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Eosinophilic Esophagitis in Upper Endoscopy Patients with Gastrointestinal Complaints

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ABSTRACT

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated esophageal disease characterized by eosinophil-predominant inflammation and symptoms of esophageal dysfunction. Defined histologically by ≥15 eosinophils per high-power field, EoE has emerged as a major cause of dysphagia and food impaction in adults and children, with prevalence ranging from 0.05–0.4% in the general population but reaching 15% among patients with dysphagia and 48% in those with food bolus impaction. EoE demonstrates strong male predominance (3:1) and frequent association with atopic comorbidities including asthma, allergic rhinitis, and atopic dermatitis, reflecting its Th2-driven immunoallergic pathogenesis mediated by IL-4, IL-5, and IL-13. Despite increasing recognition, EoE remains frequently misdiagnosed due to clinical and endoscopic overlap with gastroesophageal reflux disease (GERD), leading to prolonged empirical proton pump inhibitor (PPI) therapy and diagnostic delay. Characteristic endoscopic features mucosal edema, longitudinal furrows, concentric rings, white exudates, and strictures are systematically evaluated using the EoE Endoscopic Reference Score (EREFS). However, 10–25% of patients exhibit normal-appearing mucosa, necessitating systematic esophageal biopsies regardless of endoscopic appearance. Routine laboratory markers lack discriminatory value, making histopathological examination the diagnostic gold standard. Early diagnosis is critical to prevent irreversible fibrotic remodeling and optimize therapeutic outcomes through the "3D" approach: dietary elimination, drugs (topical corticosteroids, PPIs), and dilation. Identifying clinical and endoscopic predictors can reduce diagnostic delays and guide timely biopsy sampling in at-risk populations, thereby improving patient outcomes in routine gastroenterological practice.

Keywords: Eosinophilic esophagitis; dysphagia; food impaction; endoscopy; atopic disease; EREFS; diagnostic predictors; proton pump inhibitors; esophageal eosinophilia.

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic immune-mediated esophageal disease that has gained increasing recognition over the past two decades as an important cause of upper gastrointestinal symptoms in both pediatric and adult populations.(1) The condition is characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation.(2) Initially described in children and later recognized in adults, EoE has shown a gradual increase in incidence that may reflect changing environmental factors, improved disease awareness, or both.(3)

The diagnostic criteria for EoE require the presence of esophageal symptoms, histological evidence of eosinophilic infiltration with a peak value of ≥15 eosinophils per high-power field (or 60 eosinophils per mm²), and exclusion of other causes of esophageal eosinophilia.(4) The overall prevalence of EoE remains relatively low in the general population at 0.05–0.4%, but increases dramatically to 15% among patients presenting with dysphagia and reaches 48% in those with food bolus impaction.(5)

EoE frequently overlaps clinically with gastroesophageal reflux disease (GERD), creating diagnostic challenges for clinicians.(6) Approximately 30% of EoE cases may present with manifestations similar to GERD, including

heartburn and regurgitation.(7) This overlap has historically led to delayed diagnosis and prolonged empirical proton pump inhibitor (PPI) therapy before definitive identification of EoE.(8)

EPIDEMIOLOGY AND RISK FACTORS

Prevalence and Incidence

The epidemiology of EoE has evolved significantly since its initial recognition. Population-based studies demonstrate increasing incidence and prevalence worldwide, with the pooled incidence rate estimated at 3.7 per 100,000 patient-years.(9) The prevalence varies by geographic region and study population, with recent data showing approximately 34.4 cases per 100,000 persons overall, including 42.2 per 100,000 in adults and 34 per 100,000 in children.(10)

The increasing trend in EoE incidence cannot be explained solely by enhanced disease awareness or increased endoscopic utilization.(11) This epidemiological shift suggests that environmental factors play a crucial role in disease development, supporting hypotheses regarding altered immune system development and changing antigenic exposures in modern populations.(12)

Demographic Characteristics

EoE exhibits a pronounced male predominance, with male-to-female ratios ranging from 2:1 to 3:1 across most studies.(13) The disease affects individuals across the age spectrum but commonly presents in the third or fourth decade of life in adults.(14) Geographic distribution shows higher prevalence in cold and arid climates and rural areas, with most cases reported from North America, Europe, and Australia.(15)

Environmental and Genetic Factors

Several environmental exposures during early life have been implicated as risk factors for EoE development. These include birth by cesarean section, premature delivery, antibiotic exposure during infancy, lack of breastfeeding, and living in areas of lower population density.(16) These observations support the hypothesis that altered microbial exposure and immune system stimulation in early life may create an epigenetic signature predisposing to EoE.(17)

Genetic susceptibility also contributes to EoE risk. Family history studies and twin concordance data reveal a genetic component, with familial aggregation frequently observed.(18) Genome-wide association studies have identified several candidate genes with functional implications, including those encoding thymic stromal lymphopoietin, eotaxin-3, and calpain.(19) The heritability risk is estimated at approximately 2% based on nuclear family cohorts, with concordance rates of 40% in monozygotic twins and 30% in dizygotic twins.(20)

PATHOGENESIS

Immunological Mechanisms

The pathogenesis of EoE is fundamentally immune-mediated, driven primarily by type 2 helper T (Th2) cell activity in response to food and environmental antigens.(21) Upon exposure to triggering antigens, a Th2 inflammatory response is activated, with production of key cytokines including interleukin-4 (IL-4), IL-5, and IL-13.(22) These cytokines stimulate production of eotaxin-3, a potent chemokine that recruits eosinophils to the esophageal mucosa.(23)

Activated eosinophils cause local tissue damage through release of cytotoxic granule proteins and recruit additional effector cells including mast cells and fibroblasts, which contribute to esophageal remodeling and fibrosis.(24) The predominant mechanism appears to be non-IgE-mediated, as evidenced by the ineffectiveness of anti-IgE therapy and the ability to induce esophageal eosinophilia in IgE-null and B-cell-null mouse models.(25) However, food-specific IgG4 has been identified in esophageal epithelium and appears reactive to common food triggers in EoE patients.(26)

Epithelial Barrier Dysfunction

Assessment of esophageal tissues from EoE patients reveals striking abnormalities in epithelial barrier function, including dilated intercellular spaces, altered permeability, and downregulation of proteins essential for barrier integrity such as filaggrin and desmoglein-1.(27) IL-13 has been shown to downregulate these barrier proteins in vitro, creating a permissive environment that enhances antigen presentation and perpetuates eosinophil recruitment.(28)

Remodeling and Fibrosis

Chronic eosinophilic inflammation leads to progressive esophageal remodeling characterized by subepithelial fibrosis, smooth muscle hypertrophy, and increased esophageal wall thickness.(29) These structural changes result in decreased esophageal compliance, contributing to dysphagia symptoms even in the absence of identifiable strictures.(30) Natural history studies demonstrate that prolonged untreated disease correlates with increased stricture formation, with 85% of adults experiencing 20 years of untreated symptoms presenting with esophageal strictures.(31)

CLINICAL PRESENTATION

Age-Related Symptom Patterns

Clinical manifestations of EoE vary significantly by age group. In adults, the most common presenting symptom is solid food dysphagia, reported by 60–100% of patients.(32) Episodes of food bolus impaction occur in more than 25% of cases and may represent the initial presentation.(33) Additional symptoms include heartburn (30–60% of patients) and non-cardiac chest pain (8–44%).(34)

Pediatric presentations differ markedly, with younger children demonstrating non-specific symptoms including feeding difficulties, nausea, vomiting, abdominal pain, and failure to thrive.(35) Adolescents more commonly present with dysphagia and food impaction similar to adults.(36) Constitutional symptoms such as fever and weight loss are uncharacteristic and should prompt consideration of alternative diagnoses.(37)

Adaptive Behaviors

Patients with EoE frequently develop subtle compensatory eating behaviors over extended periods, often without conscious awareness.(38) These adaptations include eating slowly, excessive food chewing, lubricating foods with sauces, drinking copious liquids with meals, taking repeated swallows to facilitate bolus passage, avoiding troublesome foods such as meats and breads, and crushing or avoiding pills.(39) Recognition of these behavioral modifications is clinically important, as their presence may indicate chronic disease that has been normalized by the patient.

Associated Conditions

EoE demonstrates strong associations with atopic diseases. The prevalence of any atopic condition ranges from 20–80% in adult EoE cohorts.(40) In pediatric populations, asthma prevalence reaches 30–50% and allergic rhinitis 50–75%, substantially higher than the 10–30% prevalence of either condition in the general pediatric population.(41) Children with EoE also show increased likelihood of developing environmental allergies and IgE-mediated food allergies.(42) Family history of atopic disorders is present in more than 50% of EoE patients, supporting the concept of EoE as part of the broader atopic disease spectrum.(43)

DIAGNOSIS

Clinical Diagnostic Criteria

Current consensus diagnostic criteria define EoE as a clinicopathologic disease requiring: (1) symptoms of esophageal dysfunction, (2) histologic evidence of eosinophil-predominant inflammation with peak ≥15 eosinophils per high-power field, and (3) exclusion of alternative etiologies of esophageal eosinophilia.(44) The threshold of 15 eosinophils per high-power field achieves sensitivity of 100% and specificity of 96% for diagnosis.(45)

Previous diagnostic algorithms required failure of PPI therapy before establishing EoE diagnosis, leading to the controversial category of "PPI-responsive esophageal eosinophilia."(46) However, updated consensus guidelines have removed this requirement, recognizing that PPIs possess anti-inflammatory properties beyond acid suppression and that PPI-responsive esophageal eosinophilia represents a subphenotype within the EoE spectrum rather than a distinct entity.(47)

Endoscopic Findings

Characteristic endoscopic features provide important diagnostic clues, though their absence does not exclude EoE. The EoE Endoscopic Reference Score (EREFS) systematically evaluates five major findings: edema (decreased or absent vascular pattern), rings (concentric rings or trachealization), exudates (white plaques or patches), furrows (longitudinal lines or grooves), and strictures (luminal narrowing).(48)

In adult populations, common endoscopic features include linear furrows (80%), mucosal rings (64%), small-caliber esophagus (28%), white plaques or exudates (16%), and strictures (12%).(49) Pediatric series show different distributions, with normal appearance in 32%, linear furrows in 41%, esophageal rings in 12%, and white plaques in 15%.(50) Importantly, approximately 10–25% of EoE patients exhibit completely normal-appearing esophageal mucosa on endoscopy, emphasizing the critical importance of obtaining biopsies regardless of visual appearance.(51)

Additional endoscopic features include the "crepe-paper esophagus" phenomenon, characterized by linear mucosal tears occurring with minimal trauma such as endoscope passage, and increased esophageal rigidity appreciated during biopsy attempts.(52) Contrast esophagography may reveal lengthy, tapered strictures that escape detection during endoscopy, with studies showing that 71% of adults and 55% of children with EoE have narrowing evident on esophagography but not recognized endoscopically.(53)

Histopathological Examination

Histopathological assessment remains the diagnostic gold standard. The hallmark feature is increased intraepithelial eosinophil density in esophageal mucosa that is normally devoid of eosinophils.(54) Because eosinophilic infiltration may be patchy rather than uniform, current recommendations specify obtaining at least 5-6 biopsy specimens from multiple levels (typically proximal and distal esophagus) to maximize diagnostic sensitivity.(55)

Beyond peak eosinophil count, additional histologic features provide diagnostic and prognostic value. Characteristic patterns include superficial eosinophil layering along the luminal surface, eosinophil microabscesses (clusters of >4 eosinophils), basal cell hyperplasia, dilated intercellular spaces (spongiosis), and eosinophil degranulation.(56) Subepithelial fibrosis occurs in both children and adults and correlates with disease chronicity.(57)

The Eosinophilic Esophagitis Histologic Scoring System (EoEHSS) has been developed and validated to assess disease activity more comprehensively than peak eosinophil count alone.(58) This system evaluates inflammatory features (eosinophil density and distribution, basal zone hyperplasia, dilated intercellular spaces, eosinophil surface layering, eosinophil abscess formation) and remodeling features (lamina propria fibrosis, smooth muscle hypertrophy, vascular alterations), providing superior discrimination between active and treated disease.(59)

Exclusion of Alternative Diagnoses

Essential to EoE diagnosis is exclusion of secondary causes of esophageal eosinophilia. Differential considerations include GERD, achalasia, Crohn's disease, infections such as candida esophagitis, connective tissue disorders, hypereosinophilic syndrome, and drug-induced esophagitis.(60) In cases where GERD coexists with esophageal eosinophilia, clinical judgment determines the primary contributor—for example, erosive esophagitis, hiatal hernia, and typical reflux symptoms suggest GERD as the predominant process.(61)

Emerging Diagnostic Modalities

Research efforts have focused on developing less invasive diagnostic approaches. The esophageal string test captures eosinophil-associated proteins from the esophageal lumen and shows good correlation with mucosal eosinophil density in both children and adults.(62) The Cytosponge, originally developed for Barrett's esophagus surveillance, has been adapted for EoE assessment in adults.(63) Unsedated transnasal endoscopy permits mucosal biopsy without sedation.(64) Tethered confocal microscopy capsules provide cellular-level imaging data without traditional endoscopy.(65)

Advanced endoscopic techniques include endoscopic ultrasonography demonstrating deeper layer thickening, and functional luminal imaging probe (EndoFLIP) assessment of esophageal compliance and distensibility.(66) EndoFLIP has shown altered esophageal wall compliance in both adults and children with EoE and may prove valuable for stricture identification and dilation planning.(67)

Molecular diagnostics offer additional possibilities. Tissue staining for eosinophil peroxidase (EPX) can detect the eosinophil "footprint" even in the absence of intact eosinophils.(68) The EoE Diagnostic Panel (EDP) assesses expression of 96 dysregulated genes, achieving high sensitivity and specificity for diagnosis and distinguishing molecular phenotypes.(69) Both EPX staining and EDP can be performed on archived tissue, permitting retrospective analysis.(70)

TREATMENT APPROACHES

The "3D" Concept

Contemporary EoE management follows the "3D" framework: Diet, Drugs, and Dilation.(71) Treatment goals include controlling esophageal eosinophilia and inflammation (achieving <15 eosinophils per high-power field), alleviating symptoms, preventing progressive remodeling, and reversing established fibrosis where possible.(72) Combination therapies may be necessary in refractory cases.

Dietary Therapy

Dietary modification Is a nonpharmacologic treatment approach based on the central role of food antigens in EoE pathogenesis.(73) Three primary dietary strategies exist: elemental diets, allergy testing-guided elimination, and empiric elimination diets.

Elemental Diets: Amino acid-based formulas achieve the highest response rates, with meta-analysis showing 90.8% effectiveness.(74) However, clinical implementation faces substantial challenges including poor palatability (often requiring nasogastric tube placement), psychological and social disturbances, quality of life impairment, high cost, and the prolonged reintroduction phase needed to identify specific triggers.(75)

Allergy Testing-Guided Elimination: This approach uses skin prick testing and atopy patch testing to identify foods for elimination. While some pediatric studies report 53% histologic response, adult data show poor concordance between allergy tests and actual EoE triggers.(76) Recent evidence indicates EoE pathogenesis is predominantly IgG4-mediated rather than IgE-mediated, questioning the utility of IgE-based testing.(77)

Empiric Elimination Diets: The six-food elimination diet (SFED), removing cow's milk, soy, wheat, eggs, peanuts, and shellfish, achieves clinicopathologic remission in 74% of patients with better acceptance and lower cost than elemental diets.(78) After reintroduction, only 1-2 foods trigger symptoms in 65–85% of patients, most commonly dairy.(79) Step-up approaches beginning with 2-food elimination (milk and gluten) and adding foods as needed reduce endoscopy burden while maintaining 43–79% remission rates depending on the number of foods eliminated.(80)

Pharmacologic Therapy

Proton Pump Inhibitors: PPIs serve as first-line therapy based on evidence that PPI-responsive esophageal eosinophilia falls within the EoE spectrum.(81) PPIs reduce esophageal acid exposure and exert anti-inflammatory effects by blocking Th2 responses and reducing inflammatory cytokine production.(82) Recommended dosing includes 20-40 mg twice daily in adults or 1 mg/kg per dose twice daily in children.(83) Meta-analysis

demonstrates clinical remission in 60.8% and histologic remission in 50.5% of patients.(84) After achieving remission, many patients maintain control with reduced doses.(85)

Topical Corticosteroids: Swallowed topical corticosteroids represent highly effective EoE therapy. Budesonide and fluticasone propionate in viscous solutions show superior efficacy compared to standard inhaled formulations.(86) Recent trials of oral budesonide tablets achieved 58% complete remission at 6 weeks and 85% at 12 weeks, with histologic remission in 93%.(87) Symptom improvement correlates with histologic response.(88)

Long-term maintenance therapy is indicated for patients with esophageal stenosis, symptomatic relapse upon treatment discontinuation, recurrent food impaction, high-risk comorbidities, or history of perforation.(89) Maintenance dosing with 0.25 mg budesonide twice daily maintains remission for extended periods.(90) Adverse effects include esophageal candidiasis (5–30%), oral candidiasis (1%), and rarely adrenal insufficiency.(91)

Biologic Therapies: Monoclonal antibodies targeting specific inflammatory pathways show promise. Anti-IL-5 antibodies (mepolizumab, reslizumab) decrease esophageal eosinophilia and improve symptoms with acceptable safety profiles.(92) Anti-IL-13 antibodies improve endoscopic and histologic findings and restore barrier function.(93) Dupilumab, targeting the IL-4 receptor and inhibiting IL-4/IL-13 signaling, has demonstrated efficacy in both adults and children.(94) Other biologics including omalizumab (anti-IgE) and infliximab (anti-TNF-α) have shown limited or no benefit.(95)

Endoscopic Dilation

Esophageal dilation addresses fibrostenotic complications but does not treat underlying inflammation.(96) Indications include persistent dysphagia despite medical therapy after achieving inflammation remission, severe dysphagia, and history of food impaction.(97) Both bougie and balloon dilation techniques are effective and safe, with major complication rates <1%.(98) Meta-analysis of 1,820 dilations in 845 patients showed clinical improvement in 95% with very low perforation rates.(99)

Dilation should be performed gradually using the "rule of 3" (no more than 3 dilators with 2-mm incremental increases per session when resistance is encountered) and repeated every 2-3 weeks as needed to minimize complications including chest pain and perforation.(100) Approximately 58% of patients require repeat dilation, with 75% needing additional procedures within one year, highlighting the importance of concurrent anti-inflammatory therapy.(101)

MONITORING AND FOLLOW-UP

Treatment response evaluation incorporates clinical, endoscopic, and histologic assessments.(102) Response categories include complete normalization (symptom resolution, endoscopic improvement, histologic remission with <15 eosinophils per high-power field), partial response (improvement in some but not all parameters), and nonresponse.(103)

Current recommendations advise follow-up endoscopy with biopsies 8-12 weeks after treatment initiation to assess histologic response, as symptom improvement may not correlate reliably with mucosal healing.(104) Long-term surveillance strategies depend on treatment modality and individual patient factors, though optimal surveillance intervals remain incompletely defined.(105)

Emerging non-invasive monitoring approaches under investigation include blood biomarkers (IL-3, IL-5, IL-6, IL-13, eotaxin variants, TSLP, eosinophil granule proteins), urine markers (3-bromotyrosine), gene expression panels, the cytosponge device, and the esophageal string test.(106) While promising, these modalities require further validation before routine clinical implementation.(107)

PROGNOSIS AND COMPLICATIONS

EoE follows a chronic relapsing course requiring long-term management.(108) Untreated disease progresses to fibrostenotic complications, with stricture prevalence correlating with symptom duration.(109) Complications include recurrent food impaction, esophageal perforation (spontaneous or iatrogenic during endoscopy or

dilation), and rarely, malnutrition.(110) Unlike eosinophilic gastroenteritis, EoE does not increase cancer risk.(111)

Quality of life impairment is substantial, affecting dietary choices, social eating situations, medication adherence, and psychological well-being. Early diagnosis and effective treatment prevent progression and preserve esophageal function, underscoring the importance of heightened clinical awareness and systematic diagnostic approaches.(112)

CONCLUSION

Eosinophilic esophagitis has evolved from an obscure entity to a well-recognized chronic inflammatory disease with significant clinical impact. The condition requires integration of clinical history, endoscopic assessment, and histopathological confirmation for accurate diagnosis. Key clinical discriminators include atopic comorbidities, prolonged symptom duration, food impaction episodes, and characteristic endoscopic abnormalities such as mucosal edema, vertical furrows, concentric rings, and white exudates. Routine laboratory investigations provide limited diagnostic value, emphasizing the necessity of systematic esophageal biopsy sampling even in endoscopically normal-appearing mucosa. Effective management incorporates dietary modification, pharmacologic therapy with PPIs and topical corticosteroids, and endoscopic dilation for fibrostenotic complications. Early recognition and treatment prevent progressive remodeling and improve long-term outcomes. (113)

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