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SYSTEMATIC REVIEW

The microbiota in eosinophilic esophagitis: A systematic review

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Abstract

Eosinophilic esophagitis (EoE) is an atopic disease of the esophagus that has shown a significant increase in incidence and prevalence in the last 20 years. The etiology of EoE is unclear, and few studies explore the esophageal microbiota in EoE. The local microbiome has been implicated in the pathogenesis of several allergic and inflammatory diseases, such as asthma and eczema. In this study, we performed a systematic review to evaluate differences in the microbiota profile of patients with EoE compared with controls. MEDLINE, Embase, Cochrane Library, Scopus, and CINAHL (Cumulative Index to Nursing and Allied Health Literature) databases were searched to identify studies investigating the microbiota composition in EoE. Three reviewers screened the articles for eligibility and quality. Seven articles underwent full-text review, and a narrative synthesis was undertaken. The microbiota of the mouth and esophagus are correlated. Patients with active EoE present increased esophageal microbial load and increased abundance in particular species, such as Haemophilus and Aggregatibacter. On the other hand, EoE patients present a decrease in Firmicutes. High microbial load and abundance of *Haemophilus* are observed in EoE patients, but little evidence exists to demonstrate their influence on inflammation and disease. Understanding microbial signatures in EoE might contribute to the development of novel therapeutic strategies.

Introduction

Eosinophilic esophagitis (EoE) is an increasingly common chronic allergic disease characterized by eosinophilic inflammation in the esophagus and a type 2 immune profile. The pathophysiology of EoE is not entirely understood; however, evidence suggests that an impaired epithelial barrier allows contact between allergens and the esophageal mucosa, leading to the release of alarmins by the epithelium. Alarmins then initiate, through type 2 innate lymphoid cells (ILC2s) and basophils, an immune response that consists of the release of several cytokines, including IL-4, IL-5, and IL-13.[1] Those cytokines induce eosinophilic inflammation and further barrier disruption. In parallel with this process, tissue-resident antigen-presenting cells (APC) activate CD4+ T helper type 2 (Th2) cells following contact with the antigen. Through cytokine signaling, Th2 cells recruit and activate eosinophils, mast cells, and plasma cells, which induce the localized production of IgE and IgG4.[2,3] The release of IgE then triggers the release of TGF-β from mast cells, which leads to further inflammation and tissue fibrosis.[4,5]

EoE causes heartburn, dysphagia, food impaction and, if inflammation is left untreated, can progress to fibrostenosis.[6] In children, EoE can also cause feeding intolerance, nausea, vomiting, and failure to thrive.[7] The pooled incidence is 6.6 per 100 000 cases in children and 7.7 per 100 000 in adults, and the prevalence is

34.4 cases per 100 000 inhabitants. Previous research has demonstrated that sex is a significant risk factor for EoE, where males have three times increased susceptibility in comparison to females.[8] Current treatment options include dietary exclusion of trigger foods, continuous pharmacological treatment with a proton-pump inhibitor (PPI) or topical corticosteroids, and endoscopic dilations in fibrotic patients.[9]

Patients with EoE commonly present with concomitant atopic disorders such as rhinitis, asthma, and eczema. However, these conditions have not been proven to predispose to EoE.[10] The local microbiota is implicated in the pathogenesis of several atopic diseases.[11,12] Park *et al*. published a systematic review in 2020 on the esophageal microbiota in health and disease, including esophageal cancer, Barrett's esophagus, and two EoE articles.[13] The rise in microbiome studies led to a rapid increase in published articles on the microbiome in EoE. Here, we review all available articles to identify and appraise existing information from published peer-reviewed literature on the local microbiota, specifically in EoE.

Until recently, the esophagus was not considered to have a mucosa-associated microbiome, although the rise of the small ribosomal subunit (16S rRNA) gene amplicon sequencing has allowed growth-independent organism characterization, which indicates that this organ contains a resident microbial population that shifts in different health states.[14]

We hypothesize that an inflamed esophageal mucosa will impact tissue metabolism, influencing the expression of bacterial virulence factors within the microbiota. It is believed that these virulence factors may contribute to even further inflammation and eosinophil recruitment. To address this hypothesis, we synthetized peer-reviewed data to investigate the possibility of a distinct microbiome in EoE patients.

Methods

Protocol and registration. We followed the recommended approach described in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[15] The protocol for this review has been registered at the International Prospective Register of Systematic Reviews (PROSPERO) under the registration ID CRD42020172862.

Search strategy. MEDLINE, Embase, Cochrane Library, Scopus, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases were searched for relevant studies published within 1993, when EoE was described as a clinical-pathological disorder distinct from eosinophilic gastroenteritis,[16] and January 2022.

Studies were retrieved and independently screened by three authors. Based on our inclusion and exclusion criteria, relevant studies were selected to be full text screened.

The following search strategy was used for MEDLINE: eosinophilic esophagitis OR eosinophilic oesophagitis OR ee OR eoe OR esophagus OR oesophagus OR esophageal OR oesophageal OR esophagi OR oesophagi; AND microbiota OR microbiome OR microenvironment OR microflora OR flora OR microorganism OR bacteria AND 16S OR RNA OR Ribosomal. This keyword strategy was adapted and reviewed to fit the other databases. Eligible peer-reviewed articles and gray literature were included in this review. Disagreements were settled by discussion between the authors.

Inclusion and exclusion criteria. Case–control studies that identified the oral and esophageal microbial population by 16S rRNA sequencing of adult and pediatric patients diagnosed with EoE were selected for inclusion in this review. Studies with publication dates prior to 1993 were excluded, as were studies that adopted any microbial identification methods other than rRNA sequencing or that were not published in English. Reviews were also excluded.

Outcome measures. The primary outcome is to identify characteristics in the microbiota of patients with EoE, allowing us to determine if there is a typical bacterial profile in EoE. This could allow a better understanding of how commensal bacteria behave in an EoE environment. Data extracted from each study included title, year of publication, country of study, number of subjects (cases and controls), treatment status, sample type and site, 16S rRNA gene region of analysis, bacterial abundance, bacterial diversity, and final conclusions.

Quality of studies. The quality of the articles was assessed by two reviewers and scored based on the Newcastle-Ottawa Scale (NOS).[17] The NOS evaluates the quality of group selection, group comparability, and exposure for case–control studies. Each component is awarded zero or one point (marked as a star *), except for the comparability item, which may receive one or one two stars. Studies that sum up 1–3 starts are classified as low quality, 4–6 stars are moderate quality, and 7–9 stars are considered high quality.

Results

A total of 956 articles were identified in the initial literature search. Thirty duplicates were identified and excluded. After the exclusion of duplicates, 926 studies were screened. Thirty-six relevant studies were selected for full-text screening, and a final number of seven full texts and three abstracts were included in this review. The majority of studies were excluded because the subjects presented with conditions other than EoE. These results are summarized in Figure 1.

The studies included in this review analyzed esophageal biopsies or brushings, saliva, and oral swabs from adult and children with and without EoE. A total of 471 patients were included, however, due to the diversity in sample type and the employment of different primer regions for bacterial sequencing, the results could not be pooled for a single analysis, instead, we assembled comparable measures among studies. This information is outlined in Table 1, while a summary of the bacteria reported in the studies can be found in Table 2.

Oral and esophageal microbiota are comparable in eosinophilic esophagitis. Two studies analyzed the oral microbiota in EoE cohorts using 16S rRNA sequencing. Benitez *et al*.[18] compared the oral and esophageal diversity of 68 (33 cases

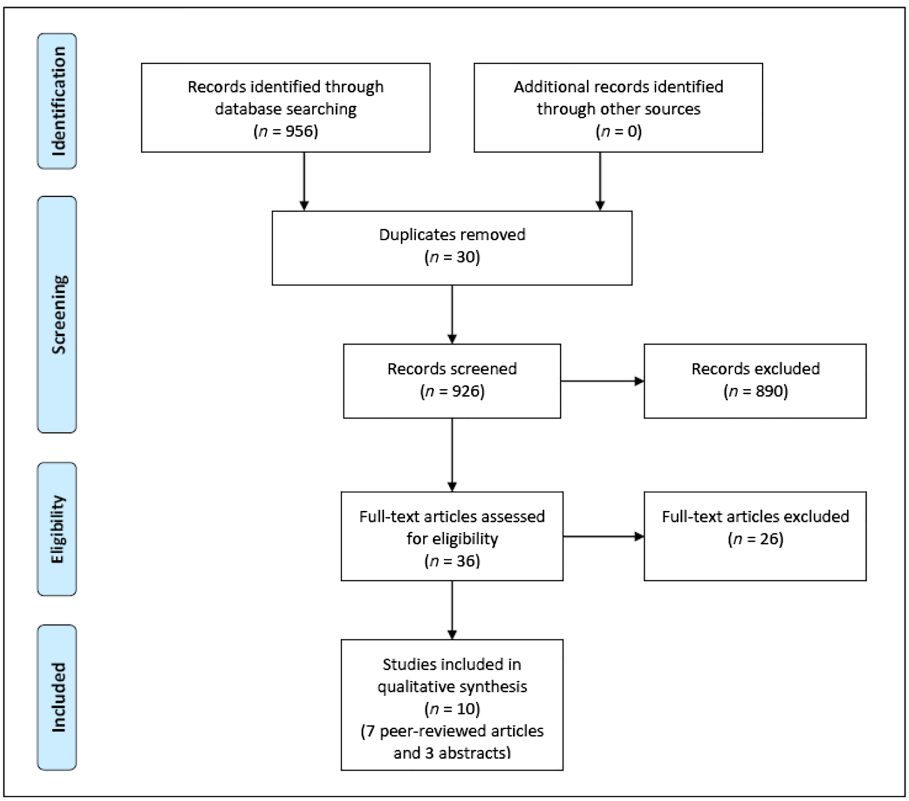

Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of selected studies.

and 35 controls) pediatric patients and showed a correlation between the two sites across patients (Mantel correlation = 0.16, $P = 0.008$; Procrustes R2: 0.15, $P = 0.009$), despite the substantial differences found between oral and esophageal microbiotas. The main differences were that some members of the phylum Firmicutes, including Clostridium, Eubacterium, Megasphaera, Mogibacterium, and Moryella were detected almost exclusively in esophageal samples regardless of disease status. The Atopobium genus of Actinobacteria phylum was predominantly seen in the esophageal biopsy but present in a few oral samples. Neisseria and Corynebacterium were enriched in EoE samples, while Streptococcus and Atopobium genera were consistently enriched in non-EoE control samples.

Dietary changes did not influence the composition of the esophageal microbiota (dietary intervention Adonis *P*-values: weighted UniFrac $P = 0.220$; unweighted UniFrac $P = 0.450$), the addition of food triggers led to an enrichment in *Granulicatella* and *Campylobacter* genera in the esophagus of EoE patients (*Granulicatella*.denovo347: $P < 0.0363$; *Granulicatella*.denovo3064: $P < 0.0358$; *Granulicatella*: $P < 0.0362$; *Campylobacter:* $P < 0.0081$. Raw Kruskal–Wallis *P*-values from significant features detected using LEfSe).

Alpha diversity was represented by sample richness, evenness, and Shannon indexes. Wilcoxon rank-sum test concluded no significant differences were detected between non-EoE controls, active EoE, and inactive EoE subjects.[18] The findings of this study suggest that an active, eosinophil-rich, inflamed tissue is associated with a distinct shift in the relative abundance of crucial esophageal microbes (*Neisseria* and *Corynebacterium*), but not in overall community structure.[18]

Hiremath *et al.*[19] analyzed the salivary microbiota of 45 (26 cases and 19 controls) children aged 6 to 18 years old. This study showed that beta diversity was comparable among the three groups: non-EoE controls, active EoE, and inactive EoE (Bray-Curtis index; $P = 0.93$). At the genus level, children with active EoE had a lower relative abundance of Leptotrichiaceae family members (base mean = 12.9726, $\log_2$ fold change = −3.3750, q value = 0.04) (base mean = 99.8522, $\log_2$ fold change = −1.4859, q value = 0.05), genus *Lactobacillus* (base mean = 8.2011, $\log_2$ fold change = −2.8941, q value = 0.05), and genus *Streptococcus* (base mean = 2543.5310, $\log_2$ fold change = −2.2904, q value = 0.06) compared with non-EoE controls, while non-EoE controls had a higher relative abundance for the *Neisseriaceae family* compared with active EoE (base mean = 75.0051, $\log_2$ fold change = 3.5347, q value = 0.006).

Additionally, a significantly higher relative abundance of *Haemophilus* (base mean = 1858.625, $\log_2$ fold change = −3.111, q value = 0.008) was observed when children with active EoE were compared children with inactive EoE. Relative abundance of *Haemophilus* had a significant correlation with esophageal mucosal abnormalities (base mean = 1942, $\log_2$ fold change = 1.4332, q value = 5.370e-10) and histopathologic severity as assessed by the EoE histology scoring system (base mean = 2014.595, $\log_2$ fold change = 5.8667, q value < 0.001).

Table 1 General characteristics of the included studies

Study	Primer region	Sample	Patient number/PPI status	Findings	Quality of the study
Benitez *et al.*[18]	V1V2	Pediatrics oral swab and esophageal biopsy	68 participants (33 EoE cases, 35 non-EoE controls),66 were on PPIs	Non-EoE controls: ↑ *Streptococcus* and *Atopobium* Active EoE: ↑ *Neisseria* and *Corynebacterium* genus In addition to food trigger to diet: ↑ *Granulicatella* and *Campylobacter* genus	8*
Hiremath *et al.*[19]	V4	Pediatrics salivary samples	45 participants (15 active EoE, 11 inactive EoE, 19 non-EoE controls), 33 were on PPIs	Active EoE: ↑ *Haemophilus* PPI use: ↑ *Streptococcus*, *Corynebacterium*, and *Rothia* Active EoE: ↓ *Leptotrichiaceae*, *Actinomyces*, *Lactobacillus*, and *Streptococcus* Non-EoE controls: ↑ *Neisseriaceae*	9*
Harris *et al.*[20]	V1V2	Pediatrics and adults, EoE and GERD using esophageal string test	70 participants (11 active EoE, 26 inactive EoE, 33 controls), some control subjects and half of the EoE subjects were on PPIs	↑ Bacterial load in active EoE, non-active EoE, and GERD EoE: ↑ *Haemophilus*, *Pasteurella*, *Fusobacterium*, and *Aggregatibacter* EoE: ↓ *Actinomyces*, *Veillonella*, and *Rothia*	8*
Arias *et al.*[21]	V4	Adult esophageal biopsy	20 participants (10 controls, 10 EoE before and after remission) PPI non-responsive EoE patients	Active EoE: ↑ bacterial load Microbial load normalized after food elimination diet	9*
Laserna-Mendieta *et al.*[22]	V4	Adult middle esophageal biopsy in active EoE and after remission through different treatments	40 participants (30 active EoE, 10 PPI responsive, 10 swallowed topical corticosteroids, 10 food-elimination diet, 10 non-EoE controls)	Control: ↑ Proteobacteria ↓ Bacteroidetes Active EoE: ↓ *Filifactor*, ↓ *Parvimonas*, ↓ *Porphyromonas* Treated with swallowed topical corticosteroid: ↓ Firmicutes, ↑ Proteobacteria, Bacteroidetes and Fusobacteria Treated with PPIs: ↓ Bacteroidetes and Fusobacteria	9*
Benitez *et al.*[23]	V1V2	Pediatric esophageal biopsy	33 active EoE, 36 inactive EoE, 10 controls (all patient were on PPIs)	Active EoE: ↑ *Haemophilus* EoE: ↓ *Alloprevotella* STC in EoE: ↓ *Haemophilus* ↑ *Candida*	8*
Johnson *et al.*[24]	V3V4	PPI non-responsive adults, mid-esophageal biopsy	24 PPI non-responsive EoE patients (all on PPI), 25 non-EoE controls (16 on PPI)	No significant differences found between EoE cases and controlsPPI use: ↑ *Burkholderia*, *Eikenella*, and *Kingella*	8*

(Continues)

Table 1 (Continued)

Study	Primer region	Sample	Patient number/PPI status	Findings	Quality of the study
Parashette *et al.*[25]	Not specified	Pediatric biopsy	22 healthy, 5 PPI-responsive EoE, 9 PPI-non responsive EoE	PPI non-responsive EoE: ↑ *Gemella*, *Hallela* PPI responsive EoE: ↑ *Actinomyces*, *Catonella*, *Porphyromonas*	abstract
Smith *et al.*[26]	V4	Pediatric cytology brush samples	18 controls, 7 reflux esophagitis, 6 active EoE, 7 treated EoE, 5 untreated IBD, 5 treated IBD	Esophagus: EoE: ↑ *Bacteroidetes* Colon: Non-active EoE: ↑ *Clostridia* Controls: ↑ *Bacteroidia*	abstract
Ghisa *et al.*[27]	Not specified	Not specified	8 active, 8 inactive	Active EoE: ↑ Actinobacillus, Alloprevotella, Spirochaetes Non-active EoE: ↑ Firmicutes	abstract

PPI use was associated with a higher abundance of *Streptococcus* (base mean = 2687.9599, $\log_2$ fold change = 3.1740, q value = 4.28e-05), *Corynebacterium* (base mean = 77.8230, $\log_2$ fold change = 3.0577, q value = 0.001), and *Rothia* (base mean = 38.4750, $\log_2$ fold change = 1.2574, q value = 0.01). Although the PPI use was not significantly associated with a difference in microbial richness, or alpha or beta diversity, the richness and alpha diversity tended to be lower in children who were using PPIs (all $P > 0.20$).

Microbial load: A comparison between eosinophilic esophagitis and gastroesophageal reflux disease (GERD). Two papers were identified in this review as investigating the esophageal microbial load in EoE.[20,21] The first by Harris *et al*.[20] analyzed the microbiota of 70 subjects, including pediatric and adult patients with active EoE, treated EoE, Gastroesophageal reflux disease (GERD) and normal controls using esophageal brushings captured with the "esophageal string test". EoE patients presented increased abundnance of *Haemophilus*, *Pasteurella*, *Fusobacterium*, and *Aggregatibacter* and reduced abundance of *Actinomyces*, *Veillonella*, and *Rothia*. *Haemophilus* was identified as significantly increased in untreated EoE compared with normal control subjects ($P = 0.047$). All groups were positive for *Haemophilus*, but the relative abundance was significantly higher in untreated EoE subjects than control subjects or GERD.

In addition, the average bacterial load detected in all subjects with EoE was greater than that determined from normal subjects ($P < 0.01$). Epithelial eosinophilia did not influence the load of bacteria. The average bacterial load found in GERD subjects was also significantly increased relative to that of the esophagus in control subjects ($P < 0.0001$), suggesting that the load of bacteria is associated with an inflamed esophagus and not only in EoE patients. However, the bacterial load was increased in subjects with EoE independent of the diagnosis, treatment, or disease activity ($P < 0.01$), indicating that high microbial load may also be associated with post-inflammation status or underlying disease processes.

Secondly, Arias *et al*.[21] analyzed the microbial load of 10 PPI non-responsive EoE patients, and 10 non-EoE controls. Biopsies from EoE subjects were taken before and after a 6-week 6-food elimination diet (FED) that induced histological and clinical remission. The average bacterial load detected in esophageal samples of subjects with active EoE was 2.85-fold higher compared with non-EoE control samples ($P < 0.002$). Microbial load subsequently normalized (1.16-fold increase) following six food elimination diet-induced disease remission ($P < 0.005$).

Analysis of bacterial abundance for predicted metabolomics content. The most recent published article on the EoE microbiota[22] uses 16S rRNA sequencing and comprehensive bioinformatics techniques to thoroughly interrogate the data. While most other studies reported here focus on the microbiota taxonomy, Laserna-Mendieta and co-authors predicted (PICRUSt2) the enzymatic functions and metabolic pathways of the EoE microbiota. Regarding microbiota composition, Firmicutes, Proteobacteria, and Bacteroidetes were the predominant phylum across all groups, respectively. This study showed

Table 2 Characteristics of bacteria found in the esophagus

Phylum	Genus	Characteristics	Results	Pathogenicity status	Previously associated with
Proteobacteria	*Neisseria*	Gram-negative, aerobic. They extract and import iron from the human host through iron-binding proteins hemoglobin, lactoferrin, and transferrin[28]	Contradicting results showed this genus to be enriched in EoE samples[18] and enriched in non-EoE controls.[19] However, the non-EoE controls in Hiremath *et al*'s[19] study presented symptoms of esophageal dysfunction.	Pathogen or opportunistic commensal[29]	Abundant in the oral cavity. • Lower respiratory tract infection[30] • *N. mucosa* found to be present in six fold higher amounts among obese participants compared with normal weight individuals[31] • Higher in tongue/pharyngeal cancer patients compared with controls[32]
Proteobacteria	*Aggregatibacter*	Formerly *Haemophilus*. Gram-negative, fastidious, non-hemolytic, capnophilic[33]	Enriched in EoE samples[20]	Pathogen or opportunistic commensal.	• Higher in fecal samples of patients with Grave's disease[34] • Oral *Aggregatibacter actinomycetemcomitans* associated with higher risk of pancreatic cancer[35]
Proteobacteria	*Pasteurella*	Gram-negative, anaerobic	Enriched in EoE samples[20]	Pathogen or opportunistic commensal capable of causing infections in humans, domestic and wild animals	• Infections resulting from animals bite or scratch wounds[36] • Meningitis[37]
Proteobacteria	*Actinobacillus*	Gram-negative, aerobic, microaerophilic or facultatively anaerobic, fermenting carbohydrates with the production of acid[38]	Enriched in EoE[39]	Pathogen or opportunistic commensal	• Periodontitis[33]
Proteobacteria	*Campylobacter*	Gram-negative, microaerophilic, presents flagella (adhesion and invasion) and produces toxins.[40]	Enriched in addition to food trigger to diet [18]	Pathogen or opportunistic commensal	• Gastroenteritis • Diarrhea • Periodontitis • Associated with Barret's esophagus, Crohn's disease and ulcerative colitis[41]
Proteobacteria	*Haemophilus*	Gram-negative, often encapsulated[42]	Enriched in active EoE,[19] Enriched in EoE samples[20]	Pathogen or opportunistic commensal	• Sinusitis • Acute tracheobronchitis • Pneumonia • Epiglottitis[43] • Exacerbation of chronic obstructive pulmonary disease[44] • Increased in middle and inferior meatus of chronic rhinosinusitis patients[45]

(Continues)

Table 2 (Continued)

Phylum	Genus	Characteristics	Results	Pathogenicity status	Previously associated with
Firmicutes	*Streptococcus*	Gram-positive, non-motile, catalase-negative, facultative anaerobic. They are classified based on their hemolytic capacity (α-, β-, γ-hemolysis).[42]	Enriched in non-EoE control samples,[18] Enriched with PPI use,[19] Decreased in active EoE [19]	Commensal, beneficial and pathogenic species [46]	• Used as a probiotic, reduces uremia[47] • High in antral gastritis patients[48] • *S. pyogenes* causes upper respiratory tract and skin infections. • *S. pneumoniae* cause infections of the respiratory tract[42]
Firmicutes	*Granulicatella*	Gram-positive, facultative anaerobic[49]	Enriched in addition to food trigger to diet [18]	Normal flora or opportunistic commensal	• Endocarditis • Infections related to prosthetic material • infections of breast implants[49]
Firmicutes	*Lactobacillus*	Gram-positive, aero tolerant anaerobes or microaerophilic, non-spore-forming	Decreased in active EoE [19]	Commensal, beneficial, commonly used as probiotics[50]	• Probiotic to reduce uremia,[47] asthma, atopic dermatitis • Improve diarrhea symptoms • Aid in weight loss[50]
Firmicutes	*Veillonella*	Gram-negative, lactate fermenting, anaerobic.[51]	Decreased in EoE samples[20]	Normal flora but have also been associated with oral diseases.	• Aids in the removal of toxic waste products from biofilm communities, due to their unusual preference for organic acid carbon sources. Produces heme, an essential nutrient required by oral pathogens [51]
Firmicutes	*Filifactor*	Gram-positive, anaerobic[52]	Decreased in active EoE[22]	Pathogen or opportunistic commensal	• Periodontitis • Gingivitis • Diabetes during pregnancy • Oral squamous cell carcinoma[52]
Firmicutes	*Parvinomas*	Anaerobic, Gram-positive[53]	Decreased in active EoE[22]	Commensal, found in the oral cavity, respiratory system, gastrointestinal tract and vagina	• Periodontitis • Meningitis • Bacteremia[53]
Bacteroidetes	*Porphyronomas*	Anaerobic, Gram-negative[54]	Decreased in active EoE[22]	Keystone pathogen	• *Porphyromonas gingivali* can manipulate complement-TLR crosstalk and increase inflammation, even at low concentrations • Periodontitis[54]
Actinobacteria	*Atopobium*	Anaerobic, catalase-negative, Gram-positive	Enriched in non-EoE control samples [18]	Normal oral flora, vaginal commensal	• Increased in the saliva of patients with esophageal squamous cell carcinoma compared with healthy controls[55,56]
Actinobacteria	*Actinomyces*	Facultative anaerobic, Gram-positive	Decreased in active EoE,[19] Decreased in EoE samples[20]	Commensal inhabitants of the oral cavity, pharynx, gut, genitourinary tract, and skin. Facultative pathogenic	• *A. odontolyticus* in the oral cavity has the ability to degrade gluten.[57] • Increased in fecal samples of pediatric Crohn's disease patients.[58]

(Continues)

Table 2 (Continued)

Phylum	Genus	Characteristics	Results	Pathogenicity status	Previously associated with
Actinobacteria	*Corynebacterium*	Catalase-positive, aerobic, Gram-positive bacilli	Enriched in EoE samples,[18] Enriched with PPI use[19]	Commensal, opportunistic.	• Respiratory infections • Wound infections • Urinary tract infections[59]
Actinobacteria	*Rothia*	Aerobic or facultative anaerobic, non-motile non-spore-forming Gram-positive cocco-bacilli	Decreased with PPI use,[19] Decreased in EoE samples[20,39]	Normal flora of the human oropharynx and upper respiratory tract, opportunistic.	• Dental caries and periodontal disease • Bacteraemia • Endocarditis • Meningitis[60]
Fusobacteria	*Leptotrichiaceae*	Obligate anaerobic or capnophilic.[61]	Decreased in active EoE[19]	Present in the oral cavities, gastrointestinal or urogenital tracts of humans and animals, containing both members of the resident microbiota and pathogens.	The *Leptotrichiaceae* family is rarely isolated and are found in mucous membranes, but when introduced into new tissue, they gain pathogenic potential.[61]
Fusobacteria	*Fusobacterium*	Obligate anaerobic Gram-negative	Enriched in EoE samples[20]	Symbiont, opportunist, commensal of the oral cavity.	• Periodontitis, endodontic infections, head and neck cancers • Inflammatory bowel disease, colorectal cancer • Produces significant LPS which may account for virulence[62]
Spirochaete	Not specified	Unique architecture embracing both Gram-positive and Gram-negative features. Treponemes and *Borrelia* lack lipopolysaccharide.[63]	Enriched in active EoE[27]	Parasitic and commensal species	• *Treponema pallidum* causes syphilis • Treponemes are present in the gum of periodontitis patients[63]
Proteobacteria	*Burkholderia*	Gram-negative, previous part of *Pseudomonas* genus[64]	Enriched with PPI use[24]	Oportunistic pathogen, obligate pathogen and commensal species. Some possess anti-fungal properties	• Nosocomial infections, especially in cystic fibrosis • Glanders[64]
Proteobacteria	*Eikenella*	Facultative anaerobic, Gram-negative.[65]	Enriched with PPI use[24]	Commensal of the mouth, intestine and genital tract	• Respiratory infecions • Bite wounds[65]
Proteobacteria	*Kingella*	Gram-negative, facultative anaerobic[66]	Enriched with PPI use[24]	Commensal organism in the oropharynx	• Epiglottitis • Oropharyngeal infections • Pneumonia[66]

that Streptococcaceae was the most abundant family in all conditions, and *Streptococcus* was the most represented genus, conflicting with Benitez *et al.*'s[18] article where *Streptococcus* was increased in non-EoE only.

Even though no substantial differences were seen between groups, control patients presented higher Proteobacteria and lower Bacterioidetes abundance compared with EoE patients. Patients treated with swallowed topical steroids showed a lower abundance of Firmicutes and a higher proportion of Proteobacteria, Bacteroidetes, and Fusobacteria. Patients treated with PPIs presented lower Bacteroidetes and Fusobacteria abundance compared with active EoE patients.

Laserna-Mendieta *et al.*[22] also showed that *Filifactor*, *Parvinomas*, and *Porphyromonas* were less abundant in active EoE than controls. Those three genera have not been identified in any of the previous studies. This study also showed that *Parvimonas* displayed a partial recovery after therapy (adjusted *P*-value = 0.679, unadjusted $P = 0.036$), while *Filifactor* and *Porphyromonas* showed a slightly lower abundance after treatment. *Porphyromonas* was the most abundant among these genera, being detected in 92% of the individuals.

Based on the microbiota composition and how its products may influence the host metabolism and affect the health state, Laserna and colleagues performed function predictions. It was identified that oxidation/reduction of sulfur groups via a ferricytochrome acceptor was notably different between treatments. The increase of this predicted oxidoreductase enzyme (EC 1.8.2) was observed in the post-swallowed topical corticosteroids (STC) group relative to EoE baseline ($P = 0.082$), post-PPI ($P = 0.060$), and post-FED groups ($P = 0.048$). PICRUSt2 assigned these functions to Proteobacteria and Bacteroidetes, particularly to ASVs in the genus *Pseudomonas* and several unidentified ASVs in the Burkholderiaceae family. Metabolism of amino acids arginine and ornithine (pathways ARGSYN and GLUTORN) were higher in active EoE than in controls. Controls indicated higher degradation of 4-aminobutanoate (pathway 5022) than active EoE and inactive post-PPI and FED. Peptidoglycan synthesis and β-lactam resistance (pathway 6470) were higher in post-FED samples than after STC treatment.

Effect of swallowed topical corticosteroid on bacteria and fungal communities. Benitez *et al.*[23] published a second paper on the microbiome of EoE, being the first to report the fungal microbiome in EoE. *Streptococcus*, *Prevotella*, and *Alloprevotella* were predominant in all groups. Despite the bacterial community composition not being significantly different between groups, *Alloprevotella* was decreased in both active ($q = 0.02$) and inactive EoE ($q = 0.001$), and the abundance of *Haemophilus* was increased in active EoE subjects, compared with non-EoE controls ($q = 0.02$).

This study also investigated the effect of STC on microbial communities. No significant differences associations with STC were found in regards to bacteria. However, the relative abundance of *Actinobacillus* was lower in the presence of STC, compared with steroid-naïve patients. The relative abundance of *Haemophilus* was lower in active STC non-responders compared with active STC-naïve subjects ($P = 0.004$), suggesting that STC reduces the *Haemophilus* signature in active EoE. In regard to fungus, Candida, Cladosporiaceae, and Malassezia were predominant fungal taxa across all groups. While *Agaricomycetes*, *Candida*, *Cladosporiaceae*, and Peniophora were most present in control samples. *Candida* was increased in controls compared with steroid-naïve EoE patients ($P = 0.002$). *Candida* was significantly increased in STC-treated in comparison to untreated subjects ($P = 0.007$), as expected based on previous observations of a higher Candida infection rate during STC therapy.

Microbial response to proton-pump inhibitors. A study lead by Johnson *et al.*[24] analyzed 24 PPI non-responsive EoE cases and 25 non-EoE controls and found no significant differences in the esophageal microbiome between cases and controls or within EoE cases based on clinical features.

However, the use of PPIs was significantly associated with five taxa, including SR1 at the phylum level and Burkholderia, Eikenella, and Kingella at the genus level in cases and controls. All cases and nine controls were on PPIs at the time of endoscopy, which prevented further exploration of additional clinical features and PPI use.

Gray literature. Parashete *et al.*[25] analyzed esophageal biopsies from 22 normal controls, 5 PPI-responsive esophageal eosinophilia, and 9 PPI-non responsive EoE subjects. There was a high presence of *Gemella* ($P < 0.01$) and *Hallela* ($P < 0.01$) in the EoE group and *Neisseria* in the control group.

Another published abstract[26] analyzed the esophageal microbiotas of 18 controls, six active EoE patients, and seven treated EoE patients and showed that untreated EoE patients had a higher average proportion of *Bacteroidetes* than controls (24.8% *vs* 10.4%, $P = 0.13$). Ghisa *et al.*[27] showed, for the first time in EoE patients, the presence of *Spirochaetes* in the mouth, esophagus, and stomach, in addition to higher abundance of this phylum in active EoE. We speculate the Spirocheates to be *Treponema*, as it is commonly found in dental plaque. However, further studies are needed to confirm.

The gray literature studies presented interesting results supporting findings from peer-reviewed papers such as the increase of Bacteroidetes in active EoE[22,26] and report of specific genus for the first time as significantly contrasting on EoE studies, such as *Spirochaetes*.[27]

Discussion

The microbiota has been linked with the initiation and/or perpetuation of inflammation in mucosal surfaces. Thus, it is compelling that we investigate the role of the microbiota in esophageal mucosa inflammation. However, the microbiota in EoE has not been widely studied. Here, we gather all EoE microbiota sequencing studies published thus far. Our main findings showed that patients with active EoE have increased microbial load, as well as increased abundance of Haemophilus and decrease of specific members of the Firmicutes phylum.

Arias *et al.*[21] showed that bacterial load and specific Toll-like receptors (TLR) are overexpressed in the esophagus of EoE patients compared with controls and that those changes were normalized after 6-FED and mucosal healing. TLRs are a type of microbial

pattern recognition present on epithelial and lamina propria cells, and are capable of differentiating pathogens and commensal microorganisms.[21] This suggests that increased exposure of the microbiota and microbial products to the impaired esophageal mucosal barrier may increase the release of alarmins by the epithelial cells in the esophagus, resulting in the advancement of esophageal inflammation.

Our systematic review highlights that the oral and esophageal microbiotas are correlated[18]; it is likely that the oral microbiota shapes the esophageal microbiota by the swallowing of microorganisms and associated products. Also, microbial load is consistently shown to be increased in the esophagus of active EoE patients. Masterson *et al*.[67] exhibited that Hypoxia-inducible factor (HIF)-1α is decreased in biopsies of active EoE patients compared with controls. The decrease of HIF-1α leads to the decrease of β-Defensins, antimicrobial peptides secreted by the epithelium.[68] We speculate that the decrease in β-Defensins, caused by the diminished HIF-1α leads to the increase microbial load in the esophageal mucosa of EoE patients.

However, in inactive EoE, the microbial load results are contradictory between studies. Harris *et al*.[20] showed that microbial load is increased independently of disease status and treatment, while Arias *et al*.[21] showed that microbial load normalized after remission was achieved. These conflicting results could have occurred due to different methodologies used for bacterial quantitative estimation or sample heterogeneity, with both studies only having a limited sample size. Harris *et al*.[20] used quantitative PCR with pan-bacterial primers targeting the small subunit ribosomal RNA (SSU-rRNA) to evaluate the mucosa of adults and children with EoE (different treatments approaches), GERD and normal mucosa controls. While Arias *et al*.[21] used primers for the V4 region of the 16S rRNA to access the mucosa of adults before and after remission through FED and normal mucosa controls. Interestingly, EoE patients from both studies were non-responsive to PPI treatment; however, half of EoE subjects in the Arias *et al*. paper were on PPIs at the time of endoscopy, while none of EoE subjects in the Harris *et al*. study were on PPIs at the time of microbiota characterization. Further studies on the microbial load and PPI status are required to clarify the connection between bacterial load, disease status and treatment in EoE.

Members of the Firmicutes phylum, such as *Streptococcus*, *Lactobacillus*, *Veillonela*, and *Parvimonas*[18–20,22] are shown to be decreased in the esophagus of EoE subjects. A previous study by Holvoet *et al*.[69] showed that supplementation with *Lactococcus lactis* NCC 2287 decrease esophageal and bronchoalveolar eosinophilia in a murine model of EoE. While the link that determines the cause and effect of the microbial composition in EoE is not clear, pre-clinical studies could be performed using those organisms as potential probiotics to replenish the microbiota with genera that are reduced in EoE patients.

Three studies[19,20,23] demonstrated that the abundance of *Haemophilus* was significantly higher in EoE subjects. Laserna-Mendieta *et al*.[22] only detected Haemophilus in one sample, however, they have shown an enrichment in Actinobacillus and Aggregatibacter, which are closely related to Haemophilus, and suggested that microbial analysis could be interpreted differently by the studies. The use of 16S amplicon sequencing provides lower taxonomic resolution and may be responsible for this variation in reported results. To overcome this, future studies should aim to characterize the microbiota populations using shotgun metagenomic sequencing (none primer-based approach, data provided for the total DNA of a given sample), which is capable of providing a non-biased species-level resolution of the community and would be necessary to validate the relationship between Haemophilus and EoE.

The capability of *Haemophilus* to enter epithelial cells[70] suggests that these organisms may be able to take advantage of the impaired barrier in EoE, which in turn contributes to chronic inflammation. *Haemophilus* is associated with a range of other Th2-mediated conditions, including recurrent pediatric asthma, chronic obstructive pulmonary disease, and rhinosinusitis,[45,71,72] strengthening the argument that this genus could be associated with the propagation of inflammation in EoE.

To our knowledge, this is the first systematic review of emerging associations between the local bacterial population and EoE. The main limitations of this review were the low number of total studies, exclusion of articles published in languages other than English, the different methodologies applied to analyze the results, for example the primer region of choice varied between studies and software of author's choice, and diverse approach in reporting the data. Given this heterogeneity, we could not perform a meta-analysis, which was our initial goal. Another limitation is the method used to sequence the microbiota, 16S rRNA sequencing, has its associated drawbacks and limitations. Firstly, the choice of sequencing primers targeting the 16S rRNA variable regions each comes with its own bias and microbiota profiles will differ based on this. Secondly, the taxonomic resolution achieved with 16S rRNA sequencing is less than that achieved with shotgun metagenomic sequencing (MGS).

In most cases 16S rRNA sequencing reads cannot be assigned to the species level, this is mostly due to the short reads generated with this technique and subsequent mapping to microbial databases limits full taxonomic assignment. Finally, 16S rRNA sequencing tends to overlook the mycobiome and virome, which can be captured with the MGS approach. From our review, studies on the local microbiota in EoE are limited. Further studies analyzing bacterial strain and metabolomics are essential to help us characterize the effect of the microbiota in EoE and possibly help identify new targets for EoE and other esophageal diseases. To improve the literature, shotgun metagenomic studies of the esophageal microbiota will be crucial to linking microbial composition to functional contributions to inflammation, and different EoE endotypes previously described by Rothenberg and colleagues.[73]

In conclusion, this systematic review suggests that the microbiota of EoE is similar in composition to the mouth. Patients with active EoE have increased microbial load and increased abundance of Haemophilus. These findings suggest Haemophilus may represent an opportunistic pathogen in EoE that is linked with esophageal inflammation.

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