# Gastroscopic Esophageal Prick Test in adult Eosinophilic Esophagitis Patients: a pilot study

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Multiple sensitizations were found using allergy tests, but most of the EoE patients have concurrent allergic diseases and the specific IgE found in serum apparently does not play a role in EoE pathogenesis. This theory is supported by the failure...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Gastrointestinal inflammatory conditions |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON42606

**Source**
ToetsingOnline

**Brief title**
EPT trial

### Condition

- Gastrointestinal inflammatory conditions
- Allergic conditions

**Synonym**
allergic esophagitis, Eosinophilic esophagitis

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Academisch Medisch Centrum
**Source(s) of monetary or material Support:** Ministerie van OC&W

## Intervention

**Keyword:** Eosinophilic esophagitis, In vitro allergic sensitization test, Local esophageal allergy test, Pilot study

## Outcome measures

### Primary outcome

1. Visible immune response to allergens injected into the esophageal mucosa,

defined as wheal and flare reaction.

2. In vitro immune response of esophageal mucosal tissue in culture medium to

added allergenic solutions, defined as release of inflammatory cytokines,

histamine and tryptase.

### Secondary outcome

Clinical parameters:

- Symptom-Based Activity Index EoE (EEsAI)

- General allergy questionnaire

- Correlation between clinical symptoms and positive wheal and flare reactions

- Evaluation allergic / atopic history

Sensitization patterns on standard allergy testing:

- Skin Prick test

- Allergen specific serum IgE testing (ImmunoCap)

Endoscopic evaluation:

- Endoscopic features (recorded by video and still images)

- Delayed esophageal hypersensitivity reaction (wheal and flare after 24 hours)

Measures of mucosal barrier function:

- Esophageal intestinal mucosal integrity measured in vivo by electrical tissue impedance spectroscopy before and after allergen injection

Laboratory investigations EPT and after in vitro allergen provocation:

- Histological evaluation of two esophageal biopsies to determine peak eosinophil count and mast cell counts after dietary treatment

- Local allergen-specific IgE production, measured as percent of tissue area labeled by IgE-positive cells in the biopsy specimens

- Esophageal immune activation (eosinophil, mast cells and inflammatory cytokines histamine and tryptase counts)

# Study description

**Background summary**

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease of the esophagus, that leads to progressive narrowing of the lumen. Histologically there is a prominent eosinophilic infiltration and inflammation of the esophagus, which can cause transient narrowing of the lumen by edema, and progressive fixed narrowing by remodeling and fibrosis. EoE presents in adults as dysphagia and food impaction. EoE is diagnosed based on symptoms of esophageal dysfunction and the presence of more than 15 eosinophils per high-power field (eos/hpf) in esophageal biopsies, which persists after the exclusion of other causes of esophageal eosinophilia.
Since EoE was first recognized in the mid-1990s, it has emerged in the past few years as the main cause of esophageal dysfunction in children and young adults. The incidence of the disease has risen extremely fast and currently in many

countries more patients are now diagnosed with EoE than with inflammatory bowel disorders such as Crohn*s and Colitis. This epidemic of EoE cannot be fully explained by increasing awareness and recognition by physicians.
Although the pathophysiology of EoE is not fully understood, it has been shown by many studies that food allergy plays an important role. The concept of EoE being an allergic disease activated by food allergens is further supported by the notion that EoE can be driven into remission by dietary treatment. The allergic esophageal inflammation in EoE is probably caused by an acute IgE-mediated and a delayed non-IgE-mediated hypersensitivity reaction.
Current pharmaceutical treatment is only moderately effective and mainly consists of topical corticosteroids, which are prescribed off label.
Side-effects such as esophageal candidiasis preclude long-term treatment and response is temporary since the disease recurs once the corticosteroids are withdrawn. Without durable treatment, progressive narrowing of the esophagus continues and repetitive endoscopic removal of food particles that got stuck in the esophagus may be required. In more severe cases dilatations of the esophagus are needed with the risk of perforation and bleeding. Apart from the significant burden to the patients, these repetitive endoscopies result in considerable costs to society.
Dietary therapy with elimination of causative allergens could potentially be the most durable long-term solution, which is desirable since the majority of patients are young adults or children. Elemental diets, based on hypo-allergenic formula, showed impressive histological and clinical response rates. Nonetheless, costs of elemental diets are high and not always reimbursed and adherence is challenging due to the poor taste. Empiric elimination diets, based on avoidance of most common food allergens, offer moderate response rates, but unfortunately many foods need to be eliminated. Furthermore in both diets a substantial number of follow-up endoscopies is required to evaluate histological response after each step in the food reintroduction process. The key to successful dietary treatment of EoE is thus to identify which foods are responsible for the allergic esophagitis in individual patients. Unfortunately, the usefulness of allergy test-directed elimination diets is questioned by low response rates. Current tests, routinely performed on serum or skin, do not allow identification of the responsible food allergens with acceptable sensitivity and/or specificity.

**Study objective**

Multiple sensitizations were found using allergy tests, but most of the EoE patients have concurrent allergic diseases and the specific IgE found in serum apparently does not play a role in EoE pathogenesis. This theory is supported by the failure of a systemic humanized anti-IgE therapy in adult EoE patients.
A possible explanation for the observation that current allergy tests fail to predict the disease triggering allergens, is that inflammatory response in EoE is limited to the esophagus. Restricted esophageal IgE production might be insufficient to be detected with allergy tests that require a systemic inflammatory response. Indeed, several studies demonstrated local esophageal

mast cell and B and T cell activation, including class cell recombination to IgE in the esophagus, local IgE production and IgE bearing mast cells in the esophageal mucosa (25)(17). Furthermore, it has been shown that mast cells, released during an allergic reaction, can alter enteric nerve and smooth muscle function. This might cause esophageal hypermotility, which can be experienced as acute dysphagia after ingestion of specific allergens. These findings suggest that esophageal mucosa is immunologically active tissue which can initiate an inflammatory response.

We hypothesize that the allergic inflammation in EoE is limited to local immune activation and that only tests based on detection of local inflammation can reveal clinically relevant sensitization patterns on which elimination diets can be based. Therefore we aim to develop the esophageal prick test (EPT), an endoscopic provocation test in which the esophageal mucosa is challenged with injected food allergens.
In parallel to the in vivo endoscopic EPT, we will investigate whether an in vitro sensitization test using esophageal tissue is feasible. An in vitro test that could accurately identify the triggering allergens in EoE would be of great value since more allergens can be tested after the gastroscopic procedure. A similar in vitro test with duodenal mucosa has been shown to be useful for identification of causative agents in intestinal food allergy. A test using esophageal mucosal biopsies could thus potentially serve as guidance for elimination diets in EoE.

## Study design

prospective diagnostic pilot study

## Study burden and risks

Upper endoscopy is a routinely performed investigation, which belongs to the standard procedures in patients with EoE. In all EoE patients, treated with elemental or elimination diet a gastroscopy is performed to evaluate histologic treatment response. This is in accordance with standard care. Therefore included patients are not exposed to additional risks, associated with the gastroscopy. Nevertheless the duration of the procedure is extended due to the esophageal prick test and in some patients an extra endoscopy will be performed.

Although a gastroscopy is a generally safe procedure patients should be aware of the possible risks which include dental or mouth injury, a sore throat, aspiration pneumonia, and esophageal injury. Patients often undergo conscious sedation during upper endoscopy, this option is offered and recommended to the patients included in the study. Sedation reduces discomfort during endoscopy. However there are sedation-related complications, which are mostly transient and of a mild degree. The general incidence of sedation-related complications is low. Sedation can affect the cardiorespiratory system, which can increase

the risk of the procedure in patients with concurrent cardiorespiratory diseases. Therefore patients will be connected to a monitor that checks heart rate and oxygen level during endoscopy.

Esophageal biopsies are taken regularly during upper endoscopy. An extremely rare but potentially severe risk of a biopsy is a perforation. In most cases perforation can be treated expectatively or endoscopically. In a minority of cases, surgery has to be performed to close the perforation. Another very rare risk of an esophageal biopsy is bleeding, which can be treated endoscopically.

Allergen provocation
The skin prick test is a safe procedure and fatal side effects such as anaphylaxis are exceedingly rare. Acute systemic anaphylactic reactions are very rare in EoE but any patients with a history of such reactions or a severe adverse reaction to skin prick test will be excluded from participation. Other possible less severe side effect might include the entire range of IgE-mediated allergic manifestations, such as urticaria, nasal congestion, sneezing, flushing, wheezing, cough, dysphagia, diarrhea, and hypotension.
We do not expect systemic allergic reactions to the EPT. In studies with a colonoscopic provocation test (COLAP), in which other parts of the gastrointestinal tract were challenged with injected food allergens in a similar way as EPT, no severe systemic reactions were observed. Nonetheless, medications for management of acute anaphylactic will be present during and after endoscopy.

Tissue impedance measurement
Tissue impedance is measured during upper endoscopy. A small probe is placed against the mucosa under an angle of 30°. An electrical current of 20 µA is injected in the mucosa through the probe. No risk is associated with this investigation

## Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

Patients
-Previous diagnosis of active EoE confirmed by histopathology e.g. presence of >15 eosinophilic granulocytes per high power field (hpf) in mid or proximal esophageal biopsies
-Macroscopic disease remission or significant mucosal healing after four weeks of treatment with an elemental or elimination diet
-Written informed consent
-Age 18 * 75 years;Healthy control group
- Written informed consent
- Age 18 * 75 years
- Absence of atopic diseases
- Absence of gastrointestinal symptoms

## Exclusion criteria

Patients
- Inability to stop topical corticosteroids
- Inability to stop beta-blockers and ACE inhibitors
- Use of oral or systemic antihistaminics, oral cromoglicates, systemic corticosteroids, leukotriene inhibitors, or monoclonal antibodies, in the month preceding the study
- Proven gastroesophageal reflux disease or other cause for esophageal eosinophilia
- History of peptic ulcer disease
- History of Barrett*s esophagus
- History of GI cancer
- History of GI tract surgery (except appendectomy)
- ASA class III, IV or V

- History of anaphylaxis
- History of a severe systemic reaction to previous allergy tests (grade 3 or 4);Healthy controls
- History of atopic diseases
- Inability to stop beta-blockers and ACE inhibitors
- Use of oral or systemic antihistaminics, oral cromoglicates, systemic corticosteroids, leukotriene inhibitors, or monoclonal antibodies, in the month preceding the study
- Proven gastroesophageal reflux disease or other cause for esophageal eosinophilia
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- History of anaphylaxis
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# Study design

## Design

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| Study type: | Observational invasive |
| Intervention model: | Other |
| Allocation: | Non-randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Basic science |

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 05-01-2016 |
| Enrollment: | 12 |
| Type: | Actual |

# Ethics review

Approved WMO

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| Date: | 23-09-2015 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

ID: 26684
Source: Nationaal Trial Register
Title:

## In other registers

| Register | ID |
|---|---|
| CCMO | NL54305.018.15 |
| OMON | NL-OMON26684 |