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Microbiota Modulation as a Therapeutic Approach in Eosinophilic Esophagitis: A Review of Current Evidence and Future Directions

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I. INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic, inflammatory, immune-mediated disease of the oesophagus characterized by symptoms such as dysphagia, food impaction, vomiting, and abdominal pain. It is the second most common oesophageal disease after gastroesophageal reflux disease (GERD)[1]. EoE is characterized by the deposition of high amounts of eosinophils in the lining of the oesophagus, which can lead to hyperplasia of basal cells, micro abscess formation, degranulation, dilated intercellular spaces, and eosinophilic infiltration. This deposition is believed to result from exposure to food, allergens, atopic conditions, other comorbidities, or acid reflux, which may damage the oesophageal tissue and lead to fibrosis and strictures[2].

The prevalence of EoE has been increasing in both adults and children[3].Forty studies meeting eligibility criteria provided data on over 288 million participants, including 147,668 patients with EoE from 15 countries across five continents. The global pooled incidence and prevalence of EoE were found to be 5.31 cases per 100,000 inhabitant-years (95% CI, 3.98–6.63; based on 27 studies with a sample population of 42,191,506) and 40.04 cases per 100,000 inhabitant-years (95% CI, 31.10–48.98; based on 20 studies with a sample population of 30,467,177), respectively.The incidence of EoE was observed to be higher in high-income countries compared to low- or middle-income countries, in males compared to females, and in North America compared to Europe and Asia. These patterns were reflected in the global prevalence of EoE as well[4].

Moreover, the pooled prevalence of EoE showed a gradual increase from 1976 to 2022, with rates rising significantly from 8.18 cases per 100,000 inhabitant-years (95% CI, 3.67–12.69) during the period 1976–2001 to 74.42 cases per 100,000 inhabit[4].

The exact pathogenesis of EoE is unknown, but molecular analysis has revealed that it arises from a primary defect in oesophageal epithelial function rather than an eosinophil defect. There is increasing evidence suggesting that factors such as premature delivery, caesarean birth, early antibiotic exposure, food allergies, lack of breastfeeding, and lack of early microbial exposure may contribute to the development of EoE[5].

The symptoms of EoE vary with age. In children, the most common symptoms include nausea, vomiting (emesis), abdominal pain, refusal to eat, and improper growth. Adults, on the other hand, experience difficulty swallowing (dysphagia), food becoming stuck in the oesophagus after swallowing (impaction), chest pain, and the backflow of digested food (regurgitation). The diagnosis of EoE includes upper endoscopy, biopsy, blood tests, and oesophageal sponge tests. Treatment options include dietary modifications, proton pump inhibitors (PPIs), hormonal therapy, and corticosteroids, all of which have been shown to influence the oesophageal microbiota. Additionally, prebiotics, probiotics, and faecal microbiota transplantation are being explored as potential treatments[6].

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SYMPTOMS	• ADULTS: Dysphagia, food impaction,chest pain,regurgitation. • CHILDREN: irritability, inappetence, regurgitation, nausea and vomiting, abdominal pain and dysphagia
DIAGNOSIS	• Endoscopy • Echoendoscopy • endotyping • Biopsy • Barium swallow • Blood test • Esophageal sponge
TREATMENT	• Lifestyle modification • Proton pump inhibitor (PPI) medications • Topical swallowed steroids (Budesonide) • Leukotriene receptor antagonist (Montelukast) • Biologics • Probiotics and prebiotics • Dilatation therapy

FIGURE 1: Overview of eosinophilic esophagitis (EoE)

PATHOGENESIS AND THE MICROBIOTA

The pathogenesis of EoE is not well defined and is currently thought to result from changes in genetic, environmental, and immunological factors. The development of 16S rRNA gene sequencing has been instrumental in investigating the oesophageal microbiota. The local production of IgE and IgG4 derived from plasma cells of the lamina propria of the oesophageal mucosa, as well as microbial pattern recognition receptors (PRRs), may play important roles in pathogenesis. Among PRRs, Toll-like receptors (TLRs) are type 1 transmembrane receptors expressed in both epithelial and lamina propria cells, capable of differentiating between pathogenic and commensal microbes[7].

The shift in understanding, particularly regarding the involvement of oesophageal epithelial function rather than just an eosinophil defect, is noteworthy. The recognition of PPI-responsive oesophageal eosinophilia blurs the lines between EoE and GERD, underscoring the importance of accurate diagnosis based on eosinophil levels and clinical presentation. The involvement of Th2 cell-mediated responses and cytokines like IL-5 and IL-13 sheds light on the immune mechanisms underlying EoE, emphasizing the intricate interplay between genetics, immunity, and environmental triggers in this condition[8].

Molecular analysis has revealed that EoE arises from a primary defect in oesophageal epithelial function rather than an eosinophil defect. Genes like CAPN14 and thymic stromal lymphopoietin (TSLP) play roles, along with cytokines like IL-4, IL-5, and IL-13. Additionally, factors like TGF-beta1 contribute to oesophageal remodelling and complications such as luminal narrowing and dysmotility. Antigenic proteins trigger a T helper type 2 (Th2) response, leading to the production of cytokines such as IL-5 and IL-13. These cytokines stimulate other resident cells, which produce eotaxin-3, resulting in oesophageal eosinophilic inflammation[8].

Recent advancements in microbiota research have highlighted the role of the oesophageal microbiota in EoE. The dysbiosis of the oesophageal microbiota in individuals with eosinophilic esophagitis (EoE) is characterized by changes in bacterial abundance, with an increase in Haemophilus and a decrease in Firmicutes compared to healthy controls. Studies have shown differences in microbial composition between children and adults with EoE, with variations in dominant taxa. While α diversity of the oesophageal microbiota has shown nonsignificant

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differences in some studies, others have reported associations between specific bacteria and disease activity. Additionally, correlations between the oesophageal and oral microbiota suggest potential implications for non-invasive microbial sampling methods using saliva. Although current research primarily relies on 16S gene sequencing, future studies could benefit from metagenomic sequencing combined with metabolomics to better understand the genetic makeup and function of microbial communities in EoE patients[8].

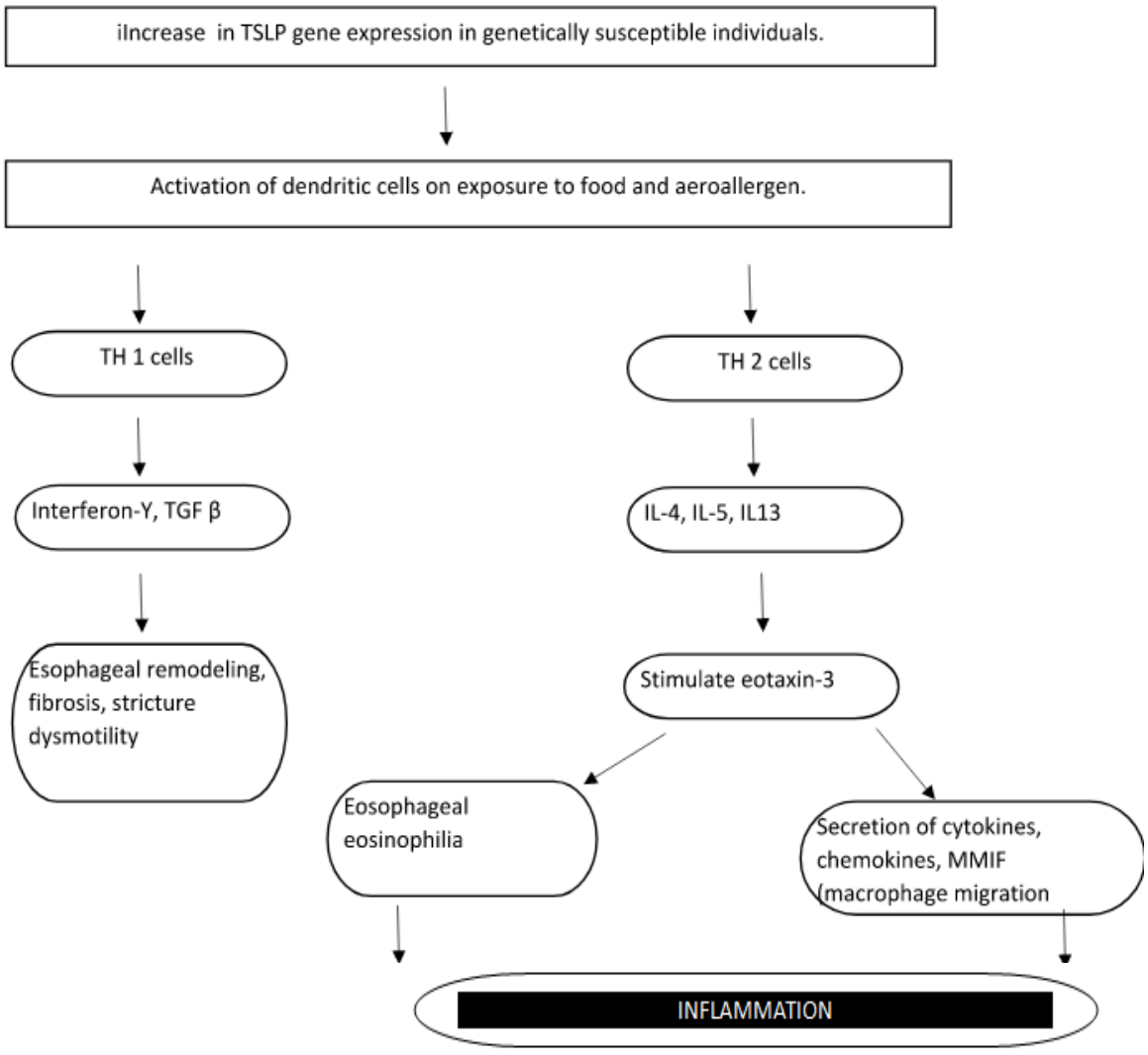

FIGURE 2: pathogenesis of EoE

ROLE OF MICROBIOTA MODULATION IN EoE MANAGEMENT

Dietary modifications and pharmacological drugs, such as PPIs and corticosteroids, are key treatment options for EoE. They can impact the oesophageal microbiota, potentially serving as biomarkers for assessing therapeutic effects. Microbial interventions also hold promise for managing EoE, highlighting the interconnectedness between treatment strategies and the microbiome.

DIETARY MODIFICATIONS

The targeted elimination diet, including the six-food elimination diet (SFED), and elemental diet have shown clinical efficacy in treating EoE. The therapeutic effect of dietary modification on EoE was first demonstrated by

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Kelly et al. in 1995. Subsequent studies have further investigated the impact of dietary interventions on EoE patients[9].

A retrospective study analyzing adult patients with EoE who received a targeted elimination diet or SFED found that symptoms improved in 71% of patients and endoscopic appearance improved in 54% of patients. Additionally, it was observed that the increased bacterial load in the esophagus normalized after SFED in adult EoE patients, as reported by Arias et al. However, conflicting findings exist in the literature regarding the effect of dietary regulation on esophageal bacterial load. While one study demonstrated no significant impact of dietary regulation on esophageal bacterial load in EoE patients, another study found enrichment of certain bacterial genera in the esophageal microenvironment following dietary modifications[10].

A recent study reported a decrease in α diversity among EoE patients who underwent a food elimination diet, along with a slight increase in the abundance of Firmicutes. These findings underscore the complex interplay between diet, microbiota, and EoE pathogenesis, suggesting that dietary interventions may have multifaceted effects on the esophageal microenvironment and microbiota composition[10].

Overall, while dietary modifications have shown clinical efficacy in treating EoE, further research is needed to elucidate the underlying mechanisms and optimize dietary strategies for managing this condition effectively[10].

PHARMACOLOGICAL DRUGS

Proton pump inhibitors

Historical Perspective of PPI Therapy for EoE:

Before the 1990s, esophageal eosinophilia was often misconstrued as a manifestation of worsening gastro-esophageal reflux disease (GERD), despite normal pH probe testing. However, seminal studies by Attwood et al and Straumann et al in the early 1990s challenged this notion. They identified a distinct clinicopathologic syndrome characterized by dysphagia and esophageal eosinophilia without evidence of GERD, leading to the recognition of idiopathic eosinophilic esophagitis as a distinct entity.In the mid-1990s, the efficacy of corticosteroids and dietary interventions in treating esophageal eosinophilia was demonstrated, shifting the focus away from GERD as the primary cause. Research by Liacouras et al and others further emphasized the role of systemic and topical corticosteroids in managing eosinophilic esophagitis, establishing these therapies in clinical practice[11].

Prior to 2007, diagnostic criteria for EoE were not standardized, and there was variability in PPI use. However, studies by Ngo et al and others highlighted that some patients with EoE responded to PPI monotherapy, sparking interest in the therapeutic potential of PPIs[11].

The term "PPI-responsive esophageal eosinophilia" (PPI-REE) was introduced to describe patients who responded to high-dose PPI therapy. However, subsequent research revealed significant overlap in clinical, histologic, and molecular characteristics between patients with PPI-REE and those with EoE, challenging the dichotomy between the two conditions[11].

In response, consensus statements and guidelines have endorsed recognizing PPI therapy as a first-line treatment option for EoE, alongside dietary modifications and topical corticosteroids. This paradigm shift reflects the evolving understanding of esophageal eosinophilia and underscores the importance of personalized approaches to EoE management[11].

Effect of PPI therapy on esophageal mast cells infiltration in EoE:

Mast cells have emerged as pivotal contributors to the pathogenesis of Eosinophilic Esophagitis (EoE), particularly in cases where eosinophilic infiltration alone does not fully explain clinical symptoms or endoscopic findings. Despite therapeutic interventions leading to the normalization of eosinophil counts, studies have demonstrated that mast cells persist and continue to drive mucosal inflammation and associated symptoms in EoE patients. Studies by Iwakura et al and Bolton et al have provided valuable insights into the role of mast cells in EoE. Iwakura et al's findings indicate that mast cell density in the esophagus may not directly correlate with responsiveness to proton pump inhibitor (PPI) therapy, suggesting a complex interplay between mast cells and treatment outcomes. Additionally, Bolton et al observed that mast cell density remains elevated even after the resolution of eosinophilic infiltration, underscoring the ongoing pathological role of mast cells in driving mucosal changes and symptomatology in EoE.Research by Kanagaratham et al has shed light on the potential mechanisms through which PPIs modulate mast cell activity. Omeprazole, a commonly used PPI, has been found to inhibit mast cell degranulation and the release of proinflammatory cytokines from activated mast cells. This inhibition likely occurs

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through the blockade of key signaling molecules involved in the IgE-mediated signaling cascade and the reduction of cytosolic calcium levels essential for inflammatory granule exocytosis. Additionally, **omeprazole** has been shown to suppress mast cell maturation, mitigate IgE-mediated anaphylaxis, and attenuate mast cell-dependent allergic inflammation in animal models of food allergy[12].

PPI therapy has emerged as a primary treatment option for EoE, there are still significant gaps in our knowledge regarding its efficacy, safety, and optimal use. Precision medicine approaches offer a promising avenue for optimizing PPI therapy in EoE, but further research is needed to validate their utility and effectiveness. By addressing these challenges, we can improve outcomes and quality of life for individuals living with EoE[12].

Hormone therapy

Steroids, as anti-inflammatory agents, play a crucial role in the management of eosinophilic esophagitis (EoE), both for inducing and maintaining remission. **Budesonide and fluticasone** are among the most commonly used steroids for this purpose, although other agents such as **prednisone,beclomethasone, mometasone, and ciclesonide** have also been employed to a lesser extent.Fluticasone spray (250 µg four puffs two times per day, last thing at night and after breakfast with no mouth washing, food, or fluid as long as possible) is suitable for adults or oral budesonide are effective but lack consistency in delivery and formulations[13].

Initially, steroids were administered systemically, but swallowed topical administration has become the preferred route of delivery. This method involves administering the steroid directly to the esophagus, targeting the site of inflammation while minimizing systemic exposure and potential side effects. Swallowed topical administration can be achieved through various formulations, including metered-dose or nebulized solutions adapted from asthma treatments, as well as compound viscous formulations[14].

In recent years, there has been a shift towards developing esophageal-specific topical steroid formulations to further optimize treatment efficacy and patient convenience. These formulations, which include oral suspensions or oro-dispersible tablets, are specifically designed for targeted delivery to the esophagus, offering a more direct and effective approach to managing EoE[14].

Overall, steroids, particularly when administered via swallowed topical delivery, represent a cornerstone of EoE therapy, providing effective anti-inflammatory action while minimizing systemic side effects. The development of esophageal-specific formulations underscores ongoing efforts to enhance treatment outcomes and patient experience in managing this chronic inflammatory condition.For patients requiring therapeutic dilatation, continuation of topical steroid maintenance therapy is essential. The long-term safety of budesonide for GI complaints is well-established, with oral thrush easily managed by oral nystatin suspension without discontinuing therapeutic steroids[14].

DRUGS		TARGET POPULATION	INDUCTION DOSE	MAINTENANCE DOSE
PPIs	Omeprazole Pantoprazole esomeprazole	Children	1-2 mg/kg daily	Not yet validated
		adult	20-40mg bid	Not yet validated
Topical steroids	Fluticasone propionate	Children	880-1760 mcg/daily	440-880 mcg/daily
		adults	1760 mcg/daily	880-1760 mcg/daily
	budesonide	children	1-2 mg/daily	1mg/daily
		adults	2-4mg/daily	2mg/daily

FIGURE 3: Dose of PPI and Topical corticosteroids

Leukotriene receptor antagonist

Montelukast is a leukotriene receptor antagonist (LTRA) that actively and selectively blocks the leukotriene D4 receptor. The dose was adjusted according to the tolerance of the patient. Initial treatment was with 10mg daily but increased if required up to a total of 100mg daily. Once the symptoms relieve, the dose is then reduced to the

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maintenance dose of 20 and 40mg per day. The use of LTRA is under investigation[15].

Biologics

Biologics have been used as investigational therapy for EoE in clinical studies over the years based on the involvement of cytokines and mediators in the pathogenesis. A variety of biological therapies have been investigated for the treatment of eosinophilic esophagitis (EoE), targeting different aspects of the inflammatory cascade. These include:

Anti-IL5 Agents: **Mepolizumab and reslizumab** are monoclonal antibodies that target interleukin-5 (IL-5), a cytokine involved in the recruitment and activation of eosinophils. By inhibiting IL-5, these agents aim to reduce eosinophilic inflammation in the esophagus.

Anti-IgE Therapy: **Omalizumab** is a monoclonal antibody that binds to immunoglobulin E (IgE), a key mediator of allergic reactions. By binding to IgE, omalizumab prevents its interaction with allergens, thereby reducing the allergic response and associated inflammation in EoE.

Anti-IL4R and Anti-IL13 Agents: **Dupilumab** is a monoclonal antibody that targets the interleukin-4 receptor alpha (IL-4Rα), blocking signaling pathways associated with both IL-4 and IL-13. Additionally, agents such as RPC4046 (cendakimab) and QAX576 (dectrekumab) directly target IL-13, a cytokine involved in allergic inflammation and tissue remodeling.

Anti-Siglec-8 Therapy: **Lirentelimab** is a monoclonal antibody that targets sialic acid-binding immunoglobulin-like lectin 8 (Siglec-8), a protein expressed on the surface of eosinophils and mast cells. By blocking Siglec-8, lirentelimab aims to modulate eosinophilic inflammation and mast cell activation in EoE.

These biological therapies represent a promising approach to EoE treatment, offering targeted inhibition of specific pathways implicated in the pathogenesis of the disease. While further research is needed to establish their efficacy and safety in EoE, these agents hold potential as alternative or adjunctive treatments for patients with refractory or severe disease[16].

MICROBIOTA INTERVENTIONS

Microbiota modulators like probiotics and prebiotics offer promise in reshaping microbiota composition to improve various diseases, including EoE. Probiotics have shown efficacy in conditions like antibiotic-associated diarrhoea, IBD, and IBS, with potential mechanisms including modulation of immune systems and secretion of bioactive metabolites. Animal studies suggest probiotics like Lactococcus lactis may inhibit IL-5 production and reduce oesophageal eosinophilic infiltration in EoE. Clostridia, which regulate lymphocyte function and epithelial permeability, could be a potential intervention target given their reduced abundance in EoE patients' gut. While prebiotics promote beneficial bacteria growth, their efficacy in EoE treatment lacks research. Faecal microbiota transplantation, known for restoring microbiota, shows promise in EoE treatment by potentially restoring oesophageal microbiota. Further preclinical and clinical studies could provide insights into its therapeutic potential for EoE[17].

DILATATION THERAPY

Dilatation for EoE has demonstrated effectiveness both in relieving acute bolus obstruction and maintaining long-term symptom relief over months or even years. While it doesn't alter the underlying inflammatory process, adequate dilatation can reduce obstruction and improve daily symptoms like dysphagia. Modifications such as the pull-through technique may enhance the procedure's efficacy. Dilating the entire oesophagus could potentially offer better symptom relief than focusing solely on the lower oesophagus or esophagogastric junction. Safety concerns surrounding dilatation in EoE have been raised in the past due to a higher risk of perforations compared to peptic oesophageal strictures, particularly when using rigid laryngoscopy or esophagoscopy for the procedure[18].

International Journal of Pharmaceutical Research and Applications
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LIFESTYLE MODIFICATIONS	• **SIX FOOD ELIMINATION DIET** • **ELEMENTAL DIET** • **TARGETED DIETARY RESTRICTIONS** • **EMPIRIC DIETARY RESTRICTIONS**
PHARMACOLOGICAL THERAPY	• TOPICAL CORTICOSTEROIDS • SYSTEMIC CORTICOSTEROIDS • LEUKOTRIENE RECEPTOR ANTAGONIST • (MONTELUKAST) • BIOLOGICS • ANTI IgE THERAPY- OMALIZUMAB • ANTI IL5 THERAPY- RESELIZUMAB, MEPOLIZUMAB • IL 4RECEPTOR ALPHA ANTAGONIST- DUPILUMAB
MICROBIOTA INTERVENTIONS	• PROBIOTIS-LACTOBACILLUS LACTIS, CLOSTRIDIA • PREBIOTICS • FECAL MICROBIOTA TRANSPLANTATION
DILATATION	ALTHOUGH PAINFUL, MAY PRODUCE LONG LASTING BENEFITS FOR SELECTED PATIENTS.

FIGURE 4: Management of EoE

CLINICAL EVIDENCES AND OUTCOME

Current treatment of EoE relies on diet, unlicensed drugs, or dilatation. The most commonly used pharmacotherapies for EoE were proton pump inhibitors (PPIs) and topical glucocorticoids, with respective clinical response rates of 51.9% and 63.4%. These response rates align with findings from other studies. However, it's important to note that clinical response or remission doesn't always correlate with histologic response. A study revealed lower-than-expected histologic response to conventional therapy with PPIs and topical steroids. A systematic review and meta-analysis, encompassing 33 studies with 619 patients, showed a pooled clinical response rate of 60.8% and a histologic remission rate of 50.5% with PPI therapy. Other studies have reported histologic response rates ranging from 25% to 57%[19].

In the literature, the expected histologic response rate to topical steroids for EoE varies, with small case series and retrospective studies reporting response rates ranging from 50% to 95%. A systematic review and meta-analysis of 5 studies, including 174 EoE patients treated with topical fluticasone and budesonide, found pooled complete and partial histologic remission rates of 57.8% and 82%, respectively. Previous data have suggested that the dose and mode of delivery of topical steroids may influence EoE treatment response, with high-dose viscous topical steroid preparations showing a more modest effect compared to low-dose topical steroids or capsules[19].

Endoscopic findings of EoE are highly suggestive but not diagnostic of the disease. Interestingly, approximately 10% of cases present with endoscopically normal EoE. Esophagrams, although not universally utilized in the diagnosis, surveillance, and management of EoE according to the most recent ACG guidelines, can provide valuable information regarding anatomic changes within the esophagus, particularly in specific subsets of patients with EoE[19].

Biological therapies such as anti-TNF agents have not been shown to be effective in treatment of EoE. Novel monoclonal antibodies have indeed emerged as promising therapeutic options for patients with refractory EoE, as

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demonstrated by phase 2 trials. These antibodies are designed to target specific molecules involved in the inflammatory cascade of EoE, offering potentially more targeted and effective treatment approaches.One notable example is vedolizumab, an anti-α4β7 integrin agent that works by inhibiting leukocyte trafficking. There have been reports in the literature suggesting its use for intractable EoE. Vedolizumab functions by mediating T-helper 2 cell (Th2) cytokine effects and binding with high affinity to eosinophils and CD4 T cells. This mechanism of action holds promise for modulating the immune response implicated in EoE pathogenesis.

Additionally, infliximab, another monoclonal antibody, has been investigated for the treatment of adult EoE in prospective translational studies, particularly in patients with steroid-dependent EoE. However, outcomes from these studies have shown mixed results, highlighting the need for further research to determine the efficacy and safety of infliximab in managing EoE.

These novel therapeutic approaches underscore the evolving landscape of EoE treatment, with ongoing efforts to develop targeted therapies that address the underlying immunological mechanisms driving the disease. Further clinical trials are warranted to evaluate the long-term effectiveness and safety of these agents in patients with EoE, particularly those with refractory disease.

It's crucial to highlight that current EoE diagnosis guidelines don't mandate the exclusion of gastroesophageal reflux disease (GERD) as a diagnosis or the initiation of a PPI trial. This suggests that while PPI therapy might be effective for some patients, it might not achieve complete histologic remission in all cases. The outcomes are not sufficiently well studied to provide a clear evidence-based algorithm of management. Endoscopy and biopsy are the cornerstone of diagnosis and management. Biopsies should be taken during the proton pump inhibitor therapy. Barium contrast radiography assessing anatomy and swallow function of the oesophagus is useful. Test of the oesophageal distensibility using Endo FLIP balloon device may prove useful in determining which patient may respond to dilatation therapy[19].

FUTURE DIRECTIONS AND CHALLENGES

Future research should focus on further elucidating the mechanisms underlying the interaction between the oesophageal microbiota and EoE. Metagenomic sequencing combined with metagenomics and metabolomics could provide valuable insights into the genetic makeup and function of microbial communities, potentially leading to the identification of biomarkers for disease monitoring and therapeutic outcomes[20].

Metagenomic sequencing, along with metatranscriptomics and metabolomics, collectively known as multi-omics approaches, hold great promise in elucidating the functional relevance of bacterial gene expression and the mechanistic role of the microbiome in eosinophilic esophagitis (EoE).

Metagenomic Sequencing: This technique involves the analysis of the genetic material (DNA) of microbial communities present in the esophagus of individuals with EoE. Metagenomic sequencing can provide comprehensive information about the taxonomic composition of the microbiome, identifying specific bacterial species and their relative abundance. By comparing the microbiome profiles between individuals with EoE and healthy controls, researchers can identify microbial dysbiosis associated with EoE and potential microbial biomarkers of disease.

Metatranscriptomics: Metatranscriptomics focuses on the analysis of microbial gene expression (mRNA) within the microbiome. By sequencing the RNA transcripts present in the esophageal microbiome, researchers can gain insight into the functional activities of microbial communities in individuals with EoE. This approach allows for the identification of active microbial pathways and processes that may contribute to EoE pathogenesis, such as the production of pro-inflammatory cytokines or the metabolism of dietary components.

Metabolomics: Metabolomics involves the profiling of small molecule metabolites produced by microbial communities in the esophagus. By analyzing the metabolite profiles of individuals with EoE, researchers can identify specific metabolites that are associated with disease pathogenesis or treatment response. Metabolomics can provide valuable information about the metabolic activities of the esophageal microbiome and its interactions with the host immune system.

Integration of Multi-Omics Data: Integrating data from metagenomic sequencing, metatranscriptomics, and metabolomics allows for a comprehensive characterization of the functional activities of the esophageal microbiome in EoE. By correlating changes in microbial composition with alterations in gene expression and metabolite production, researchers can gain a deeper understanding of the complex interplay between the

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microbiome and host immune response in EoE. This multi-omics approach has the potential to identify novel therapeutic targets and biomarkers for EoE, leading to personalized treatment strategies tailored to the individual's microbiome profile[21].

It's fascinating to see the range of technologies being developed to assess and predict the progression of EoE (eosinophilic esophagitis). From advanced endoscopy techniques like chromoendoscopy to non-invasive monitoring methods like microRNA genetic signatures and serum IL-5 levels, there's a concerted effort to improve diagnosis and management. The era of personalized medicine seems promising for targeting therapy more effectively based on specific biomarkers and molecular diagnostics. Exciting times ahead for the field of EoE research and management.

The invasive nature of esophagogastroduodenoscopy (EGD) poses challenges for both the diagnosis and monitoring of eosinophilic esophagitis (EoE). Consequently, there is a growing interest in identifying noninvasive biomarkers and office-based minimally invasive tests to facilitate the management of this condition.

Several biomarkers have been investigated as potential indicators of EoE, including eosinophil granule proteins and surface and intracellular markers. However, the available data on these biomarkers are limited, and various factors, such as concomitant atopy, need to be taken into account when interpreting results.In a proof-of-concept study, urine 3-Bromotyrosine (3-BT) levels were found to differ between individuals with EoE and atopic and non-atopic controls. This suggests that urine 3-BT may serve as a potential biomarker for EoE, although further validation studies are needed.

Other tests under investigation for the diagnosis and long-term monitoring of EoE include the esophageal string test and the swallowed cytosponge test. These minimally invasive tools offer the potential to assess disease activity without the need for traditional endoscopic procedures. Initial data suggest that these tests correlate well with esophageal eosinophilia, providing valuable insights into disease activity and treatment response.

Additionally, unsedated in-office transnasal endoscopy represents another less invasive method for monitoring EoE. This approach allows for visualization of the esophagus without the need for sedation or traditional EGD, offering a convenient and cost-effective alternative for disease monitoring.Overall, the development of noninvasive biomarkers and minimally invasive tests represents an important advancement in the management of EoE, offering the potential to improve diagnostic accuracy, monitor disease activity, and assess treatment response in a less burdensome manner for patients. Continued research and validation of these approaches are essential to their integration into routine clinical practice[21].

Exploring patient-reported outcomes (PRO) beyond current instruments like PEESS v2.0 and PedsQL is crucial for understanding the full spectrum of symptoms experienced by EoE patients. Chronic symptoms and potential coping mechanisms can lead to significant impacts on quality of life, highlighting the need for holistic assessment tools. Integrating PRO data with clinical and histological findings could provide a more comprehensive approach to EoE management, ensuring that patient perspectives are central to treatment decisions[22].

II. CONCLUSION

Eosinophilic esophagitis is a complex, chronic condition with a multifactorial etiology. While the exact pathogenesis remains unclear, recent research has highlighted the role of the oesophageal microbiota in disease development and progression. Modulating the microbiota through dietary modifications, pharmacological drugs, and microbial interventions shows promise in managing EoE. However, further research is needed to elucidate the mechanisms involved and optimize treatment strategies. By exploring new technologies and integrating patient-reported outcomes, the field of EoE research and management is poised for exciting advancements in the coming years.

Emerging evidence suggests that the esophageal mucosa harbors a resident microbiota, and alterations in microbial composition, including increased bacterial load and the presence of specific taxa such as Streptococcus and Haemophilus, have been observed in individuals with eosinophilic esophagitis (EoE). However, the causal relationship between these microbial changes and EoE pathogenesis remains unclear.

At present, there is limited understanding of the cause-effect relationship underlying these microbiota changes in EoE, and rational interventions for modulating the esophageal microbiota are not yet feasible. Further research, particularly immunological studies, is needed to elucidate the mechanisms by which the esophageal

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microbiota may contribute to EoE development and progression. These studies may uncover novel therapeutic targets and alternative treatment strategies for EoE that aim to restore microbial homeostasis and mitigate disease activity.

In conclusion, continued investigation into the interaction between the esophageal microbiota and EoE pathophysiology is crucial for advancing our understanding of this complex inflammatory disorder and identifying innovative approaches for its management.

Keywords: Eosinophilic esophagitis, oesophageal microbiota, microbiota modulation, probiotics, prebiotics, faecal microbiota transplantation, dietary modifications, pharmacological drugs, dilation therapy, clinical outcomes, future directions.

REFERENCES:

[1]. Mennini M, Tambucci R, Riccardi C, Rea F, De Angelis P, Fiocchi A, et al. Eosinophilic Esophagitis and Microbiota: State of the Art. Frontiers in Immunology. 2021 Feb 19;12.

[2]. Bauer M, Nguyen N, Liacouras CA. Clinical Evaluation of the Child with Eosinophilic Esophagitis. Immunology and Allergy Clinics of North America [Internet]. 2024 Jan 9 [cited 2024 Mar 29]; Available from: https://www.sciencedirect.com/science/article/abs/pii/S0889856123001078#:~:text=Clinical%20Evaluation%20of%20the%20Child%20with%20Eosinophilic%20Esophagitis

[3]. Kaylani Angerami Almeida, de E, Burns G, Hoedt EC, Mattes J, Keely S, et al. The microbiota in eosinophilic esophagitis: A systematic review. Journal of Gastroenterology and Hepatology. 2022 Jul 12;37(9):1673–84.

[4]. Hahn JW, Lee K, Shin JI, Cho SH, Turner S, Shin JU, et al. Global incidence and prevalence of eosinophilic esophagitis, 1976–2022: A systematic review and meta-analysis. Clin Gastroenterol Hepatol [Internet]. 2023;21(13):3270-3284.e77. Available from: http://dx.doi.org/10.1016/j.cgh.2023.06.005

[5]. UpToDate [Internet]. Uptodate.com. [cited 2024 Apr 12]. Available from: https://www.uptodate.com/contents/eosinophilic-esophagitis-eoe-genetics-and-immunopathogenesis

[6]. Parmar CD, Attwood SE. Emerging clinical evidence in the treatment of eosinophilic esophagitis. Clin Investig (Lond) [Internet]. 2012;2(5):527–35. Available from: https://www.openaccessjournals.com/articles/emerging-clinical-evidence-in-the-treatment-of-eosinophilic-esophagitis.pdf

[7]. Zhang X, Zhang N, Wang Z. Eosinophilic esophagitis and esophageal microbiota. Frontiers in Cellular and Infection Microbiology [Internet]. 2023 Aug 3 [cited 2023 Sep 26];13. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10434796

[8]. Hirano I, Aceves SS. Clinical implications and pathogenesis of esophagealremodeling in eosinophilic esophagitis. Gastroenterol Clin North Am [Internet]. 2014 [cited 2024 Apr 12];43(2):297–316. Available from: https://pubmed.ncbi.nlm.nih.gov/24813517/

[9]. Hirano I, Furuta GT. Approaches and challenges to management of pediatric and adult patients with eosinophilic esophagitis. Gastroenterology [Internet]. 2020 [cited 2024 Apr 12];158(4):840–51. Available from: http://dx.doi.org/10.1053/j.gastro.2019.09.052

[10]. Doerfler B, Lam AY, Gonsalves N. Dietary management of eosinophilic esophagitis. Gastroenterology & Hepatology. 2023;19(11):680.

[11]. Urquhart SA, Quinn KP, Ravi K, Loftus EV Jr. The clinical characteristics and treatment outcomes of concomitant eosinophilic esophagitis and inflammatory bowel disease. Crohns Colitis 360 [Internet]. 2021 [cited 2024 Apr 12];3(2). Available from: http://dx.doi.org/10.1093/crocol/otab018

[12]. Franciosi JP, Mougey EB, Dellon ES, Gutierrez-Junquera C, Fernandez-Fernandez S, Venkatesh RD, et al. Proton pump inhibitor therapy for eosinophilic esophagitis: History, mechanisms, efficacy, and future directions. J Asthma Allergy [Internet]. 2022 [cited 2024 Apr 12];15:281–302. Available from: http://dx.doi.org/10.2147/jaa.s274524

[13]. Khan S, Guo X, Liu T, Iqbal M, Jiang K, Zhu L, et al. An update on eosinophilic esophagitis: Etiological factors, coexisting diseases, and complications. Digestion [Internet]. 2021 [cited 2024 Apr 12];102(3):342–56. Available from: https://pubmed.ncbi.nlm.nih.gov/32570246/

[14]. Franciosi JP, Gordon M, Sinopoulou V, Dellon ES, Gupta SK, Reed CC, et al. Medical treatment of eosinophilic esophagitis. Cochrane Libr [Internet]. 2023 [cited 2024 Apr 12];2023(7). Available from: http://dx.doi.org/10.1002/14651858.cd004065.pub4

[15]. Vinit C, Dieme A, Courbage S, Dehaine C, Dufeu CM, Jacquemot S, et al. Eosinophilic esophagitis: Pathophysiology, diagnosis, and management. Archives De Pediatrie: OrganeOfficiel De La SocieteFrancaise De Pediatrie [Internet]. 2019 Apr 1 [cited 2022 Oct 17];26(3):182–90. Available from: https://pubmed.ncbi.nlm.nih.gov/30827775

[16]. Snyder DL, Dellon ES. Biologics in the treatment of eosinophilic esophagitis: Ready for use? Clin Gastroenterol Hepatol [Internet]. 2023;21(13):3230–3. Available from: http://dx.doi.org/10.1016/j.cgh.2023.07.025

[17]. Researchgate.net. [cited 2024 Apr 12]. Available from: https://www.researchgate.net/publication/350459101_Esophageal_microbiome_in_active_eosinophilic_esophagitis_and_changes_induced_by_different_therapies

[18]. Lucendo AJ, Molina-Infante J. Esophageal dilation in eosinophilic esophagitis: Risks, benefits, and when to do it. Curr Opin Gastroenterol [Internet]. 2018 [cited 2024 Apr 12];34(4):226–32. Available from: https://journals.lww.com/co-gastroenterology/abstract/2018/07000/esophageal_dilation_in_eosinophilic_esophagitis_.7.aspx

[19]. Feo-Ortega S, Lucendo AJ. Evidence-based treatments for eosinophilic esophagitis: insights for the clinician. Therap Adv Gastroenterol [Internet]. 2022 [cited 2024 Apr 12];15:175628482110686. Available from: http://dx.doi.org/10.1177/17562848211068665

[20]. Kumar S, Choi SS, Gupta SK. Eosinophilic esophagitis: current status and future directions. Pediatr Res [Internet]. 2020 [cited 2024 Apr 12];88(3):345–7. Available from: https://www.nature.com/articles/s41390-020-0770-4

[21]. Busing JD, Buendia M, Choksi Y, Hiremath G, Das SR. Microbiome in Eosinophilic Esophagitis—Metagenomic, Metatranscriptomic, and Metabolomic Changes: A Systematic Review. Front Physiol [Internet]. 2021 [cited 2024 Apr 12];12. Available from: http://dx.doi.org/10.3389/fphys.2021.731034

[22]. Trompette A, Gollwitzer ES, Yadava K, Sichelstiel AK, Sprenger N, Ngom-Bru C, et al. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. Nat Med [Internet]. 2014 [cited 2024 Apr 12];20(2):159–66. Available from: https://www.nature.com/articles/nm.3444