

Approaches to diet therapy for eosinophilic esophagitis

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Purpose of review

The aim of this review is to highlight recent advances in dietary therapy for eosinophilic esophagitis (EoE).

Recent findings

An empiric elimination diet step-up strategy is now well established as the initial approach for dietary treatment. The most common food triggers are by far cow's milk, followed by wheat and egg. Legumes seem to be important solely in Spain and other Mediterranean countries, where they are regularly consumed. Retrospective efficacy data on cow's milk elimination diet in children vary from 25 to 65%. The recently described esophageal prick test did not detect local reaction to the most common food triggers described for EoE.

Summary

Within the step-up approach, the specific food group or groups to be first eliminated and whether if it will depend on the geographical setting and food consumption habits remain unknown. Prospective studies on cow's milk elimination diet in children and adults are definitely warranted. Better food allergy testing, identifying specific antigens involved in each food group, should be developed for an individualized therapy. As for disease prevention, we undoubtedly need to understand why foods we have been consuming since the Neolithic age have caused EoE just over the past few decades.

Keywords

diet, eosinophilic esophagitis, milk, step-up

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic, immune/ antigen-mediated disease, isolated to the esophagus, characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation [1]. Since 1995, when refractory esophageal eosinophilia, theoretically attributed to gastrointestinal reflux disease, was successfully treated with an amino acid-based formula (elemental diet) in eight children [2], we are aware that EoE is a disease predominantly, but not exclusively, triggered by food antigens. Available food allergy testing for evaluating conventional food allergy (skin-prick test, atopy-patch test) cannot adequately predict causative foods involved in EoE [1], neither in children nor in adults. In 2006, an empiric diet consisting of eliminating six food groups that accounted for the majority of IgE-mediated food reactions (milk, wheat, egg, soy/legumes, nuts, fish/seafood) in children from Chicago led to complete histologic remission in three out of four pediatric patients with EoE [3]. Serial single-food reintroductions in patients who achieved histological remission with the six-food elimination diet (SFED) led to the identification of specific causal food antigen(s). Though it became the standard in clinical practice, the SFED turned out to be very unpopular for both patients and physicians because of its high level of restriction and the need for numerous endoscopic procedures. The SFED starts with the highest possible dietary restriction and progresses as a 'top-down' strategy. Understanding the food reintroduction

Curr Opin Gastroenterol 2020, 36:000-000 DOI:10.1097/MOG.000000000000645

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KEY POINTS

- A step-up empiric elimination diet is currently accepted as the initial dietary approach for EoE.
- Food groups to be first and subsequently eliminated might depend on local food consumption habits and the patient's age.
- Children, especially those less than 8 years of age, likely should start with a cow's milk elimination diet, whereas adult may initially need a combination of cow's milk and either wheat, egg or legumes.
- Elimination of more than four food groups should be reserved for exceptionally motivated patients, as the probable existence of three or more food triggers might make long-term restrictions unfeasible.
- Development of refined food allergy testing is urgently needed for individualizing therapy.

process, in which up to three-quarters of responders to an SFED were found to have just one or two causative foods (after six separate food challenges and six accompanying endoscopic procedures), and the negligible role played by nuts, fish, and seafood, paved the way for implementation of a simpler and easier elimination diet, the so-called four-food elimination diet (FFED) [4]. The FFED in turn was instrumental in refining the step-up approach, which is currently our standard therapy in clinical practice. This review aims to update and summarize the most relevant information on dietary therapy for pediatric and adult EoE patients.

ELEMENTAL DIET: JUST A BRIDGE THERAPY

Elemental diet consists of feeding exclusively by a single amino acid-based formula, devoid of antigenic capacity. Its overall effectiveness to achieve histologic remission of EoE was estimated in a recent metaanalysis around 90% in both children and adults [5]. It is, by far, the most effective dietary approach for EoE. However, this dietary strategy seems unfeasible in clinical practice for a variety of reasons, including its poor palatability (this issue has been recently resolved with novel flavoring), social, psychological, and quality of life impairment related to complete avoidance of all kinds of table food, and the high cost of an elemental diet, which is not universally reimbursed. A potential role for elemental diet may be for refractory patients who wish to remain in remission while investigating the casual role of unusual foods and aeroallergens in their disease, or as a bridge therapy while waiting for

investigational drugs; these potential utilities, however, have not yet been assessed. In children under two years old or with known feeding dysfunction, avoidance of solid food may lead to delayed oralmotor skill development.

THE FAILURE OF FOOD ALLERGY TESTING IN EOSINOPHILIC ESOPHAGITIS

A relatively recent metaanalysis revealed that allergy testing-based elimination diet led to histologic remission in 45.5% of patients, with wide heterogeneity (I^2 : 75%) indicating a low reproducibility [5]. Of note, its effectiveness was significantly lower in adults than in children (32.2 versus 47.9%) [7]. Data in children have come mostly from a single center, and numerous pediatric studies have not replicated that center's efficacy rates using skin prick or atopy patch test. Results in adults are consistently disappointing [6,7], so the lack of usefulness of currently available food allergy tests have been reemphasized in the most recent iteration of guidelines for EoE management [1].

A novel esophageal prick test, which directly challenges the esophagus with local injection of allergen extracts, has been reported recently [8]. Among eight EoE patients, five patients showed immediate mucosal blanching and/or total luminal obstruction after mucosal injection of soy (n=2), banana, apple, oats, and hazelnut. In all patients, luminal obstruction improved rapidly, allowing the passage of the endoscopy around 10 min later, and disappearing entirely by the day after [8]. No patient showed reaction to milk, wheat, or egg, the most common food triggers in EoE. Although this study documents the ability of the esophagus to react immediately to local food allergen injection, the usefulness of the esophageal prick test for guiding dietary therapy appears to be questionable.

EMPIRIC ELIMINATION DIET: FROM TOP-DOWN TO STEP-UP

The aforementioned rationale for reducing dietary restrictions and endoscopic procedures led to the development of the FFED, which avoids the most common food triggers in EoE identified in SFED studies (cow's milk, wheat, eggs, and legumes) [4]. A first prospective multicenter study conducted in 52 Spanish adult EoE patients showed a 54% rate of histologic remission [4]. Half of adult responders to an FFED were found to have cow's milk, wheat or both as causative foods. These results were corroborated in a first multicenter study in 78 children from the USA in whom the histologic remission rate was

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even higher than in adults (64%) [9]. The most common food triggers were cow's milk (85%), egg (35%), wheat (33%), and soy (19%). Of note, 55% of pediatric responders to an FFED had cow's milk as the only food trigger identified by individual food reintroduction.

In summary, both FFED studies showed that the food triggers found in over half of responders (especially children) could have been identified by starting with an even simpler approach, that is, a two-food elimination diet (TFED) that withdraws cow's milk and wheat. These findings were key for the development of our step-up approach for dietary therapy in EoE (in other words, eliminating at first the one or two most common food triggers and subsequently increasing the level of restriction in nonresponders). This approach was first assessed in 2018 in the biggest multicenter study conducted so far for diet in EoE, gathering 130 consecutive patients from 14 centers, mostly from Spain [10^{••}]. In this study, all patients underwent a TFED (milk and wheat) and nonresponders were offered to escalate to an FFED, and eventually to a SFED if histological remission (esophageal biopsies showing <15 eos/HPF) was not observed. A TFED achieved both histologic and symptomatic remission of EoE in 43% of patients, with no differences between pediatric and adult patients. In nonresponders to a TFED, stepping up to an FFED (60%) and a SFED (79%) led to remission rates similar to those previously reported. Compared with a top-down strategy, this step-up approach resulted in numerous advantages, mainly reducing endoscopic procedures and shortening the diagnostic process time by 20%, while avoiding unnecessary dietary restrictions (43% of study patients could find their triggering foods without eliminating egg, legumes, nuts and fish/seafood, and up to 60% while consuming nuts and fish/seafood). Additionally, 90% of responders to a TFED or FFED were found to have just one or two causative food groups, thus identifying responders with few food triggers relatively rapidly and without need of a SFED. These responders with few food triggers for EoE are clearly the best candidates for maintenance dietary therapy requiring the fewest dietary restrictions. Of note, responders to a SFED with previous failure to a TFED and FFED were found to have three or more food triggers, including nuts and fish/seafood. Therefore, the higher the level of restriction required with the step-up approach, the higher the likelihood of having more food triggers. Taking into consideration these results, a SFED might be discouraged within the step-up strategy, or merely reserved for exceptionally motivated patients who still want to

elucidate their food triggers, even though they might be numerous.

The efficacy results obtained with dietary treatment in this initial step-up elimination diet approach have been confirmed in a recent retrospective European registry of children from 13 countries [11[•]]. The efficacy rates were: SFED 68%, a three-food elimination diet (milk, wheat, and egg) 46%, and a TFED 32%. A recent study has also evaluated through a computer-based simulation model the most promising empiric elimination strategies based on reported prevalence values for foods that activate EoE [12"]. In all simulations, which always start with elimination of dairy products, the 1,4,8-food and 1,3-food strategies appeared to be the most efficient in identifying EoE food triggers, resulting in the highest rate of correct identification of food triggers balanced by the number of endoscopies required to complete the food elimination strategy.

Interestingly, reintroduction of eliminated foods in responders to identify food triggers in the aforementioned European registry revealed a marginally significant trend (p < 0.1) toward milk and legumes being more frequently involved in Mediterranean countries than in Central and Northern European countries [11[•]]. This phenomenon has been also observed with legumes, which seem to be relevant food triggers in Spanish studies, but not the United States or Australian studies in [4,10^{••},12[•]]. Therefore, food groups to be eliminated in different populations might depend on local food consumption habits. Regular consumption of a specific food group (e.g., legumes in Mediterranean countries) might make it more likely to be involved in EoE as a food trigger.

COW'S MILK ELIMINATION DIET

According to the aforementioned argument, every step-up approach should begin with a cow's milk elimination diet, which is the most common food trigger in both children and adults. Promising results (efficacy around 60%) have been published in three small series, mostly retrospective. Recent results from a retrospective European registry show much more disappointing results (25%). These studies are summarized in Table 1.

Indirect estimates from FFED and TFED studies show that cow's milk as the only food trigger was found in 18 [4] and 25% [11[•]] of adult patients, whereas higher rates were found in children (33 [11[•]], 56%). Prospective studies specifically designed to assess the efficacy of milk elimination diet in children and adults are definitely warranted.

First author, country of origin, year of publication	Study Population Design	Sample size	Histologic remission rate (<15 eos/HPF)
Teoh T, Canada, 2019 [13]	Children ≤16 years old Mean age: 9 years old Retrospective	31	58% (63% still on remission after transition from a strict to a liberalized diet)
Hoofien A, European Registry, 2019 [11 [•]]	Children Retrospective	-	25%
Kruszewski PG, US, 2016 [14]	children ≤18 years old Mean age: 12 years old Prospective	20	64% (proton pump inhibitor therapy given concomitantly with diet)
Kagalwalla AF, US, 2012 [15]	Children and adolescents Mean age: 5 years old Retrospective	17	65%

Table 1. Results from studies published on cow's milk elimination diet in children

POTENTIAL WAYS TO OVERCOME COW'S MILK-INDUCED EOSINOPHILIC ESOPHAGITIS

Even though the specific protein in milk triggering EoE remains unknown, modifying protein content in milk might prevent allergen sensitization and avoid disease activation. This strategy comes from studies on IgE-mediated food allergy. In this regard, baked cheese [16], baked milk [17], and hydrolyzed milk [18] have recently been found to be tolerated in patients with milk-induced EoE without disease reactivation. In contrast, a recent double-blind, placebo-controlled study, failed to show any benefit from epicutaneous milk immunotherapy in 20 children with milk-induced EoE [19].

CONCLUSION

Major advances have been accomplished in dietary therapy for EoE over the past two decades. These include the definition of EoE as a food allergendriven disease that emerged from studies on elemental diets, and understanding the lack of utility of any available food allergy testing, and the development and refining of empiric elimination diets from a topdown toward a step-up strategy. Within the step-up approach, the specific food group or groups to be first eliminated in each specific setting are to be elucidated. Evidence is hinting at the possibility that the list of food triggers in each setting might depend on food consumption habits. Prospective studies on cow's milk elimination diet in children and adults are definitely warranted. Better food allergy testing, identifying specific antigens involved in each food group, should be developed for an individualized approach to therapy. And last but not least, as for disease prevention, we undoubtedly need to understand why foods we have been consuming since the Neolithic era have caused EoE just over the past few decades.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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