERD

Many current guidelines recommend PPIs as first line of treatment for GERD,[61–63] although prolonged use may contribute to persistent symptoms, as the underlying etiology is not fully addressed. Thus, addressing the microbiome directly may be warranted. There are several mitigation strategies that have been proposed for treatment of GERD. Thus, focusing on a personalized regimen for each patient may be a better strategy than long-term PPI use (Table 2).[64–69]

Prebiotics

Prebiotics are non-digestible food ingredients that selectively promote the growth of beneficial bacteria in the GI tract, primarily

Lactobacilli and *Bifidobacterium spp.*, which can improve gut barrier function and reduce inflammation.[64] In addition to promoting selective fermentation by probiotics and interacting with pathogens to prevent colonization, prebiotics are also absorbed into the intestine and exert anti-inflammatory properties. These benefits, however, may not be universal for all patients and may have many factors which influence their potential effects, including diet, demographics, and genetics.[70]

A case series reported a study of 24 patients with GERD who were given food-grade maltosyl-isomaltooligosaccharides (MIMO) soluble fiber supplements.[64] Orally ingested MIMOs have been shown to selectively increase populations of certain gram-positive organisms such as *Bifidobacterium* and *Lactobacillus spp*. Albeit a small sample size, they found that 88% of their study cohort had improved symptoms of GERD after weeks of daily consumption. Subgroup analysis showed that two of the patients who were previously PPI-dependent for symptom control were able to eliminate PPI therapy after prebiotic initiation. The authors proposed that the likely mechanism involves a change in the microbiome via restoration of the protective and balanced symbiotic relationship in the esophagus.

Probiotics

Probiotics are live microorganisms that are intended to alter the composition and function of the gut microbiome in a beneficial way.[65] Studies have suggested that certain probiotics, such as *Lactobacillus ssp.* and *Bifidobacterium ssp.*, can reduce acid reflux symptoms through modulating immune responses and inhibiting potential pathogens by producing short-chain fatty acids, such as lactic acid.[66] Probiotics may also increase gastric emptying by interacting with mucosal receptors on the stomach, which may result in a transient relaxation of the lower esophageal sphincter, one of the pathophysiological mechanisms associated with GERD.[71,72] Several probiotic supplements have demonstrated modest efficacy in reducing heartburn symptoms.[66,67,73] An interesting study, still in progress, hypothesized that long-term PPI use and its effect on microbiome disturbances could affect concomitant probiotic use.[74] In this randomized, double-blind, placebo control trial, Liu *et al*. plan to enroll 120 eligible patients with GERD and place them either in a PPI (rabeprazole) plus probiotic (LiHuo probiotic) arm or a PPI alone arm. Results of this study should provide new insight regarding the effects of concurrent probiotic administration with PPI on the determinantal effects of GI tract homeostasis.

Probiotics may be beneficial for small intestinal bacterial overgrowth, which can impair immunity and/or intestinal motility.[75] Dietary intake or addition of probiotic-containing foods has also been evaluated as a means for microbiome manipulation as a symptom-mitigating mechanism for GI-related diseases, such as prevention of intestinal disorders, reduction in symptoms of irritable bowel syndrome, and protection against some cancers.[76] Intake of probiotic-containing yogurt decreases symptom severity in functional dyspepsia.[77] Thus, enrichment of foods with probiotics may be another effective mechanism to achieve this therapeutic effect.[78,79]

Fecal microbiome transplantation (FMT)

FMT involves introducing the feces of a healthy donor into a diseased individual in order to restore the normal microbial composition of the lower GI tract. It is particularly effective and has been extensively studied in conditions such as refractory *Clostridium difficile* infection, and to a lesser degree in other conditions including irritable bowel syndrome, inflammatory bowel disease, and constipation.[80–83] However, according to a recent study, the same may apply to GERD.[68] Zheng *et al*. utilized a form of FMT called washed microbiota transplantation (WMT), looking specifically at NERD. WMT is a microbiota transplantation method that is similar to traditional FMT but adds the safety measure of washed microbiota. WMT is prepared by an intelligent microorganism separation system, which subjects the sample to a multi-level filtration system, washing the bacterial solution prior to use. It has better safety, quality control for bacterial flora disorders, and effectiveness.[84] Twenty-seven adults (aged 18-85) were divided into WNT (n = 15) and PPI (n = 12) groups. WMT was delivered via a transendoscopic enteral tubing through one of two routes; either into the jejunum via gastroscopy or into the caecum via enteroscopy. At 1 month after treatment, the total remission rate in the WMT and PPI groups was 93.3% and 41.7%, respectively. Compared with the PPI group, the WMT group showed better results in GERDQ scores ($p = 0.004$) and RDQ scores ($p = 0.003$), as well as in the remission months ($p = 0.002$); nine patients showed sustained remission for more than 6 months in the WMT groups, while there were only two in the PPI group. Furthermore, the patients in the WMT group achieved an associated, better improvement in symptoms of heartburn, acid regurgitation, chest pain, regurgitation, and sleep disturbance compared to the PPI group.

Diet and lifestyle changes

Diet and lifestyle play an extremely critical role in determining the composition of the gut microbiome. Based on a recent systematic review, dietary factors such as protein and fat intake, and lifestyle factors such as alcohol consumption (except beer and wine) and low mental state were all positively correlated with GERD.[61] Citrus intake between meals, sweet and spicy foods, and poor eating habits were positively correlated with GERD. There were also correlations with non-dietary related factors such as higher education, less sleep time, sedentary and physical occupational activities, night work, and less exercise. Conversely, vegetarian diets, fruits, vegetables, vitamins, coffee, and fiber were negatively correlated with GERD.[61,85,86]

There also appears to be specific changes in the microbiome related to alterations in sugar. A recent small study evaluating obese individuals noted resolution of their GERD symptoms within two weeks after switching to a low-carbohydrate diet. Notably, there were no significant changes in body weight, thereby the authors suggested the benefit was through the dietary change alone.[87] They did not, however, consider that these dietary changes may have had a beneficial effect on the esophageal microbiome, thereby promoting GERD improvement. Another study demonstrated that a very low-carbohydrate diet significantly reduced distal esophageal acid exposure and improved symptoms in obese individuals with GERD.[88] An additional study looked at 12 patients who were enrolled to observe acid changes in GERD with varying types of food and found that high-carbohydrate diets could increase acid reflux in the lower esophagus and exacerbate reflux symptoms.[89] Furthermore, a more recent randomized control trial enrolled 98 veterans with symptomatic GERD and randomly assigned them to either a high total/high simple, high total/low simple, low total/high simple, or low total/low simple carbohydrate diet for nine weeks to determine the effect of carbohydrate reduction on the symptoms of GERD. Reflux episodes and esophageal acid exposure time measured by pH monitoring were significantly improved and correlated with improvements in GERD symptoms. There was a significant

main effect of diet treatment on acid exposure time ($p = 0.001$) and on the total number of reflux episodes ($p = 0.003$). These findings suggest that reducing simple sugars in the diet can be effective in improving GERD symptoms.[90] Although likely causally associated at least to some degree, the effects of these dietary changes and related potential beneficial effects on the esophageal microbiome have not yet been studied.

Stress

Patients with NERD can have acute stress induced dilated epithelial intercellular spaces (DIS). Similarly, exposure of rats to acute stress was found to induce DIS and increase esophageal mucosal permeability to small molecules.[91] Esophageal mast cells also appear to be closely related to stress, as stress-induced permeability occurs. One study showed that the stress response mediator corticotrophin-releasing hormone receptor subtype 2 was expressed in the rat esophageal mucosa.[92] Lastly, patients with a diagnosis of GERD report a higher symptom burden with increased stress, suggesting the underlying mechanism may involve not only increased central sensitization to acid, but peripheral sensitization driven by permeability changes at the level of the esophageal mucosa.[91] These studies further demonstrate that GERD-related symptoms and mucosal changes may be related to factors beyond direct acid esophageal contact. Stress may have multiple effects on the microbiome via alterations in diet, inflammatory processing, sleep, and immune function, among other adverse functional changes. The specific effects of stress on the esophageal and GI microbiome, however, have yet to be defined.

Conclusion

We reviewed the current evidence regarding GERD and the GI microbiome. There is emerging data to suggest a paradigm shift in focus from GERD as a result of direct contact-mediated acidic injury towards an altered microbiome and induction of an inflammatory cytokine cascade. The effects of this microbiome cytokine cascade can have clinically significant consequences involving inflammatory changes in the esophagus. The emerging data implicate an ever-increasing spectrum of esophageal diseases ranging from GERD, BE, esophageal carcinoma, EoE, esophageal dysmotility, and laryngopharyngeal reflux. This review serves to suggest a translational message with clinical implications. Clearly, more robust studies and randomized controlled trials are necessary to better elicit the mechanisms involved in the microbiome-GERD relationship and to help elucidate mitigation strategies where appropriate. There is, however, emerging evidence that there may be a paradigm shift from the traditional treatment of GERD using acid-reducing medications towards focusing on treating the dysbiotic microbiome.

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Author contributions

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