NICOLAUS COPERNICUS UNIVERSITY IN TORUŃ

Quality in Sport. eISSN 2450-3118.

Journal Home Page
https://apcz.umk.pl/QS/index

STRZEWICZEK, Aleksandra and SZAMOCKA, Karolina. Modern Diagnostic Methods and Pathomechanisms of Eosinophilic Esophagitis – A Review. Quality in Sport. 2026;54:70170. eISSN 2450-3118. https://doi.org/10.12775/QS.2026.54.70170

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).
The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 23.03.2026. Revised: 01.04.2026. Accepted: 05.04.2026. Published: 07.04.2026.

Modern Diagnostic Methods and Pathomechanisms of Eosinophilic Esophagitis – A Review

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ABSTRACT

Introduction. Eosinophilic esophagitis (EoE) is a chronic immune-mediated disease characterized by eosinophil-predominant inflammation of the esophageal mucosa. Over the last two decades, the incidence and prevalence of EoE have increased significantly, making it one of the most important causes of dysphagia and food impaction in children and adults. The disease results from complex interactions between genetic predisposition, environmental factors, and immune system dysregulation, particularly involving Th2-mediated inflammatory pathways.

Aim of the Study. The aim of this review is to summarize current knowledge regarding the pathomechanisms underlying eosinophilic esophagitis and to analyze modern diagnostic methods used in clinical practice and research. Particular emphasis is placed on immunological mechanisms, molecular pathways, biomarkers, and emerging technologies that may improve early detection and disease monitoring.

Materials and Methods. A literature review was conducted using major scientific databases including PubMed, Scopus, and Web of Science. Articles published between 2000 and 2025 were analyzed using keywords such as "eosinophilic esophagitis," "pathophysiology," "diagnostic methods," "biomarkers," and "immunology." Only peer-reviewed studies and reviews focusing on molecular mechanisms, clinical diagnostics, and emerging technologies were included.

Conclusion. Current evidence suggests that EoE is driven primarily by Th2 immune responses involving cytokines such as IL-4, IL-5, and IL-13, leading to eosinophil recruitment, epithelial barrier dysfunction, and progressive esophageal remodeling. Advances in diagnostic technologies, including molecular profiling, minimally invasive sampling, and artificial intelligence–assisted histology, are expected to significantly improve disease detection and personalized management.

Keywords: Eosinophilic esophagitis, Th2 inflammation, IL-13, biomarkers, molecular diagnostics

1. Introduction

Eosinophilic esophagitis is a chronic inflammatory disease of the esophagus characterized by eosinophil infiltration of the esophageal epithelium and symptoms related to esophageal dysfunction. The disorder was first recognized as a distinct clinical entity in the early 1990s, and since then its prevalence has steadily increased worldwide [1,2].

The disease is strongly associated with allergic disorders, including asthma, atopic dermatitis, allergic rhinitis, and food allergies. These associations suggest that EoE is part of the spectrum of **allergic and immune-mediated diseases** involving a dysregulated Th2 immune response [3]. The hallmark of the disease is the presence of at least **15 eosinophils per high-power field in esophageal biopsy specimens**, together with clinical symptoms such as dysphagia, food impaction, and chest discomfort [4].

Recent advances in molecular biology and immunology have improved our understanding of the disease. It is now recognized that EoE results from interactions between **genetic predisposition, environmental exposures, epithelial barrier dysfunction, and immune dysregulation** [5].

2. Aim of the Study

The aim of this review is to analyze the current knowledge regarding:

1. The **pathomechanisms of eosinophilic esophagitis**, including immunological and molecular mechanisms.
2. The role of **cytokines, chemokines, and genetic factors** in disease development.
3. Modern **diagnostic methods**, including molecular diagnostics, biomarkers, and emerging technologies.
4. Recent advances in **therapeutic antibodies and targeted therapies**.

3. Materials and Methods

This review was conducted using a narrative literature analysis. Scientific publications were identified through database searches including PubMed, Scopus, and Web of Science.

Keywords used in the search included:

- eosinophilic esophagitis
- pathophysiology
- diagnostic methods
- cytokines

- biomarkers
- monoclonal antibodies

Articles were included if they met the following criteria:

1. Published in peer-reviewed journals.
2. Focused on pathophysiology, molecular biology, or diagnostic methods of EoE.
3. Provided experimental or clinical evidence.

A total of **35 publications** were selected for analysis.

4. Pathophysiology of Eosinophilic Esophagitis

4.1. Immunological Mechanisms

Eosinophilic esophagitis is primarily mediated by a **type-2 helper T cell (Th2) immune response** triggered by food and environmental allergens [7].

When allergens penetrate the esophageal epithelium, epithelial cells release cytokines such as:

- thymic stromal lymphopoietin (TSLP)
- interleukin-25 (IL-25)
- interleukin-33 (IL-33)

These cytokines activate dendritic cells and innate lymphoid cells, which stimulate Th2 lymphocytes [7].

Activated Th2 cells produce cytokines including:

- IL-4
- IL-5
- IL-13

These cytokines play a critical role in eosinophil recruitment and activation [8].

4.2. Role of Cytokines and Chemokines

Among these cytokines, **IL-13 is considered the key mediator of EoE pathogenesis**. Studies have shown that IL-13 expression is markedly increased in esophageal tissue of EoE patients [9].

IL-13 induces the expression of **eotaxin-3 (CCL26)**, a chemokine responsible for attracting eosinophils to the esophageal mucosa [10].

Experimental studies demonstrated that IL-13 stimulation of esophageal epithelial cells leads to significant transcriptional changes, producing an EoE-specific transcriptome pattern [10].
IL-5 is also important because it promotes:

- eosinophil proliferation
- survival
- activation

in inflamed tissues [11].

4.3. Epithelial Barrier Dysfunction

An important component of EoE pathogenesis is **disruption of the esophageal epithelial barrier**.
IL-13 reduces expression of proteins involved in epithelial integrity, including:

- desmoglein-1
- filaggrin
- involucrin [12].

This disruption increases epithelial permeability and allows allergens to penetrate deeper tissues.
Recent studies have identified the **CAPN14 gene**, which encodes the protease calpain-14, as a key factor involved in epithelial barrier dysfunction [13]. CAPN14 expression is strongly induced by IL-13 and leads to degradation of structural proteins in epithelial cells [13].

4.4. Genetic Factors

Genome-wide association studies have identified several genetic variants associated with EoE susceptibility. The most significant loci include:

- **TSLP gene**
- **CAPN14 gene**
- **FLG gene** [14].

CAPN14 is particularly interesting because its expression is almost exclusively restricted to the esophageal epithelium, suggesting a unique disease-specific pathway [13].

5. Modern Diagnostic Methods

5.1. Endoscopic Diagnosis

Endoscopy remains the primary diagnostic method for EoE. Typical endoscopic features include:

- esophageal rings
- linear furrows
- white exudates
- mucosal edema
- strictures [7].

However, endoscopic findings may sometimes be subtle or absent, which necessitates histological confirmation.

5.2. Histological Examination

Histological evaluation of esophageal biopsies is the gold standard for diagnosis. Diagnostic criteria include:

- ≥15 eosinophils per high-power field
- basal cell hyperplasia
- dilated intercellular spaces [4].

Nevertheless, manual eosinophil counting is time-consuming and subject to interobserver variability.

5.3. Artificial Intelligence in Diagnostics

Recent studies have demonstrated the potential of **machine learning algorithms** to automate eosinophil detection in biopsy samples.

Deep neural networks trained on histological images have achieved diagnostic accuracies above **90%**, enabling automated quantification of eosinophils and classification of disease activity [15].

Such technologies may significantly improve diagnostic consistency and reduce pathologist workload.

5.4. Molecular Biomarkers

Advances in molecular biology have led to the identification of several potential biomarkers for EoE.

Examples include:

- eotaxin-3
- periostin
- major basic protein [16].

Gene expression profiling of esophageal tissue has revealed a unique **EoE transcriptomic signature**, which may allow differentiation between EoE and gastroesophageal reflux disease [17].

5.5. Dissection endotypes:

A new division has been proprosed:

- EoEe1 – normal appearing oesophagus;
- EoEe2 – connected to inflammation type-2 and steroid resistant;
- EoEe3 – beginning in adult age, connected with stenosis of fiber and without epithelial gene expression.
  Treatment includes Budesonid – soluble in the mouth and Dupilumab – biological therapy as first choice [33].

6. Biological Therapies and Monoclonal Antibodies

Recent clinical trials have investigated targeted biological therapies for EoE.

6.1. Anti-IL-13 antibodies

Blocking IL-13 reduces esophageal eosinophilia and improves epithelial barrier function [18].

6.2. Anti-IL-5 therapy

Therapies targeting IL-5 reduce eosinophil numbers but have shown limited clinical improvement in symptoms [11].

6.3. Dupilumab

Dupilumab blocks the IL-4 receptor α subunit, inhibiting both IL-4 and IL-13 signaling pathways. Clinical trials have demonstrated significant improvements in histological inflammation and patient symptoms [18].

7. Progress in Research

Recent research focuses on several promising areas:

- molecular diagnostics
- genetic susceptibility
- microbiome interactions

- personalized medicine

Advances in transcriptomics and epigenetics are expected to improve understanding of disease heterogeneity and treatment responses [12]. Cooperation of gastroenterologists and allergists-immunologists can bring new point of view of multi-faceted approach for patients' prognosis[33].

8. Conclusion

Eosinophilic esophagitis is a complex immune-mediated disease characterized by eosinophilic inflammation and progressive esophageal remodeling. Current evidence indicates that the disease results from interactions between genetic susceptibility, epithelial barrier dysfunction, and Th2-mediated immune responses.

Advances in molecular biology, artificial intelligence diagnostics, and targeted biological therapies are rapidly transforming the diagnostic and therapeutic landscape of EoE. Continued research is essential to develop personalized treatment strategies and improve long-term outcomes for affected patients.

Eosinophilic esophagitis is a complex immune-mediated disease characterized by eosinophilic inflammation and progressive esophageal remodeling. Current evidence indicates that the disease results from interactions between genetic susceptibility, epithelial barrier dysfunction, and Th2-mediated immune responses.

In addition to these core mechanisms, environmental factors such as dietary antigens and early-life exposures are increasingly recognized as important contributors to disease onset and progression. Food allergens, in particular, play a central role in triggering and sustaining inflammation, as elimination diets often lead to clinical and histological improvement. This highlights the importance of identifying specific patient triggers, which remains a challenge due to the heterogeneous nature of the disease and variability in individual immune responses.

At the cellular level, eosinophils release cytotoxic proteins, cytokines, and growth factors that contribute not only to inflammation but also to tissue remodeling, including fibrosis and stricturing of the esophagus. Over time, these structural changes can lead to dysphagia, food impaction, and a significant reduction in quality of life. Furthermore, the involvement of other immune cells, such as mast cells and basophils, underscores the complexity of the inflammatory network in EoE and suggests that multiple pathways may need to be targeted for effective disease control.

Advances in molecular biology, artificial intelligence diagnostics, and targeted biological therapies are rapidly transforming the diagnostic and therapeutic landscape of EoE. Continued

research is essential to develop personalized treatment strategies and improve long-term outcomes for affected patients. Emerging biomarkers, including gene expression profiles and non-invasive sampling techniques, offer promising tools for earlier diagnosis and monitoring of disease activity. At the same time, biologic agents targeting key cytokines such as interleukin-4, interleukin-5, and interleukin-13 are showing encouraging results in clinical trials, providing new hope for patients with refractory disease.

Ultimately, a multidisciplinary approach that integrates clinical, endoscopic, histological, and molecular data will be crucial for optimizing patient care. As our understanding of the disease deepens, there is growing potential to shift from symptom management toward precision medicine, where therapies are tailored to the individual patient's underlying pathophysiology.

Disclosure:

Author contributions

Conceptualization: Karolina Szamocka

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All authors have read and agreed with the published version of the manuscript.

Funding Statement:

The study did not receive special funding.

Institutional Review Board Statement:

Not applicable.

Informed Consent Statement:

Not applicable.

Data Availability Statement:

Not applicable.

Conflict of Interest Statement:

The authors of the paper report no conflicts of interest.

In preparing this work, the authors used ChatGPT (chatGPT.com) as a tool for translation support in preparing this work. After using this tool, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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