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Eosinophilic Esophagitis: Advances in Pathophysiology, Diagnostic Challenges, and Emerging Therapeutic Strategies

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ABSTRACT

Eosinophilic esophagitis (EoE) has evolved over the past two decades from a poorly recognized condition to one of the most prevalent chronic immune-mediated diseases of the esophagus. Its rising incidence reflects changes in environmental exposures, dietary patterns, and immune response profiles across populations. EoE is now understood as a complex disorder driven by epithelial barrier dysfunction, type 2 immune activation, and eosinophilic infiltration, ultimately leading to progressive esophageal remodeling. This comprehensive narrative review synthesizes the most recent advances in the understanding of EoE pathogenesis, emphasizes the diagnostic challenges that continue to complicate clinical practice, and explores the expanding landscape of therapeutic strategies, including dietary interventions, topical corticosteroids, proton pump inhibitors, endoscopic approaches, and biologic therapies. No original data were collected.

KEYWORDS

eosinophilic esophagitis, eosinophils, biologics, GERD

MAIN ARTICLE

INTRODUCTION

Eosinophilic esophagitis has emerged as a major cause of dysphagia and food impaction, particularly in young adults, and is now recognized as a chronic, antigen-driven inflammatory disease of the esophagus. Initially considered a rare pediatric condition, EoE is currently one of the most frequent indications for esophageal biopsies in many centers worldwide. The disease results from a complex interplay between genetic susceptibility, environmental exposures, allergic sensitization, and immune dysregulation. Central to its pathophysiology is a chronic type 2 immune response within the esophageal mucosa. This leads to eosinophil recruitment, epithelial barrier dysfunction, tissue injury, and, over time, fibrostenotic remodeling. Understanding these mechanisms is essential, as EoE exhibits a heterogeneous clinical presentation ranging from intermittent dysphagia to fixed strictures and narrow-caliber esophagus.

METHODS

This review includes narrative synthesis of studies published between 2014 and 2024 identified via PubMed, Embase, and Web of Science using terms related to eosinophilic esophagitis, type 2 immunity, epithelial barrier dysfunction, biologic therapy, and esophageal remodeling. Original research, systematic reviews, expert consensus statements, and clinical trials were prioritized. No original data were generated.

PATHOPHYSIOLOGY OF EOSINOPHILIC ESOPHAGITIS

EoE is fundamentally a chronic, antigen-driven disease that arises from impaired epithelial barrier function combined with a highly polarized type 2 immune response. One of the earliest abnormalities detected in EoE is disruption of the epithelial integrity, characterized by reduced expression of junctional proteins such as filaggrin and desmoglein. This barrier defect facilitates the penetration of food antigens and aeroallergens into the subepithelial layers, where they stimulate local antigen-presenting cells. Genetic variants affecting epithelial barrier function, including polymorphisms in TSLP and filaggrin, further increase susceptibility.

Once antigens cross the weakened epithelial barrier, they activate dendritic cells, which in turn promote differentiation of naïve T cells into Th2 lymphocytes. These Th2 cells secrete large quantities of interleukin-4, interleukin-5, and interleukin-13, cytokines that orchestrate eosinophil recruitment, immunoglobulin E class switching, and mucosal inflammation [1]. Interleukin-13, in particular, plays a central role by suppressing barrier proteins, promoting

eosinophil chemotaxis through eotaxin-3, and inducing epithelial remodeling. As eosinophils accumulate within the mucosa, they release cytotoxic granule proteins that contribute to epithelial damage, nerve activation, and eventually subepithelial fibrosis.

Longstanding inflammation results in deposition of collagen and expansion of the lamina propria, leading to esophageal rigidity and strictures. This progressive transition from an inflammatory phenotype to a fibrostenotic phenotype explains the evolution from inflammatory EoE in younger patients to fibrostenotic disease in adults. In addition, esophageal smooth muscle dysfunction and neural remodeling contribute to dysmotility, impaired bolus transport, and persistent dysphagia. The multifactorial and progressive nature of these changes underscores the importance of early diagnosis and treatment.

DIAGNOSTIC CHALLENGES

Despite significant advances, diagnosing EoE continues to pose challenges due to its clinical overlap with other esophageal disorders, notably gastroesophageal reflux disease (GERD). Many patients present with nonspecific symptoms such as heartburn, chest discomfort, or intermittent dysphagia, making clinical distinction difficult. The response to proton pump inhibitors further complicates diagnosis, as both EoE and GERD can improve with PPI therapy, not through acid suppression alone but via anti-inflammatory mechanisms that modulate cytokine signaling [2].

Endoscopy is a key diagnostic tool, yet findings may be subtle in early disease. Classic features such as rings, furrows, whitish exudates, edema, and strictures form the basis of the EREFS scoring system, which has improved diagnostic consistency. However, normal-appearing mucosa does not exclude EoE; biopsies remain essential in all patients with unexplained dysphagia. Obtaining at least six biopsies from proximal and distal segments enhances diagnostic sensitivity.

Emerging diagnostic tools reflect growing recognition of EoE as a systemic allergic disorder. Biomarkers such as eotaxin-3, periostin, and serum IgG4 subclasses have shown promise, although none are yet validated for routine clinical practice. Novel technologies like the esophageal string test and minimally invasive cytosponge collection device are being investigated as alternatives to repeated endoscopy [3]. Together, these advances signal a shift toward more accessible, non-invasive diagnostic strategies.

THERAPEUTIC STRATEGIES

Management of EoE focuses on reducing inflammation, alleviating symptoms, and preventing fibrostenotic remodeling. Dietary therapy is among the most effective approaches, targeting the disease at its root by eliminating antigenic triggers. The six-food elimination

diet remains the most validated strategy, although simplified approaches such as two-food or four-food elimination diets have demonstrated comparable efficacy with better adherence. Targeted elimination based on allergy testing has been explored but shows variable results due to limited reliability of current allergy tests in EoE.

Topical corticosteroids, including budesonide and fluticasone, represent a cornerstone of pharmacological therapy. Their efficacy in inducing histologic remission has been demonstrated across numerous trials, and newer formulations designed for esophageal mucosal retention have further improved outcomes [4]. Unlike systemic steroids, topical formulations offer local anti-inflammatory activity with minimal systemic absorption.

Proton pump inhibitors maintain an important role in management, not merely for acid suppression but for their anti-inflammatory properties. PPIs downregulate Th2 cytokine activity and reduce eotaxin-3 expression, contributing to mucosal healing in a subset of patients.

Endoscopic dilation remains indispensable in patients with fixed strictures or narrow-caliber esophagus. While highly effective for symptom relief, dilation does not address underlying inflammation and is typically combined with anti-inflammatory therapy.

The recent introduction of biologic therapies marks a turning point in EoE treatment. Dupilumab, an IL-4 and IL-13 receptor blocker, has demonstrated significant improvements in both symptoms and histologic inflammation, establishing it as the first approved biologic for EoE [5]. Ongoing trials investigating anti-IL-5 agents, anti-TSLP therapies, and Janus kinase inhibitors highlight the growing trend toward targeted immunomodulation.

CONCLUSION

Eosinophilic esophagitis has emerged as a major chronic immune-mediated disease with a rapidly expanding scientific and clinical footprint. Advances in understanding the interplay between epithelial integrity, type 2 immune activation, and esophageal remodeling have significantly improved our grasp of its pathogenesis. Yet diagnosis remains challenging due to symptom overlap and evolving disease phenotypes. The therapeutic landscape has broadened considerably, transitioning from dietary and steroid-based strategies toward precision biologic therapies capable of interrupting key immunological pathways. Early diagnosis and individualized treatment are essential to halt disease progression and prevent fibrostenotic complications. Continued research in biomarkers, minimally invasive diagnostics, and targeted therapeutics promises to further refine the management of EoE.

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