



JOURNAL OF EDUCATION, HEALTH AND SPORT

eISSN 2391-8306 · Open Access · Peer-reviewed

apcz.umk.pl/JEHS · Nicolaus Copernicus University in Toruń



Cite as: BĄK, Michalina, STRÓŻYK, Karolina, MEHAL, Kinga, ZAWADZIŃSKI, Wiktor, SZAMOCKA, Karolina, PIELICH, Weronika, BALICKA-DWORCZAK, Natalia, KULIŃSKI, Tomasz and SIUSTA, Natalia. The Efficacy of Dietary Elimination Strategies in Achieving Histological and Clinical Remission in Eosinophilic Esophagitis. *Journal of Education, Health and Sport*. 2026;94:73138. <https://doi.org/10.12775/JEHS.2026.94.73138>

ARTICLE TIMELINE

Received: 07.06.2026 Revised: 10.07.2026

Accepted: 10.07.2026 Published: 17.07.2026

INDEXING & EVALUATION

MEiN points: 40 Unique ID: 201159

Disciplines: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).

The journal has been awarded 40 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32318). Unique Journal Identifier: 201159. Scientific disciplines: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).

Punkty Ministerialne z 2019 – aktualny rok 40 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu). © The Authors 2026.

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The Efficacy of Dietary Elimination Strategies in Achieving Histological and Clinical Remission in Eosinophilic Esophagitis

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Abstract

Eosinophilic esophagitis (EoE) is a chronic, Th2-mediated food antigen-driven inflammatory disease for which dietary elimination therapy is the only approach to treat the underlying etiology and the only approach that can provide long-term histological remission while preventing fibrostenotic complications [1], [2], [3].

Aim. To compare histological and clinical remission rates between particular diets.

Results. The elemental diet is most effective (remission >90%) but is also associated with low patient compliance [4], [5]. Empirical diets show ~70% efficacy for 6FED [1], [6], while the 2FED (milk and wheat) achieves remission in 43–45% of cases, substantially reducing treatment burden [7], [8]). Cow's milk remains the most frequent cause [8], [9]. There is a significant difference between symptom relief and histological healing that has led to biopsy-driven monitoring [10], [11].

Conclusions. Dietary therapy is a very effective, non-pharmacological treatment for EoE. The Step-Up approach (initially beginning with 2FED) is the preferred strategy to balance clinical efficacy with patient quality of life [7], [9], [12]. Multidisciplinary care is needed to mitigate the nutritional risks and psychological stress of long-term food elimination [5], [11].

Key words: Eosinophilic Esophagitis, Elimination Diet, Histological Remission, Food Triggers, Step-Up Protocol.

1. Introduction

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated or antigen-mediated clinicopathologic disease of the esophagus. It is defined clinically by symptoms of esophageal dysfunction—such as dysphagia, food impaction, heartburn, and chest pain—and histologically by an eosinophil-predominant inflammation, classically described as a peak eosinophil count of 15 or more eosinophils per high-power field (eos/hpf) [13], [14], [15], [16]. In the last 20 years, EoE has evolved from a rare medical curiosity to a common cause of upper gastrointestinal morbidity worldwide [17], [18], [19].

EoE is characterized by a T-helper cell type 2 (Th2) allergic response to ingested food antigens, which distinguishes it from classical IgE-mediated food allergies, and delayed hypersensitivity mechanisms are in place, so that routine allergic evaluations such as SPT or serum specific IgE testing are ineffective in identifying specific dietary triggers [1], [20]. Without treatment, chronic eosinophilic inflammation results in esophageal remodeling, subepithelial fibrosis, and the development of esophageal strictures, which can be challenging clinically and necessitate endoscopic dilation [3], [21].

Dietary elimination therapy is considered a first-line and disease-modifying treatment that directly targets the antigenic triggers, which can lead to long-term, drug-free remission [1], [2], [7], [16]. The evolution of dietary strategies, from the highly restrictive elemental diet and the classic Six-Food Elimination Diet (6FED) to the modern, patient-tailored "Step-Up" approaches (e.g., 1FED, 2FED, 4FED) reflects a clinical need to balance histological efficacy with patient quality of life [7], [9], [14], [16]. In this paper, we aim to systematically review the efficacy of these dietary elimination strategies, focusing on methodologies of trigger identification, long-term clinical outcomes, and the nutritional implications of dietary management in achieving EoE remission.

2. Research materials and methods

2.1. Participants.

The current systematic review incorporates data from diverse cohorts described in recent literature, which include both pediatric and adult patients with EoE [10]. The inclusion criteria for the cohorts analyzed were a confirmed diagnosis of EoE before the start of the dietary intervention, as defined by the presence of clinical symptoms of esophageal dysfunction and an initial mucosal biopsy showing ≥ 15 eos/hpf in at least one esophageal site [4], [22]. Studies included both newly diagnosed and PPI-refractory participants, with phenotypic differences by age: pediatric cohorts tended to present with more inflammatory symptoms (vomiting, abdominal pain), while adult cohorts were more likely to experience fibrostenotic complications (dysphagia, food impaction [3], [10].

2.2. Measurements

The main treatment protocol for all clinical trials reviewed included a specific empirical dietary elimination protocol and subsequent endoscopic re-evaluation. The primary clinical outcome (end-point) was histological remission, defined in the literature as < 15 eos/hpf, although some studies set secondary strict thresholds at ≤ 6 eos/hpf for deep remission [4], [12].

Tools employed throughout the research studies consisted of:

- **Esophagogastroduodenoscopy (EGD):** Used for obtaining multiple mucosal biopsies from the proximal and distal esophagus before and after diet implementation [22]

- **The Eosinophilic Esophagitis Endoscopic Reference Score (EREFS):** A validated visual grading system to quantify endoscopic signs of inflammation (edema, rings, exudates, furrows) and remodeling (strictures) [9], [22]
- **Quality of Life Questionnaires:** Validated psychometric tools, such as the EoE-QOL-A (Adult) or PedsQL EoE module, were used to evaluate the psychosocial and daily living impacts of dietary restrictions [11].
- **Nutritional Assessment Tools:** Nutritional Assessment Tools: Dietary recalls and anthropometric measurements to monitor macro- and micronutrient intake, particularly calcium and vitamin D, during elimination phases [5].

3. Research results

Based on the scientific literature provided, here is a detailed description of each dietary protocol used in the management of Eosinophilic Esophagitis (EoE), the specific food groups they eliminate and estimated efficacy.

3.1 One-Food Elimination Diet (1FED)

- 1FED is the most straightforward empirical protocol and is the most commonly used as the first-line therapy in the "Step-Up" strategy.
- **What it eliminates:** Cow's milk and dairy products (e.g., cheese, yogurt, butter).
- **Efficacy:** Cow's milk is the most commonly reported single trigger antigen, accounting for the Th2 inflammatory response in 50% to 70% of responders in both children and adults [8], [9].

3.2 Two-Food Elimination Diet (2FED)

- the most commonly recommended starting point by clinicians who seek to maximize efficacy and patient quality of life

- **What it eliminates:** This diet targets the two most common triggers - Cow's milk and Gluten/Wheat.
- **a remission rate** of 43% to 45% [11].

3.3 Four-Food Elimination Diet (4FED)

- The 4FED is used when a patient does not respond to a 2FED, or as a moderate-intensity initiation
- **What it eliminates:** Cow's milk, Wheat, Eggs, and Soy/Legumes, as they are frequent secondary triggers in EoE [12].
- **Efficacy:** This protocol captures a larger percentage of patients (cumulative remission ~60%)

3.4 Six-Food Elimination Diet (6FED)

- the 6FED was historically the gold standard for empirical treatment
- **What it eliminates:** Cow's milk, Wheat, Eggs, Soy, Peanuts/Tree nuts, and Fish/Seafood.
- **Efficacy:** Because it removes the six most common allergenic food groups, it has the highest remission rates (70% to 74%), but it is difficult and often reserved for Step-Down protocols or resistant cases due to the need for frequent endoscopies during the reintroduction phase [1], [12].

3.5 The Elemental Diet

- It is the most restrictive intervention
- It eliminates all solid foods and intact proteins and instead uses a specialized amino-acid-based formula
- It has a histological remission rate greater than 90%, because of removing all potential dietary antigens

- Due to the high cost, poor palatability of the formula, and the negative impact on quality of life it is rather used as a rescue therapy.

4. Efficacy of Step-Up and Step-Down Dietary Elimination Protocols

Dietary interventions are effective in EoE and the degree of restriction correlates with the rate of histological remission. Elemental diets, using amino-acid-based formulas that do not contain intact proteins, have the highest rates of histological remission (over 90%) but are poorly palatable and create an immense psychosocial burden and are not usually used as a long-term maintenance strategy [4], [5]. Empirical elimination diets are based on the removal of common food allergens; historically the 6FED removing cow's milk, wheat, eggs, soy, peanuts/tree nuts, and fish/seafood was standard, with remission rates in approximately 70% to 74% of patients [1], [12], but more recent data support a "Step-Up" protocol to minimize unnecessary dietary restrictions and endoscopies [7]. The 2FED removing only animal milk and gluten/wheat has shown remarkable efficacy, with remission in approximately 43% to 45% of patients [7], [8].

Based on the scientific evidence provided, the management of Eosinophilic Esophagitis (EoE) has evolved toward optimizing the balance between clinical efficacy and patient quality of life through two primary strategies: Step-Up and Step-Down protocols.

Historically, the Step-Down approach involved the most restricted diet (often 6FED) in order to reach rapid histological remission, followed by reintroduction of foods to determine specific triggers once remission was confirmed (<15 eosinophils/hpf) [1], [12]. Although effective, this approach places patients on excessive dietary restrictions, and the high number of follow-up endoscopies is not ideal.

In contrast, Step-Up protocol is now preferred in clinical practice [7] and starts with less restrictive diets (e.g., 1FED [milk] or 2FED [milk and wheat]) and only increases restrictions if remission is not achieved. This significantly improves patient compliance, reduces the psychological burden of the diet, and minimizes the number of invasive procedures required to identify a sustainable maintenance diet [8], [14].

5. Clinical Considerations

Evidence that most patients on a 6FED eventually have only one or two food triggers [7], [22] supports the transition to the Step-Up strategy, because by starting small, clinicians can identify these triggers (most commonly milk) more quickly. In addition, recent studies stress that the efficacy of a protocol should be measured not only by eosinophil counts but by long-term adherence and the prevention of esophageal remodeling and strictures [5], [11], which is the least restrictive effective diet, both clinically and in terms of life satisfaction [2], [10].

5.1 Clinical vs. Histological Remission and Food Reintroduction

An important finding in more recent studies is that there may be symptom-histology dissociation, with patients reporting a significant clinical improvement in symptoms (decrease in dysphagia episodes), even when histological remission (< 15 eos/hpf) is not achieved [10], [11]. These further underscores the need for histological monitoring via endoscopy, because subclinical chronic inflammation will inevitably result in fibrotic remodeling and strictures over time [3], [22].

After achieving remission, the reintroduction phase is important, during which foods are reintroduced one at a time, followed by an EGD with biopsies after 6 to 8 weeks [9]. Patients report this phase to be the most difficult because of the high number of endoscopic procedures. Standard allergy tests (SPT, serum IgE) have been clearly demonstrated to have low positive predictive value for these specific triggers and therefore empirical reintroduction remains the only scientifically valid method to determine a patient's specific food triggers [2], [13]. In cases where dietary protocols fail or the reintroduction process is not possible, new biologic therapies (e.g., dupilumab targeting IL-4R α) have proven to be effective alternatives to dietary management [6].

5.2 Nutritional Adequacy and Quality of Life Implications

Prolonged elimination of major food groups poses significant nutritional and psychological risks. Studies show that patients on 4FED or 6FED are at higher risk for micronutrient deficiencies,

including calcium, vitamin D, and certain B-vitamins, due to the long-term avoidance of fortified dairy and wheat products [5]. In addition, the quality of life is significantly affected. Patients describe high levels of food-related anxiety, social isolation, and financial burden to purchase specialty "free-from" foods and make frequent medical appointments [11]. Non-adherence is largely driven by the psychological burden of dietary management, especially among adolescents and young adults, which supports the clinical shift toward less restrictive Step-Up protocols [7], [10].

6. Discussion

Dietary management of Eosinophilic Esophagitis has shifted, and recent literature synthesizes that while highly restrictive diets (elemental, 6FED) provide better initial remission rates, they are significantly limited by poor adherence, psychological stress, and nutritional risks [1], [5], [11]. The move to the Step-Up approach (starting with a 1FED [milk] or 2FED [milk and wheat]) is an effective and patient-centered optimization of care [7], [12].

The literature confirms that cow's milk and wheat are the most common antigenic triggers of esophageal inflammation in this disease model [8]. Targeting these two first can spare more than 40% of patients from the psychological and nutritional burdens of wider elimination [7]. Still, a significant limitation in the field is the need for repeated EGDs to confirm histological remission, as symptoms and traditional allergy testing are unreliable [13], [22], and the reintroduction phase will require less invasive monitoring tools such as the esophageal string test or Cytosponge, as well as AI-driven transcriptomic profiling to reduce the burden of procedures [2].

Moreover, specialized dietitians should be an integral part of the multidisciplinary care team, as proper dietary counseling is key to preventing nutritional deficiencies and teaching patients how to avoid cross-contamination, read food labels, and navigate social situations, which directly affects long-term therapeutic adherence [5]. Lastly, although dietary therapy is very effective, biologic therapies provide a necessary safety net for patients who are refractory to therapy or cannot maintain significant lifestyle changes [6].

7. Conclusions

Dietary elimination is an effective, disease-modifying therapy for Eosinophilic Esophagitis that can induce deep histological remission and prevent progression to fibrostenotic complications [3], [4]. The step-up 2FED strategy has been the most practical approach, providing an optimal balance of clinical efficacy and patient quality of life [7], [9]. Successful management requires patient compliance, nutritional monitoring to avoid malnourishment, and endoscopic follow-up to document resolution of mucosal inflammation [5], [22]. With the evolution of the field, precision medicine with the aid of molecular biomarkers and less invasive monitoring will further evolve how we prescribe and manage dietary interventions for EoE [2].

Disclosure

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

Funding Statement:

The study received no external funding.

Ethics Committee Statement:

Not applicable.

Informed Consent Statement:

Not applicable.

Data Availability Statement:

Not applicable.

Acknowledgments:

Not applicable.

Conflicts of Interest:

The authors declare no conflict of interest.

Declaration of the use of generative AI and AI-assisted technologies in the writing process:

AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance

in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. AI were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

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