



Use of allergy tests to identify dietary and environmental triggers of eosinophilic esophagitis: protocol for a systematic review

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Summary

Purpose Eosinophilic esophagitis (EoE) is a chronic immune-mediated esophageal disease. Most EoE patients have atopic comorbidities and they test positive when allergy tests are performed. Our aim is to critically assess the relation of allergens detected by allergy tests with clinically confirmed triggers of EoE.

Methods A systemic review and meta-analysis will be conducted, which will involve searching electronic databases using predetermined search terms, in order to identify relevant studies. Studies will be indepen-

dently screened against predefined eligibility criteria and subgroup analysis will be used for the outcomes. **Results and conclusion** The findings of this review are going to help clinicians and allied health professionals in treatment decisions.

Keywords Eosinophilic esophagitis · Allergens · Allergy tests · Diet · Systemic review

Background

Eosinophilic esophagitis (EoE) has been a separate clinical entity since the 1990s [1, 2]. Ever since, incidence and prevalence have increased with a current estimated prevalence of 50 patients per 100,000 individuals [3–5].

EoE is a chronic, local, immune-mediated disease of the esophagus, affecting both children and adults, clinically characterized by symptoms related to esophageal dysfunction [6]. Endoscopy often reveals characteristic findings while esophageal biopsies show the eosinophil-predominant inflammation; six biopsies from different locations are required, demonstrating >15 eosinophils per high power field [6]. EoE has characteristics of allergic inflammation, dominated by eosinophils, mast cells, and Th2 cytokines. Most EoE patients have atopic comorbidities (allergic rhinoconjunctivitis, atopic dermatitis, asthma, and IgE[immunoglobulin E]-mediated food allergy), with positive allergy tests [7].

Medications and/or dietary restrictions are used for the therapy of EoE inflammation. Endoscopic dilation is used to treat established strictures if medical treatment is not an option [8]. Although the impact of offending food allergens and immune-mediated response of the esophagus to them are still unclear, dietary manipulation is extensively used and often successful to cure EoE. There are three different dietary

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approaches to EoE: elemental, empirical, and allergy-test-driven diets, each with advantages and disadvantages.

Elemental diets consisting of free amino acids, medium chain triglycerides, and corn syrup solids, seem to be very effective to induce clinical and histopathological remission in both children and adults [9]. Their effectiveness is lower in adults due to compliance problems and insufficient dietary intake, which hamper prolonged use [10]. Six food empiric elimination diets are based on eliminating a group of foods rather than individual ones, for about a 2-month period, and then reintroducing them while performing repeated esophageal biopsies to evaluate the results [8]. They seem to be effective and easier to be follow for adults than elemental diets. Allergy-test-driven diets are tailor-made, based on allergy testing with skin prick tests (SPT) and atopy patch tests (APT), and patients have to avoid only food allergens to which they are positive in tests. These are much more tolerable, but study outcomes on their efficacy are controversial [11–18].

In vivo and in vitro allergy tests are the cornerstone of the diagnosis of allergy. Allergy tests are performed to detect an immunologic reaction against allergens, in both IgE-mediated and cell-mediated allergies. Skin prick tests (SPT) and specific IgE (sIgE) detect IgE-mediated allergic inflammation, whereas atopy patch tests (APT) are used for the detection of cell-mediated allergic inflammation. Serum IgG4—considered a protective factor for IgE-mediated allergy—has been studied as a biomarker of allergen immunotherapy's efficacy [19]. Recently serum IgG4 antibodies have also been reported to be associated with EoE [20].

Although there are clues that food and environmental allergens trigger EoE inflammation, it is not clear whether their removal can ameliorate EoE symptoms. In order to address the existing evidence on the relation of allergens detected by allergy tests with the clinically confirmed triggers of EoE symptoms, a systematic review and meta-analysis is planned and the protocol is presented herein.

Methods

This systematic review and meta-analysis will follow PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [21, 22]. AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews) will be used to provide an accurate and comprehensive summary of the results [21, 22]. The methodology has been reviewed and approved by all authors.

Search strategy

The search will be performed in four electronic sources: PubMed, Scopus, EMBASE, and Cochrane

Library. Grey literature will be searched and the reference lists of included studies will be screened to identify relevant studies.

A systematic reviewer (KP), in consultation with the other authors, has developed the search strategy on PubMed and adapted it for the other databases. All databases will be searched from inception to 31 July 2020.

The following Medical Subject Heading (MeSH) terms and text words will be used in the queries: “eosinophilic esophagitis”, “eosinophilic oesophagitis”, “EoE” combined with “skin prick tests” OR “SPT”, “specific IgE” OR “sIgE”, “atopy patch test” OR “APT” and “IgG4”.

Population

Participants of all ages with EoE will be included.

Types of studies

This systematic review will be focused on allergy testing for the detection of environmental allergens that may affect the accumulation of eosinophils in the esophageal mucosa and trigger EoE symptoms. Studies referring to food and airborne allergens will be included. Studies using allergy testing for the detection of IgE-mediated allergy (skin prick test and specific IgE) and cell-mediated allergy (atopy patch tests), as well as of the detection of serum sIgG4, will also be included.

Comparator

This systematic review will compare the results of allergy testing (SPT, sIgE, APT, IgG4) with confirmed triggers of EoE. Confirmed allergenic triggers include food or airborne allergens exposure to which causes a histologically confirmed onset or relapse of EoE (i.e., re-introduction of a food allergen after an exclusion diet that caused a marked remission of EoE, or seasonal relapse of EoE linked with pollen to which the patient is sensitive). Otherwise, the remission of histological and clinical symptoms of EoE, after the exclusion of a single allergen, can confirm the diagnosis of allergy to the specific allergen.

Study outcomes

The primary aim of this systematic review is to detect the relationship of allergy tests with the confirmed triggers of EoE. Allergy tests include cutaneous or laboratory noninvasive tests that are readily available for allergists, namely SPT, APT, specific IgE (ImmunoCAP and ISAC) and serum IgG4.

A secondary objective of this systemic review is to determine if allergy tests are useful as positive predictor that can be used for the exclusion of food allergens in allergy-driven diets. Another secondary objective

is to find evidence on the use of allergy tests for airborne allergens as a factor affecting the clinical course of EoE.

Inclusion criteria

Observational (prospective and retrospective) and interventional studies examining the correlation of allergy tests with the triggers of EoE on humans will be included in this systematic review. One of the following allergy tests should have been performed in the primary studies: SPT, sIgE, APT, sIgG4. Confirmed triggers of EoE will be compared to the results of allergy tests, and thus only studies with confirmed histological diagnosis of EoE (>15 eosinophils/high-power field) and confirmed allergenic triggers of the esophageal inflammation will be considered. There will be no restrictions in terms of age, sex, and race. No language restrictions will be imposed.

Exclusion criteria

- Case reports, case series, reviews, opinion articles, editorial articles.
- Studies on laboratory animals.
- *In vitro–ex vivo* studies not directly referring to clinical data (EoE symptoms), or with an irrelevant outcome (i.e., study of IL-5).
- Outcomes of studies on oral induced intolerance or food immunotherapy. They are considered biased, due to the frequent development of EoE as a side-effect.
- Studies without allergy tests.
- Studies involving therapeutic procedures, either surgical actions or medication use, that do not allow the study of allergens as triggers of the inflammation.
- Studies that do not include the allergy tests as described in the inclusion criteria and refer to other tests, for example, the use of skin patch test, instead of APT, total IgE or total IgG instead of sIgE or IgG4. The term “skin patch test” describes the use of drops of commercially prepared antigens (the ones used for SPT) placed on a filter paper disc, secured with petrolatum in 12 mm Finn chambers [23].
- Studies on tissue IgG4. It is not included in allergy tests since its detection needs invasive methodology and is still used only for experimental needs.

Study selection and quality assessment strategy

Two investigators (CP and EV) will scrutinize independently the eligibility of the identified titles and abstracts, based on the elements of the research question. The Rayyan QCRI web tool will be used to assist study selection [24]. Data extraction will be done twice. A third author (CV) will help resolve disagreements between the first two authors and reach consensus. A list of included and excluded studies will

be provided. Excluded papers will be published as an online supplementary appendix.

Detailed information on the included studies will be provided in a table describing study participants (number and age groups), research designs, interventions (allergy testing), comparators, and outcomes. Sources of funding for the studies included in the review will be reported. GPT and MP will describe the data from the studies. CP will serve as a reviewer of the information.

Two reviewers (KP and CP) will carry out an independent quality assessment on each eligible study of the final list. Different assessment tools will be used for different study designs. Risk of bias (RoB) of included randomized controlled trials will be evaluated using the Cochrane Collaboration RoB Tool [25]. In order to assess the quality of evidence in non-randomised interventions, ROBINS-I will be used [26]. AC, ANW and IT will review the results.

Each item in the assessment criteria will be given a score of 1 if fulfilled in the article and a score of 0 if not fulfilled or if there is insufficient evidence to make a clear statement. If a criterion is not considered in a study, it will be marked as not applicable. The total score of each study will be calculated by dividing the number of items included by the number of applicable items, yielding a score between 0 and 1. The methodological quality will be considered low for a score between 0 and 0.5 and high between 0.51 and 1.

Data extraction, analysis, and synthesis

SB and GKN will conduct separate analyses for each one of the outcomes. When possible, subgroup analyses by allergy test, study design and risk of bias will be performed to investigate potentially different effects on risk.

Heterogeneity of pooled results will be examined using the Cochran's Q test, with a 0.10 level of significance and the I^2 statistic, which describes the percentage variation across studies due to heterogeneity rather than chance [27, 28]. A narrative synthesis of the data will also be undertaken.

Discussion

Allergy tests are useful to detect atopy, which is a comorbidity of EoE, and can help to identify and avoid allergens that trigger atopic diseases. Reviews regarding use of allergy tests in EoE have already been published [29–31] and some questions have been addressed with instructions for dietary management in adult EoE [7]. However, it is not clear whether the outcomes of allergy tests can be used effectively for treatment decisions in the case of EoE.

In this systematic review and meta-analysis, with a state-of-the-art methodology, we will study environ-

mental allergens as direct triggers of EoE and shall try to help in treatment decisions.

Conflict of interest A. Nowak-Wegzyn reports grants from NIH NIAID, grants from DBV Technologies, grants from FARE, personal fees from Regeneron-Sanofi Aventis, personal fees from Gerber Nutrition Institute, grants from Nutricia, grants from Nestle, personal fees from UpToDate, personal fees from Ann All Asthma Immunol, outside the submitted work. C. Pitsios, K. Pantavou, I. Terreehorst, A. Cianferoni, C. Vidal, E. Vas-silopoulou, M. Papachristodoulou, G. P. Tsigkrelis, S. Bonovas and G.K. Nikolopoulos declare that they have no competing interests.

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