

# **What's new for eosinophilic oesophagitis?**

## **A case-based discussion of patient care**

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# Exploring the pathophysiology and clinical manifestations of EoE

**Dr Stuart Carr**

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United Arab Emirates



# Perinatal factors and risk of EoE

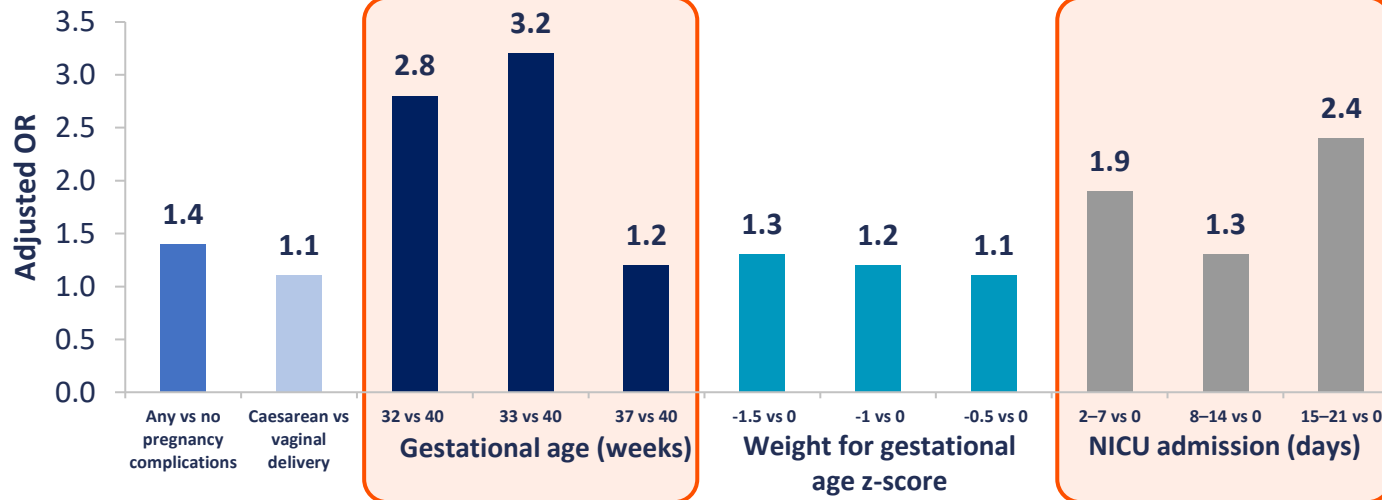


Population and registry case-control study in Denmark, including all paediatric patients with EoE with birth years 1997–2018



n=393 EoE cases, n=3,659 controls (after exclusions for missing data)

## Association of perinatal factors with the development of EoE



Perinatal factors, particularly preterm delivery and NICU admission, are associated with the development of EoE

# Metal contaminants in drinking water and EoE

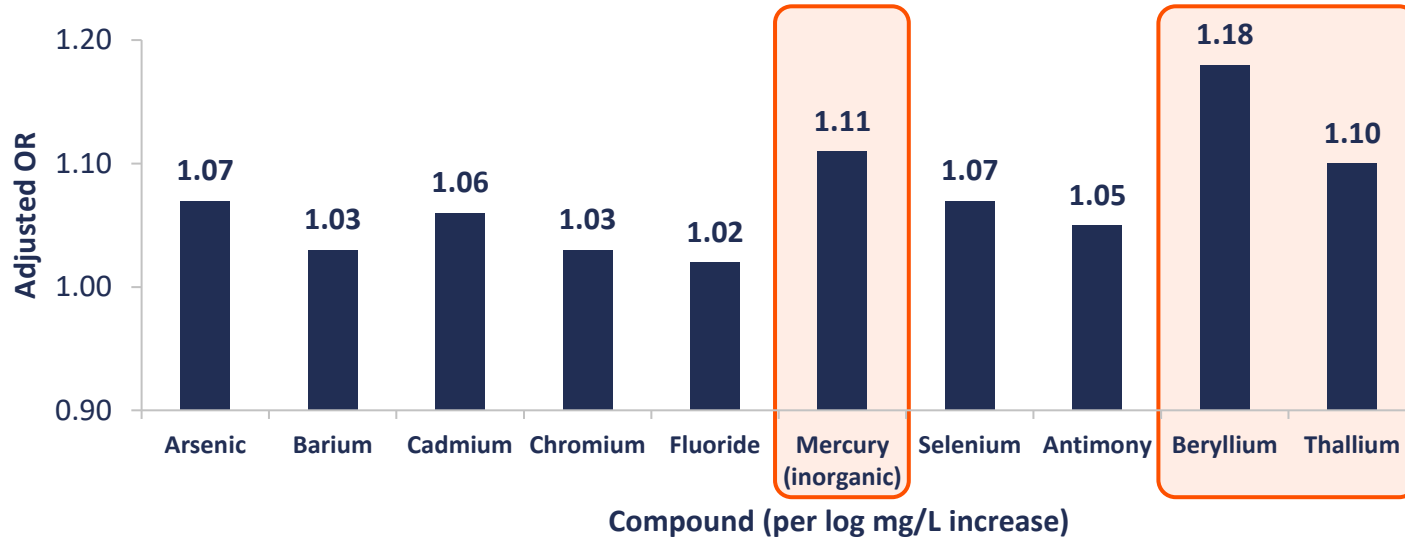


US-based case-control study in a pathology database of oesophageal biopsies



n=29,560 EoE cases, n=587,826 controls

## Association between metal contaminants\* in drinking water and having EoE



Data show a positive association between certain metal contaminants\* in drinking water and having EoE, in particular thallium, inorganic mercury and beryllium

\*Generated through manufacturing, mining, and refining processes.

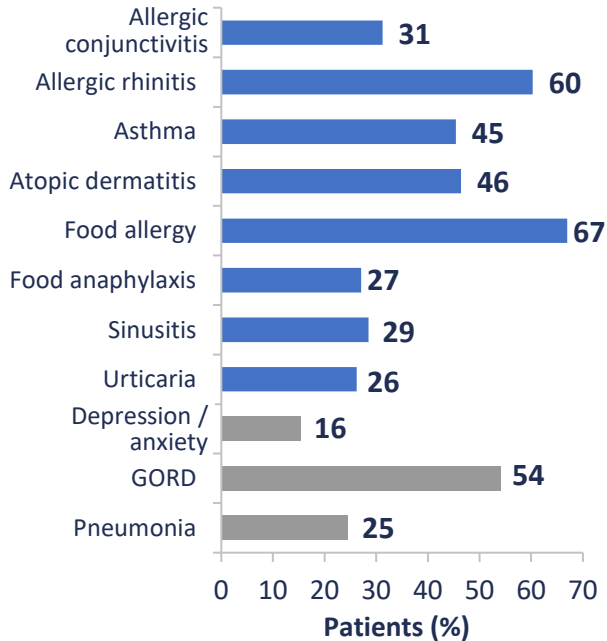
EoE, eosinophilic oesophagitis; OR, odds ratio.

Siebrasse A, et al. Presented at: DDW 2022, Virtual/San Diego, CA. 21–24 May 2022. Poster Su1191.

# EoE and other type 2 inflammatory diseases

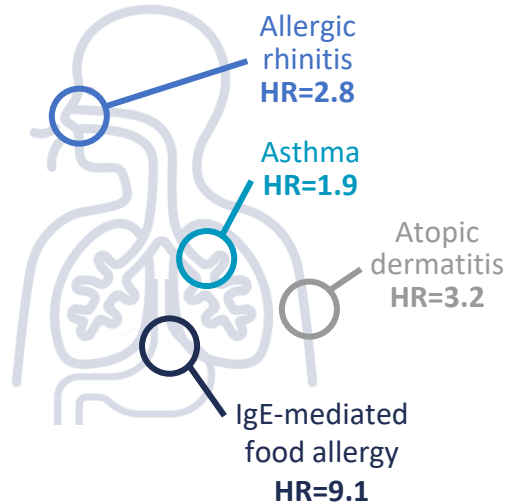
Comorbidities are prevalent in paediatric and adult patients with EoE<sup>1</sup>

## Comorbidities in patients with EoE



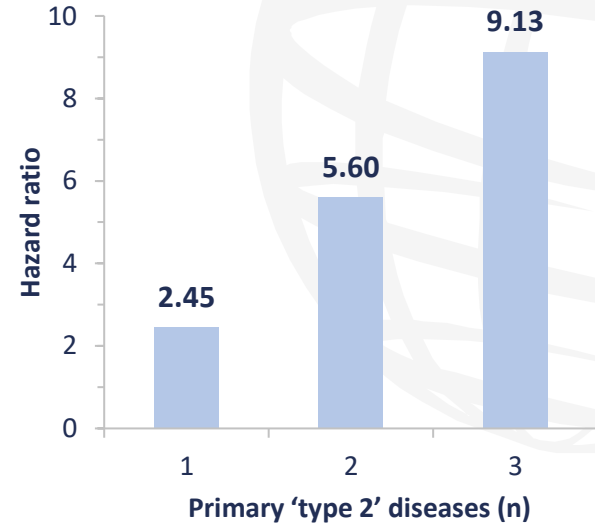
Primary type 2 diseases increase likelihood of a secondary EoE diagnosis<sup>2</sup>

## Likelihood of secondary EoE diagnosis in patients with primary type 2 disease



Rate of EoE diagnosis is higher in those with  $\geq 1$  comorbid allergic disease<sup>2</sup>

## Rate of EoE diagnosis by number of primary allergic diseases



EoE, eosinophilic oesophagitis; GORD, gastro-oesophageal reflux disease; HR, hazard ratio; IgE, immunoglobulin E.

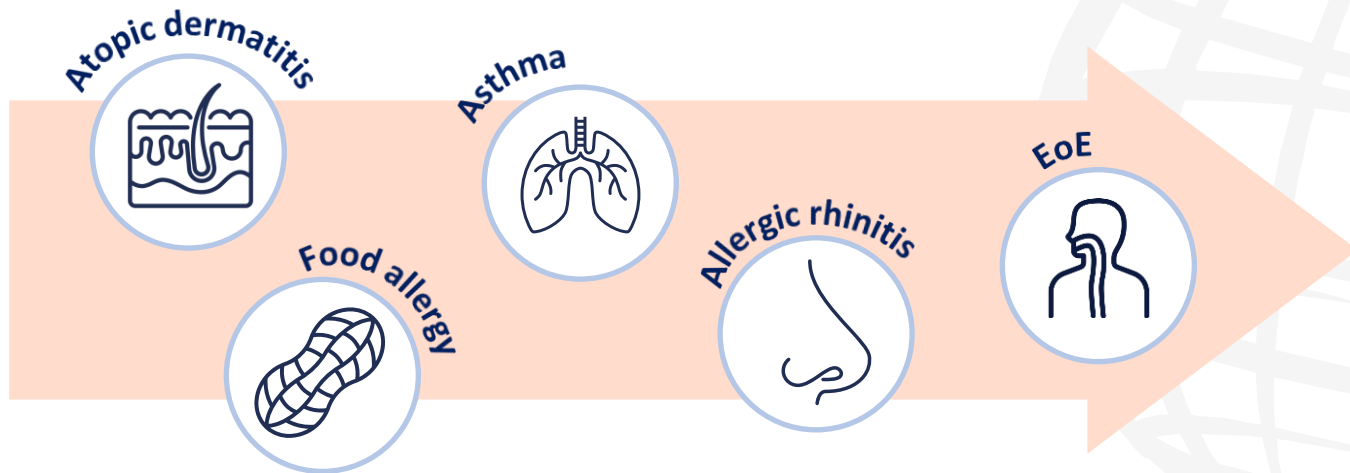
1. Chehade M, et al. *J Allergy Clin Immunol Pract.* 2018;6:1534-44; 2. Hill DA, et al. *J Allergy Clin Immunol Pract.* 2018;6:1528-33.

# Allergic/atopic march

## Influencing factors<sup>1,2</sup>



## Allergic/atopic march<sup>1,2</sup>



EoE, eosinophilic oesophagitis; eos/hpf, eosinophils per high power field.

1. Capucilli P, Hill DA. *Clin Rev Allergy Immunol.* 2019;57:111–27; 2. Maiello N, et al. *Children (Basel).* 2022;9:450.

# The role of IgG4 in EoE: Data from AAAAI 2022

Masuda M, et al.<sup>1</sup>

Prospective assessment of food-specific IgG4 levels in plasma and upper GI tract in adults undergoing upper endoscopy

Controls (n=15)  
Active EoE (n=24)  
Inactive EoE (n=8)

Median IgG4 for milk and wheat were elevated in plasma and throughout the upper GI tract in patients with active EoE vs controls

Erwin E, et al.<sup>2</sup>

Investigation of the role of milk-specific IgG4 in EoE, in paediatric patients undergoing OGD

EoE (n=66)  
Non-EoE controls (n=113)

Associations between IgG4, symptoms and disease provide evidence that milk may be causal for EoE

Li R-C, et al.<sup>3</sup>

Pilot study investigating co-localization of IgG4 and milk proteins in patients from the UVA EoE cohort undergoing oesophageal biopsy

Active EoE (n=5)  
Remission (oral steroids; n=5)  
Remission (diet; n=5)  
Non-EoE controls (n=5)

IgG4-milk deposits were present in active EoE but significantly decreased in remission and controls; direct interactions may occur between IgG4 and milk proteins



Study details



Study groups



Key findings



# Clinical manifestations of EoE

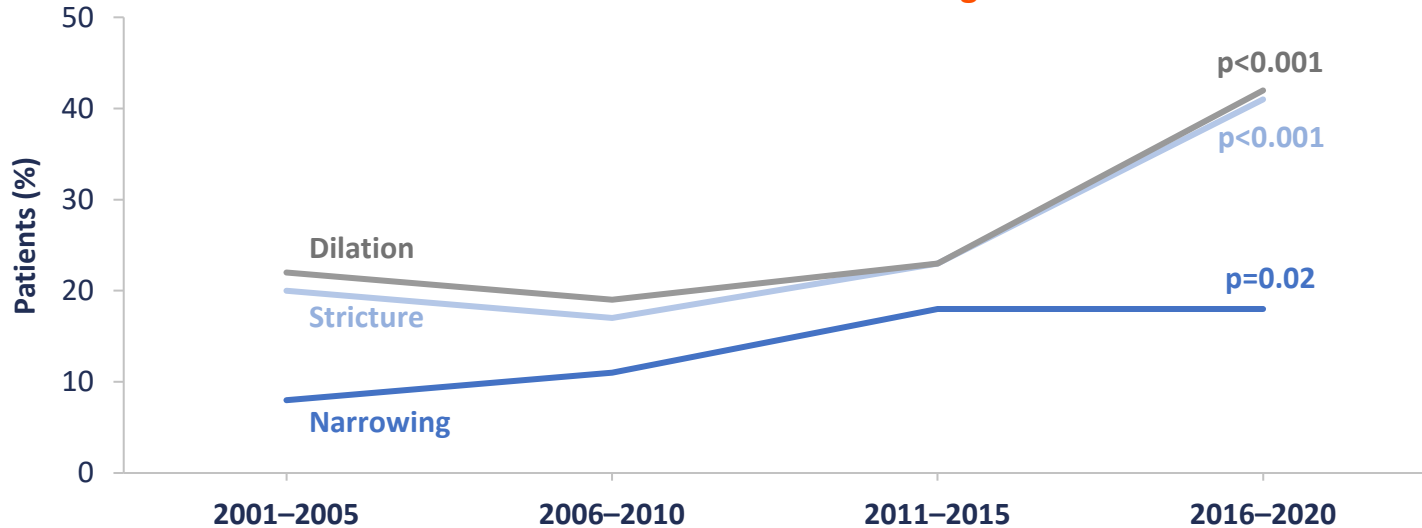


Retrospective cohort study of patients in the University of North Carolina EoE Clinicopathologic Database



• N=1,064 adults and children with EoE

## EoE clinical characteristics at diagnosis

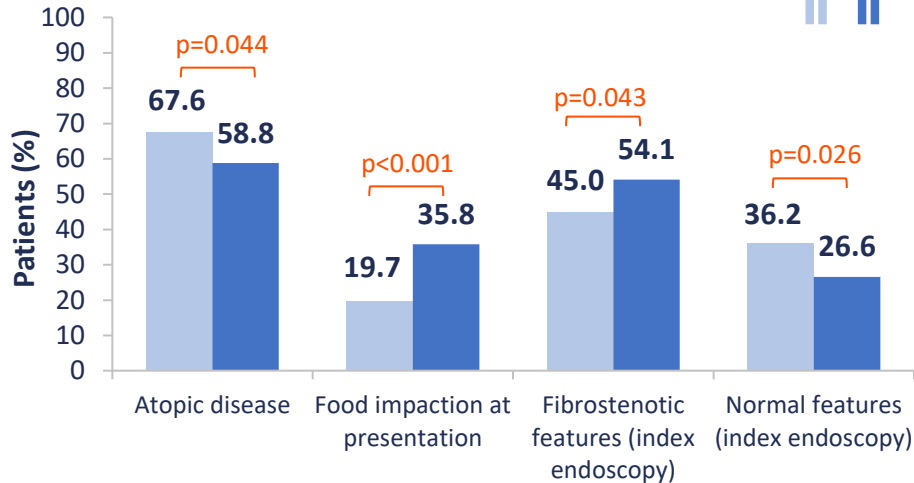


**18% increase in odds of stricture annually** after accounting for age and symptom length pre-diagnosis (aOR 1.18, 95% CI 1.12–1.23)

# Clinical manifestations of EoE

US-based retrospective single-centre observational study of medical records of patients with EoE (n=489)<sup>1</sup>

## Sex differences in EoE clinical features



Odds of dilation, males vs females: **OR 1.985**, p<0.01

US-based retrospective, case-control study on patients with food bolus who had OGDs (N=146, n=51 with EoE)<sup>2</sup>

## Seasonal variation in food bolus cases

Spring/summer vs autumn/winter

Patients with EoE



Patients without EoE



aOR, adjusted odds ratio; CI, confidence interval; OGD, oesophago-gastro-duodenoscopy; EoE, eosinophilic oesophagitis; OR, odds ratio.

1. Folga R, et al. Presented at: DDW 2022, Virtual/San Diego, CA. 21–24 May 2022. Poster EP1110; 2. Alali F, Piper MS. Presented at: DDW 2022, Virtual/San Diego, CA. 21–24 May 2022. Poster Su1198.

# Managing EoE: Diagnosis and treatment of paediatric patients

**Dr Mário Vieira**

Centre for Paediatric Gastroenterology  
Hospital Pequeno Príncipe  
Curitiba, PR, Brazil



# Case presentation

## Presentation and history



**Age:** 6 years

**Presentation:** Feeding difficulties, mild abdominal pain, occasional vomiting, gagging when eating since 4 years of age. Avoids meat and fruit unless pureed, prefers liquids and eats slowly. His mother reports that he drinks after every bite. His weight gain began to slow a year ago, then stopped completely 6 months ago

**Personal medical history:** Asthma and allergic rhinitis

**Family history:** Father has asthma and reflux symptoms with frequent heartburn



## Clinical examination



**Endoscopy:** White exudates, mucosal oedema and linear furrows



**Biopsy:** up to 63 eos/hpf

**Blood tests:** Complete blood count and basic biochemical tests were normal, no eosinophilia

# Clinical manifestations of EoE during childhood

## Infants and toddlers<sup>1</sup>



- Feeding aversion/intolerance
- Vomiting
- Food refusal
- Choking during meals
- Failure to thrive
- Sleep disturbance

## Children<sup>1</sup>



- Dysphagia
- Food impactions
- Vomiting/regurgitation
- Choking/gagging with coarse textures
- Abdominal/chest pain
- Throat pain
- Nausea
- Sleep disturbance
- Decreased appetite

## Adolescents<sup>2</sup>

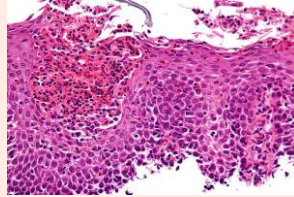


- Dysphagia
- Food impactions
- Heartburn
- Gastro-oesophageal reflux

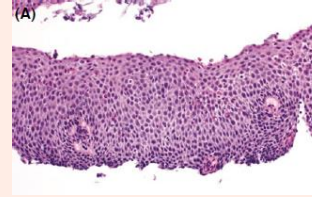
# Endoscopic and histopathological manifestations of EoE



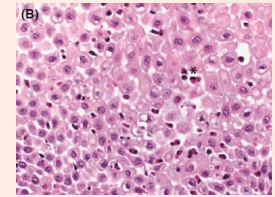
## Histopathological findings



$\geq 15$  eos/hpf<sup>1</sup>  
(required for diagnosis)



Basal cell  
hyperplasia<sup>2</sup>



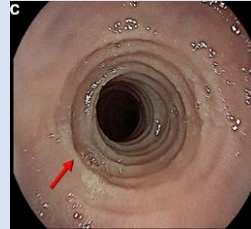
Dilated  
intercellular spaces<sup>2</sup>



## Endoscopy findings (EREFS)



Oedema<sup>3</sup>



Concentric rings<sup>3</sup>



Vertical furrows<sup>4</sup>



White exudates<sup>4</sup>

EoE, eosinophilic oesophagitis; eos/hpf, eosinophils/high-power field; EREFS, endoscopic reference score.

1. Image from Wikimedia Commons. Eosinophilic esophagitis – very high mag. Available at: [https://commons.wikimedia.org/wiki/File:Eosinophilic\\_esophagitis\\_-\\_very\\_high\\_mag.jpg](https://commons.wikimedia.org/wiki/File:Eosinophilic_esophagitis_-_very_high_mag.jpg) (accessed 18 July 2022). License for use under the Creative Commons Attribution-Share Alike 3.0 Unported (<https://creativecommons.org/licenses/by-sa/3.0/deed.en>); 2. Warners MJ, et al. *Aliment Pharmacol Ther.* 2018;47:940–50; 3. Racca F, et al. *Front Physiol.* 2022;12:815842; 4. Images provided courtesy of Dr Mário Vieira.

# Treatment approach for children with EoE

## Step 1

Discuss available treatment options with patient and carer<sup>1-3</sup>



### Considerations:<sup>2</sup>

- Age
- Treatment burden
- Anticipated efficacy
- Disease severity
- Availability of treatments and staff, e.g. dietitians

## Step 2

Initiate treatment

### Diet therapy<sup>1,3</sup>

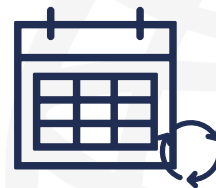
- Empiric elimination
- Elemental

### Medical therapy<sup>1,3,4</sup>

- PPIs
- TCS
- *Dupilumab*\*

## Step 3

Review clinical and histological response regularly<sup>1,2</sup>



### Response:<sup>1,3,5</sup>

- Maintain current regimen

### No response:

- Rule out non-adherence
- Escalate current regimen
- Switch/add treatment
- Mechanical dilation

\*Dupilumab is approved by the FDA for patients  $\geq 12$  years of age with EoE weighing  $\geq 40$  kgs.

EoE, eosinophilic oesophagitis; FDA, US Food and Drug Administration; PPI, proton pump inhibitor; TCS, topical corticosteroids.

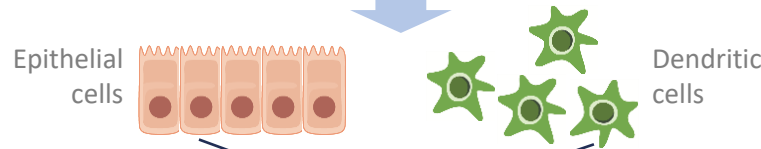
1. Barni S, et al. *Ital J Pediatr.* 2021;47:230; 2. Hirano I, Furuta GT. *Gastroenterology.* 2020;158:840-51; 3. Gutiérrez Junquera C, et al. *An Pediatr (Engl Ed).* 2020;92:376.e1-376.e10;

4. FDA. Dupilumab PI. 2022. Available at: [www.accessdata.fda.gov/drugsatfda\\_docs/label/2022/761055s040lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761055s040lbl.pdf) (accessed 7 June 2022);

5. Gonsalves NP, Aceves SS. *J Allergy Clin Immunol.* 2020;145:1-7.

# Agents in development targeting EoE pathophysiology<sup>1-5</sup>

Food allergens, aeroallergens, microorganisms



**Additional factors increasing disease susceptibility**

- Atopy
- Genetic factors
- Environmental factors

**Reduced barrier function**

*Basal cell hyperplasia, dilation of intracellular spaces that can contribute to mucosal permeability changes and immune cell infiltration*

Cell homing, retention and activation



**Dupilumab, cendakimab**

IL-4, IL-13

Eotaxin-3

Granulocyte recruitment and infiltration

**Mepolizumab**

IL-5

**Lirentelimab**

Siglec-8

Mast cell

Basophil

Eosinophil

TGF- $\beta$ 1

TNF- $\alpha$

**Benralizumab**

IL-5 $\alpha$

*Fibroblast activation, collagen deposition, smooth muscle hyperplasia and hypercontractility*

**Furrows, white exudates, oedema, concentric rings, longitudinal shearing, strictures, fibrosis**

EoE, eosinophilic oesophagitis; IL-5 $\alpha$ , interleukin-5 receptor  $\alpha$ ; ILC2, type 2 innate lymphoid cells; Siglec-8, sialic acid-binding Ig-like lectin 8; SP1R, sphingosine-1-phosphate receptor; TGF- $\beta$ , transforming growth factor- $\beta$ ; Th2, T-helper cell type 2; TNF- $\alpha$ , tumour necrosis factor- $\alpha$ ; TSLP, thymic stromal lymphopoietin.

1. Muir A, Falk GW. *JAMA*. 2021;326:1310-8; 2. Racca F, et al. *Front Physiol*. 2022;12:815842; 3. Furuta GT, Katzka DA. *N Engl J Med*. 2015;373:1640-8;

4. Hill DA, Spergel JM. *J Allergy Clin Immunol*. 2018;142:1757-8; 5. Lam AY, et al. *Curr Opin Pharmacol*. 2022;63:102183.



# Monitoring disease activity in children with EoE

## Currently used monitoring tools and techniques

### Histologic/ endoscopic

Endoscopy and biopsy (eos/hpf, EREFS, additional features, e.g. basal cell hyperplasia)<sup>1,2</sup>

### Clinical/ symptoms

Dysphagia Symptom Questionnaire (DSQ), Pediatric EoE Symptom Score (PEESS) v2.0<sup>2</sup>

## Emerging monitoring tools and techniques

### Histologic/ endoscopic

Transnasal endoscopy, oesophageal string test, oesophageal sponge, biophotonic imaging, EoEHSS<sup>1-3</sup>

### Functional

Functional lumen imaging probe, mucosal impedance, high-resolution manometry, endoscopic ultrasound<sup>1-4</sup>

### Biomarkers

Serum/blood/urine, immunohistochemical, epigenetic<sup>3,5</sup>

### Clinical/ histologic/ endoscopic

Index of Severity for EoE (I-SEE)<sup>6</sup>

EoE, eosinophilic oesophagitis; EoEHSS, the EoE Histologic Severity Score; eos/hpf, eosinophils per high power field; EREFS, endoscopic reference score.

1. Nguyen N, et al. *Front Pediatr.* 2021;9:713027; 2. Godwin B, et al. *Ann Allergy Asthma Immunol.* 2020;124:240-7; 3. Hiremath G, Gupta SK. *Clin Gastroenterol Hepatol.* 2017;15:1655-64; 4. Pytrus T, et al. *Pediatr Rep.* 2022;14:13-9; 5. Votto M, et al. *Acta Biomed* 2021;92(Suppl. 7):e2021530; 6. Dellon ES, et al. *Gastroenterology.* 2022; 163:59-76.

# Index of Severity for EoE (I-SEE)

## Scoring:



### Total score:

<1: Inactive EoE

1–6: Mild active EoE

7–14: Moderate active EoE

≥15: Severe active EoE



Points are accrued for each EoE feature a patient has



Assessed at initial diagnosis and each subsequent visit

## Features assessed:

### Symptoms

Based on frequency of occurrence: weekly, daily, multiple times per day or when disrupting social functioning

### Complications

Food impaction requiring ER visit or endoscopy; hospitalization due to EoE; perforation; malnutrition; need for elemental formula, systemic steroids or immunomodulatory treatment

### Inflammatory features

**Endoscopic:** localized or diffuse oedema, furrows, and/or exudates

**Histologic:** 15–60 eos/hpf or >60 eos/hpf

### Fibrostenotic features

**Endoscopic:** rings/strictures present, but endoscope passes easily or requires dilation

**Histologic:** basal zone hyperplasia, lamina propria fibrosis or surface epithelial alteration and dyskeratotic epithelial cells

# Managing EoE: Diagnosis and treatment of adult patients

**Prof. Arjan Bredenoord**

Amsterdam University Medical Center  
Amsterdam  
Netherlands



# Patient case

## Presentation and history

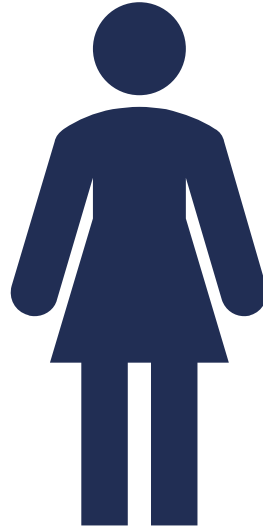


**Age:** 29 years

**Presentation:** Symptoms of epigastric discomfort, heartburn and dysphagia over the past 5 years, which has led to adaptation of eating habits, e.g. drinking after every bite of food

**Personal medical history:** Allergies to nuts, soy and legumes. The patient attempts to maintain a targeted elimination diet for her allergies, but admits she is not consistently adherent

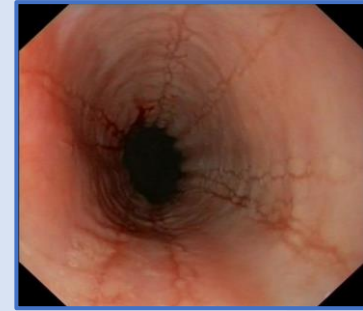
**Family history:** None reported



## Clinical examination











**Endoscopy:** Furrows, rings, mucosal oedema



**Biopsy:** Up to 63 eos/hpf

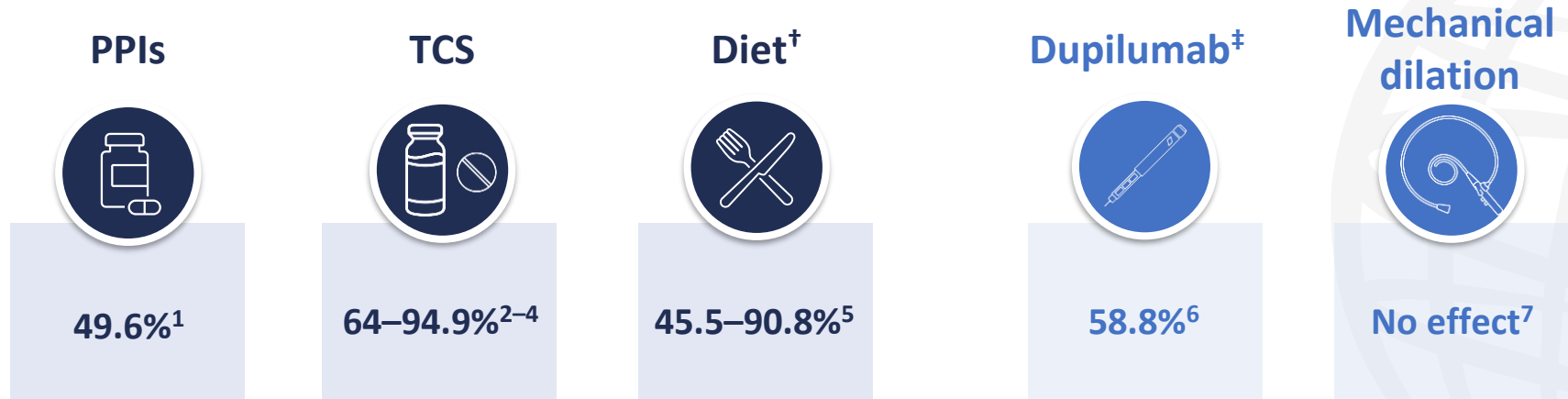
**Blood tests:** Complete blood count and basic biochemical tests were normal, no eosinophilia

# GORD: A key differential diagnosis for EoE<sup>1,2</sup>

Feature	EoE	GORD
 <b>Dominant symptom</b>	Dysphagia	Heartburn, regurgitation
 <b>Food impaction</b>	Common	Uncommon
 <b>Gender</b>	Male predominance (3:1)	Male = female
 <b>Endoscopic findings</b>	Oedema, rings, exudates, furrows, strictures, crêpe paper oesophagus, narrow calibre oesophagus. Minority have normal findings	Erosions, ulcers, Barrett's adenocarcinoma, strictures. Majority have normal findings
 <b>Histology, eos/hpf</b>	≥15	<5
 <b>Aetiology</b>	Immune-mediated or antigen-mediated response	Acid reflux
 <b>Associated atopic conditions</b>	Allergic asthma, atopic dermatitis and allergic rhinitis	None
 <b>Ambulatory pH testing</b>	Usually negative, sometimes positive	Positive

# Current treatment options for adults with EoE

Proportion of patients achieving histological remission (<15 eos/hpf)\*



\*Data are from trials that differed in therapy, dosage and administration methods, but with homogeneous cut-offs of <15 eos/hpf indicating histologic remission; <sup>†</sup>Response varied by diet type: allergy test-directed food elimination was associated with lowest remission rates, elemental diet has highest remission rates; <sup>‡</sup>In the US.

EoE, eosinophilic oesophagitis; eos/hpf, eosinophils/high power field; PPI, proton pump inhibitor; TCS, topical corticosteroids.

1. Lucendo AJ, et al. *Clin Gastroenterol Hepatol*. 2016;14:13–22; 2. Lucendo AJ, et al. *Gastroenterology*. 2019;157:74–86; 3. Butz BK, et al. *Gastroenterology*. 2014;147:324–33; 4. Dellon ES, et al. *Gastroenterology*. 2019;157:65–73; 5. Arias Á, et al. *Gastroenterology*. 2014;146:1639–48; 6. Rothenberg M, et al. *J Allergy Clin Immunol*. 2022;149:AB312; 7. Visaggi P, et al. *Ther Adv Gastroenterol*. 2021;14:doi: 10.1177/1756284820980860.

# Emerging therapies for adults with EoE

SP1R



Th2 cell

**Etrasimod**<sup>1,2</sup>

Phase II: NCT04682639 (VOYAGE)

Age 18–65 years

May 2023

IL-13



**Cendakimab**<sup>1,2</sup>

Phase III: NCT04753697, NCT04991935

Age 12–75 years

July 2024; August 2026

IL-5



**Mepolizumab**<sup>1,2</sup>

Phase II: NCT03656380

Age 16–75 years

July 2022

IL-5R $\alpha$



**Benralizumab**<sup>1,2</sup>

Phase III: NCT04543409 (MESSINA)

Age 12–65 years

May 2024

Siglec-8



**Lirentelimab**<sup>1,2</sup>

Phase II/III: NCT04322708 (KRYPTOS)

Age 12–80 years

May 2022

IL-4R $\alpha$



IL-13R $\alpha$ 1

**Dupilumab**<sup>1,2</sup>

Phase III: NCT03633617 (LIBERTY EoE TREET)

Age  $\geq$ 12 years

July 2022

Phase IV: NCT05247866

Age 6–25 years

September 2025

EoE, eosinophilic oesophagitis; IL, interleukin; IL-4R $\alpha$ , IL-4 receptor  $\alpha$  subunit; IL-5R, IL-5 receptor; IL-5R $\alpha$ , IL-5 receptor  $\alpha$  subunit; IL-13R $\alpha$ 1, IL-13 receptor  $\alpha$  subunit-1; siglec-8, sialic acid-binding Ig-like lectin 8; SP1R, sphingosine-1-phosphate receptor; Th2, T-helper cell type 2.

1. Racca F, et al. *Front Physiol.* 2022;12:815842; 2. ClinicalTrials.gov. Available at: <https://clinicaltrials.gov/ct2/home> (accessed 15 June 2022).

# Monitoring disease activity and treatment response in adults with EoE

## Currently used monitoring tools and techniques

<b>Clinical/ symptoms</b>	Dysphagia Symptom Questionnaire (DSQ), EoE Activity Index (EEAI) <sup>1,2</sup>
<b>Histological</b>	Biopsy (eos/hpf, additional features, e.g. basal cell hyperplasia) <sup>1,2</sup>
<b>Endoscopy</b>	EREFS <sup>1,2</sup>
<b>Quality of life</b>	Adult EoE Quality of Life Instrument (EoO-QOL-A) <sup>1,2</sup>

## Emerging monitoring tools and techniques

<b>Histological</b>	String test, oesophageal sponge <sup>1,2</sup>
<b>Functional</b>	Functional lumen imaging probe, high-resolution manometry, endoscopic ultrasound <sup>1,3-6</sup>
<b>Biomarkers</b>	Serum/blood, immunohistochemical, epigenetic <sup>7-10</sup>

EoE, eosinophilic oesophagitis; eos/hpf, eosinophils per high power field; EREFS, endoscopic reference score.

1. Lucendo AJ, et al. *United European Gastroenterol J.* 2017;5:335–58; 2. Schoepfer A, et al. *Dis Esophagus.* 2016;29:959–66; 3. Pannala R, et al. *VideoGIE.* 2022;7:1–20;

4. Visaggi P, et al. Presented at: DDW 2022, Virtual/San Diego, CA. 21–24 May 2022. Poster Su1189; 5. Wong S, et al. *JGH Open.* 2020;4:851–5;

6. Pytrus T, et al. *Pediatr Rep.* 2022;14:13–9; 7. Votto M, et al. *Acta Biomed.* 2021;92(Suppl. 7):e2021530; 8. Venkateshaiah SU, et al. *Int J Basic Clin Immunol.* 2021;4:1–8;

9. Sarbinowska J, et al. *Biomolecules.* 2021;11:890; 10. Bhardwaj N, et al. *Allergy Rhinol (Providence).* 2020;11:2152656720953378.