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Protocol for a systematic review of the diagnostic test accuracy of tests for IgE-mediated food allergy

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Abstract (237 words)

Background: The European Academy of Allergy and Clinical Immunology (EAACI) is in the process of updating the guidelines on the diagnosis and management of food allergy. The existing guidelines are based on a systematic review of the literature until 30th September 2012. Therefore, a new systematic review must be undertaken to inform the new guidelines. This systematic review aims to assess the accuracy of index tests to support the diagnosis of IgE-mediated food allergy.

Methods: The databases Cochrane CENTRAL (Trials), MEDLINE (OVID) and Embase (OVID) will be searched for diagnostic test accuracy studies from 1st October 2012 to 30th June 2021. Inclusion and exclusion criteria will be used to select appropriate studies. Data from these studies will be extracted and tabulated, and then reviewed for risk of bias and applicability using the QUADAS-2 tool. All evaluation will be done in duplicate. Studies with a high risk of bias and low applicability will be excluded. Meta-analysis will be performed if there are three or more studies of the same index test and food.

Results: A protocol for the systematic review and meta-analyses is presented and was registered using Prospero prior to commencing the literature search.

Discussion: Oral food challenges are the reference standard for diagnosis but involve considerable risks and resources. This protocol for systematic review aims to assess the accuracy of various tests to diagnose food allergy, which can be useful in both clinical and research settings.

Key message: The protocol for the systematic review of the literature about the accuracy of index tests to support the diagnosis of IgE-mediated food allergy is presented and this systematic review will inform the update of the guidelines on the diagnosis and management of food allergy of the European Academy of Allergy and Clinical Immunology (EAACI).

Keywords: basophil activation test, component-resolved diagnostics,diagnosis, diagnostic tests, food allergy, IgE-mediated, mast cell activation test, skin prick test, specific IgE

Background

The global prevalence of food allergy is about 10% with an increase in its incidence in the last 20-30 years[1,2]. Food allergies are more common in Westernized countries, affecting children more than adults[3]. Any food can be a potential allergen; however, a large proportion of food allergies are caused by cow's milk, egg, wheat, soya, peanut, tree nuts, fish and shellfish. There are, however, geographic differences[4] – for instance, while peanut allergy is relatively common in the UK, USA, Canada and Australia, it is very rarely seen in Africa and Asia, excluding Japan. Overall, cow's milk and egg allergies appear to be the most common food allergies in young children in the UK and most parts of Europe, USA, Canada, Asia and Australia[5].

Food allergies can be classified as immunoglobulin E (IgE) mediated and non-IgE mediated, with the former being the most common and the focus of this systematic review. IgE-mediated food allergies usually induce immediate reactions, i.e. reactions that occur up to 2 hours (usually a few minutes) after exposure to the allergen, and these can be severe, and sometimes life-threatening. By contrast, non-IgE mediated allergies prompt a delayed response, with symptoms taking up to two days to evolve, or manifest chronically[6]. Clinical manifestations of food allergy include skin, gastrointestinal (GI) and respiratory reactions, with skin reactions being the most prevalent and presenting as urticaria, angioedema and erythema[7,8]. GI symptoms include abdominal pain, diarrhoea, nausea and vomiting. Rhinorrhoea, nasal obstruction, bronchospasm and oedema of the larynx are possible respiratory symptoms[2]. Allergic reactions can vary in severity, ranging from local reactions such as tingling in the mouth to anaphylaxis, a severe life-threatening allergic reaction affecting breathing or circulation[8,9].

The diagnosis of IgE-mediated food allergy is usually based on the clinical presentation and evidence of IgE sensitisation to the specific allergen, as documented by skin prick test (SPT) or serum specific IgE[10]. The gold standard to diagnose food allergy is the oral food challenge (OFC), in which the suspected food is administered orally in gradually increasing doses until either a reaction occurs or all doses are consumed without developing any symptoms. The OFC can be used to confirm the diagnosis, to assess tolerability in people with a confirmed allergy, or to detect the reaction threshold. In cases with a recent history of an allergic reaction, detectable IgE specific to the culprit allergen can be enough to confirm the diagnosis, dispensing OFC. OFC is associated with the risk of an allergic reaction of variable severity. OFC are resource-intensive as they must be conducted in a controlled environment with intensive care facilities in easy reach, and not all clinical settings can

offer this service. Additionally, this risk of reaction may lead to significant anxiety in patients and their families, therefore a reliable and cost-effective alternative to OFC is needed.

Several tests have been used to support the diagnosis of food allergy, namely SPT, specific IgE and cellular tests. SPT and sIgE detect the presence of IgE antibodies to a particular food. They detect allergic sensitisation, which does not necessarily correlate to a clinical reaction. Approximately half of children sensitised to a food are able to tolerate it without reaction. SPT and sIgE therefore generally have high sensitivity but poor specificity to diagnose food allergy. Increasing magnitude of these tests are associated with increased risk of clinical reaction, and thresholds with high probability of food allergy have been identified for some foods (e.g. for peanut: SPT >=8mm or sIgE >=15 have 95%PPV) which preclude the need for OFC in some settings. Reported thresholds vary in the literature, likely due to differences in study design and patient characteristics. Component-resolved diagnosis (CRD) refers to the determination of specific IgE levels to specific proteins in food[11]. Cellular tests include the basophil activation test (BAT) and the mast cell activation test (MAT); however these are currently not used in routine clinical practice. CRD are becoming more routine practice and have high specificity for some foods. BAT and MAT offer an improvement on sensitivity and specificity compared to traditional SPT or sIgE tests.

The European Academy of Allergy and Clinical Immunology (EAACI) is currently in the process of updating their food allergy guidelines. Thus, systematic reviews of existing literature will be carried out to inform the new guidelines. This systematic review aims to assess the diagnostic accuracy measured by sensitivity and specificity of index tests for IgE-mediated food allergy compared to the gold-standard OFC. Furthermore, comparison among index tests will be conducted if sufficient evidence is available.

Methods

Research question

We defined the question overarching to the systematic review in the PICO format (**Box 1**) and describe its components in the sections below.

Search strategy

Search terms are indicated in **Table 1**. The following databases will be searched:

- Cochrane CENTRAL (Trials)
- MEDLINE (OVID)
- Embase (OVID)

These databases will be searched for entries between the period of 1st October 2012 to the 31st May 2021. This aligns with the end date of the search entries used in a previous systematic review on the same subject[12]. Studies which were published earlier and included in the previous systematic review will be evaluated for inclusion in the current systematic review. Forward and backward citation analysis will be used in all included studies to pinpoint other relevant studies. Any additional studies discovered by the review team who are experts in the field may be included. Only published, peer-reviewed full reports will be included.

Condition/domain being studied

The main domain being investigated is IgE-mediated food allergy. We will explore any food allergen. Food allergens will be ranked by the frequency of available studies and index test, with the most commonly investigated allergen prioritised, if necessary. This is because we will assume that more studies will raise more high-quality studies, thus firming evidence. Next, the more recently developed tests (CRD, BAT, MAT) will be prioritised according to the frequency of reports. The previous EAACI Food Allergy Guideline paper has already given recommendations for SPT and specific IgE, and we aim to summarise novel evidence on SPT and specific IgE if this seems warranted.

Population

Studies of children and adults, irrespective of age, with suspected IgE-mediated allergy to any food will be considered.

Interventions

Any index tests to diagnose food allergy in the included studies will be reported. Priority will be placed on the more recently developed test strategies of specific IgE to allergen components, BAT and MAT as described above.

Comparator

The comparator to define the accuracy for immediate-type food allergy diagnosis will be OFC, including both open food challenge or double-blind placebo-controlled food challenge, performed in at least a proportion of study participants.

Inclusion criteria

Studies fulfilling the following criteria will be included:

- Studies containing sufficient data to calculate sensitivity and specificity, to get a measure of the diagnostic accuracy.
- Diagnostic test studies with any sequence of index test and reference standard test performed and with any algorithm or procedure of participant selection. These characteristics will be part of the risk of bias assessment and evaluation of reasons for heterogeneity as laid out below.

Exclusion criteria

Studies fulfilling the following criteria will be excluded:

- Conference abstracts
- Narrative reviews, editorials and correspondence
- Systematic reviews (reference lists will first be scanned for relevant original articles)
- Qualitative studies
- Case reports and case series
- Animal studies
- Studies in which allergies are defined based on sensitization tests alone without a history following ingestion.
- Studies may be excluded based on risk of bias and applicability

Each study will be screened by two reviewers independently based on the title and abstract according to the inclusion and exclusion criteria (described below). If there are any discrepancies between the reviewers, a third reviewer will adjudicate. When the studies have been selected, the full texts will be reviewed to confirm they meet the inclusion criteria. Data will be extracted from these studies and the quality will be assessed for risk of bias and applicability. Studies which satisfy the inclusion criteria but are not in English will be translated prior to data extraction and quality assessment.

Data extraction and management

The details that will be collected from the selected studies are represented in **Box 2**. Data extraction will be conducted by two independent reviewers and subsequently recorded using COVIDENCE. Any discrepancies will be resolved by a third reviewer.

Quality assessment (risk of bias)

All included studies will be assessed for risk of bias and their applicability based on the QUADAS 2 instrument[13]. The four key domains covering patient selection, index test, reference standard

(comparator), and flow and timing will be evaluated. Any studies deemed to have a high risk of bias i.e. scoring 'high' for three or more of the four risk of bias domains, or concerns regarding applicability i.e. scoring 'high' for two or more of the three applicability domains will be excluded from further meta-analyses.

Strategy for data synthesis

When possible, data extracted for sensitivity and specificity will be analysed using random effects meta-analysis using hierarchical summary receiver operating characteristic (ROC) curve analysis in case of three or more studies for a given combination of index test and food.

The GRADE approach will be used to assess heterogeneity[14,15], and will not solely rely on statistical methods such as the I^2 statistic. Depending on the included studies, the following reasons for heterogeneity will be discussed:

- Multiple definitions of target condition
- Multiple thresholds of test positivity for index and/or comparator
- Age of the participants
- Origin of study population as indication for patient spectrum/pre-test probability
- All domains of risk of bias of the included studies

The GRADE approach will be used to evaluate the certainty of the body of evidence.

Sensitivity analysis

Sensitivity analysis may be carried out if three or more studies are retained for a given combination of index test and food allergen following exclusion of studies which are suspected to contribute to heterogeneity or limiting to studies with low risk of bias, i.e. studies with 'low' in all four risk of bias domains of the QUADAS-2.

Dissemination plans

The final report will be published in one of the scientific journals affiliated with EAACI and will be used to inform the update of the EAACI Guidelines on Food Allergy. The findings of the systematic review will be presented at scientific conferences, namely the EAACI annual congress and at the EAACI Food Allergy and Anaphylaxis Meeting. A summary of the findings will be made available in lay language on the EAACI website.

Discussion

The EAACI Food Allergy Guidelines need to be updated, including the section on diagnostic tests for food allergy. The systematic review of the literature on diagnostic tests that informed the current EAACI Food Allergy Guidelines was conducted prior to 2014, thus a new systematic review is needed, especially since new and emerging tests such as CRD, MAT and BAT were not included in the previous review. We report herein the protocol for a systematic review of the literature, as registered at PROSPERO (CRD42021259186), and provide a description of the rationale and methods chosen for the review.

Since the previous guideline was published, newer tests such as CRD have entered mainstream use in Europe and other regions[16-19]. Also, studies assessing the efficacy of novel diagnostic tests such as BAT and MAT have been published[20-29]. All of these new tests must be reviewed to assess whether they are acceptable diagnostic tools for use in routine clinical practice. For more established allergy tests, such as SPT and sIgE, new studies have been performed since the previous review which may require updating of the previous recommendation. We aim to evaluate the diagnostic test accuracy of any index test, from SPT, sIgE to extracts, sIgE to individual allergens, sIgE to allergen peptides, BAT and MAT. Thus, we do not include search terms for the index test. We apply a specific filter for diagnostic test accuracy studies, though, which implicitly captures studies on diagnostics and/or tests. We only include search terms for "challenge" as part of the common terminology for the comparator, i.e. oral food challenge, to have a sensitive search regarding the comparator test.

The population of interest will include all ages and diverse clinical settings and geographical locations. We deliberately do not include search terms to specify the target population and studies that do not have evidence from all populations will be included in the review and judged for risk of bias. We expect to encounter very few if any diagnostic test accuracy studies conducted in animals; however, we will refrain from specifying search terms that will exclude animal studies because of the risk of falsely excluding studies on animal allergen sources. Certain food allergies are more prevalent in different areas. As such, we will include studies focussing on any food, to be inclusive to all populations, although we anticipate that there will be more studies on milk, egg and peanut allergies.

Although the gold standard is DBPCFC, we will also include studies where open oral food challenges are performed and allow for the inclusion of studies where a small proportion of patients were diagnosed without an oral food challenge due to previous severe or anaphylactic reactions. Studies focusing only on IgE sensitisation will be excluded, as some patients who experience sensitisation to foods are not necessarily allergic. It is important to note that the comparator reference standard test is oral food challenge and as such, the systematic review will inform on the diagnostic accuracy of

potential alternative tests. However, the systematic review will not clarify which of these tests is best used in subjects in whom the oral food challenge is contraindicated.

As outcomes we are assessing sensitivity and specificity as measures of diagnostic test accuracy. The positive and negative predictive value of the test, which depends on the prevalence of the given food allergy in the population, is not within the scope of this systematic review. The details collected as part of the quality assessment and risk of bias will allow us to select high-quality studies at low risk of bias. The planned sensitivity analyses on these features may help to identify factors that influence the performance of the test and the modulation of the identified diagnostic cut-offs. If sufficient high quality studies are identified, the planned meta-analyses will provide evidence which may help to reduce the number of patients that have to undergo an OFC procedure.

In conclusion, we present and discuss herein the protocol that we have developed for the systematic review of the literature and meta-analyses on the use of diagnostic tests to support the diagnosis of food allergy, aiming to use all relevant studies to summarise their diagnostic accuracy as measured by sensitivity and specificity in comparison to the allergic status determined, at least in a proportion of subjects, by OFC. We will use the results of this systematic review to inform the recommendations produced as part of the new EAACI Food Allergy Guidelines.

Tables and Figures:

Question: What is the diagnostic accuracy by means of sensitivity and specificity of any index tests for IgE-mediated food allergy compared to the reference standard of oral food challenge or previous clear history of anaphylaxis to the food and evidence of allergic sensitization?

PICO

- **Population:** humans (irrespective of age) with a suspected IgE-mediated allergy to any specific food
- **Intervention:** any index test
- **Comparator:** IgE-mediated food allergy diagnosis determined by oral food challenges (but any method including open food challenge or double-blind placebo-controlled food challenge) in at least a portion of study participants.
- **Outcome:** sensitivity and specificity of the test.

Box 1. Question central to the systematic review in the PICO format

388 **Box 2.** Data to be extracted from the full-length articles selected for the systematic review

- Number of participants
- Age of participants
- Geographical location
- Origin of the study population (general population, outpatient clinics, interventional study)
- Study design (case-control, prospective)
- The tested food
- Index test performed with detailed methods (e.g. SPT – fresh food or extract, type of lancet used; specific IgE: ImmunoCAP, Siemens etc.; Microarray: ISAC, ALEX, BAT: commercial kit or in house method, stimulants, identification and activation markers used, outcome of BAT; MAT: cell line or primary cells, activation marker used)
- Comparator (gold-standard) and details on this test: proportion with food challenge, type of food challenge, alternative clinical diagnosis (history of IgE-mediated symptoms and allergic sensitization), blinding, placebo control, period between allergen and placebo control feeding
- Number of participants in index test group(s) and comparator group(s)
- Identified cut offs (optimal, negative, positive) or other criteria for positive test
- Raw numbers of true positives, true negatives, false-positives and false-negatives for each index test, compared to the comparator
- Sensitivity and specificity

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390 **Table 1.** Search terms used in the systematic review.

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	Search Term (OVID)	**Detail/Strategy**
1	"food hypersensit:".mp OR "food allerg:".mp OR "food sensit:".mp OR "Food-dependent exercise-induced anaphylaxis".mp OR "cow?? adj2 allerg:".mp OR "milk adj2 allerg:".mp OR "peanut? adj2 allerg:".mp OR "egg? adj2 allerg:".mp OR "nut? adj2 allerg:".mp OR "hazelnut? adj2 allerg:".mp OR "walnut? adj2 allerg:".mp OR "pistachio? adj2 allerg:".mp OR "almond? adj2 allerg:".mp OR "brazil adj2 allerg:".mp	Clinical condition Most likely to be captured by the first four general search terms but augmented by terms specific for foods in combination with terms for allergy in varying order (e.g. "cashew allergy", "cashew nut allergy", "allergic to cashew"

	OR “macadamia adj2 allerg:”.mp OR “pecan adj2 allerg:”.mp OR “cashew? adj2 allerg:”.mp OR “sesame adj2 allerg:”.mp OR “soy? adj2 allerg:”.mp OR “lentil? adj2 allerg:”.mp OR “pea? adj2 allerg:”.mp OR “chickpea? adj2 allerg:”.mp OR “rice adj2 allerg:”.mp OR “celery adj2 allerg:”.mp OR “peach adj2 allerg:”.mp OR “apple? adj2 allerg:”.mp OR “wheat adj2 allerg:”.mp OR “gluten adj2 allerg:”.mp OR “mustard adj2 allerg:”.mp OR “meat adj3 allerg:”.mp OR “beef adj2 allerg:”.mp OR “pork adj2 allerg:”.mp OR “alpha-gal adj2 allerg:”.mp OR “fish adj2 allerg:”.mp OR “seafood adj2 allerg:”.mp OR “shrimp? adj2 allerg:”.mp	will all be captured by “cashew adj2 allerg:”)
2	challeng:.mp. OR provocation:.mp. OR anaphylaxis.mp	broad term for reference standard (i.e. oral food challenge or provocation) or anaphylaxis in instances when oral challenges were not conducted
3	sensitiv:.mp. OR “predictive value:”.mp. OR accurac:.tw.	McMaster HiRU filter with best balance of

		sensitivity and specificity to identify diagnostic test accuracy studies
4	1 AND 2 AND 3	
5	MEDLINE: limit 3 to dt=20121001-20210531 EMBASE: limit 3 to dd=20121001-20210531	Date since end of the search from previous systematic review

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