Diagnosing and treating patients with EoE: Tackling the difficulties

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Recognizing eosinophilic oesophagitis in the clinic

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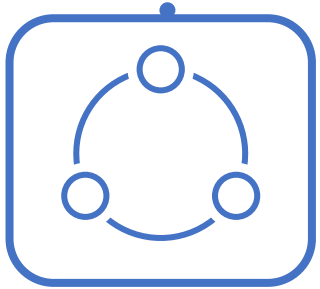
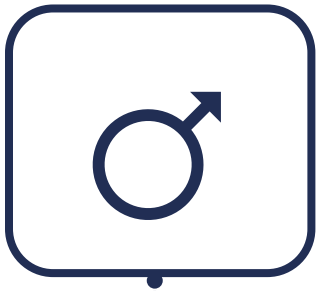
What are the risk factors for eosinophilic oesophagitis and how do patients typically present?

Risk factors for EoE development

Atopy[1]

EoE diagnosis is higher in those with ≥1 comorbid disease[2]





Male sex[1]

~3:1 male to female ratio[3]

Genetics[1]

Over 30 candidate genes identified, primarily affecting epithelial barrier function or Th2-mediated immune response[4,5]

Family history: A clustering of EoE in families may largely be attributed to the common family environment[3]

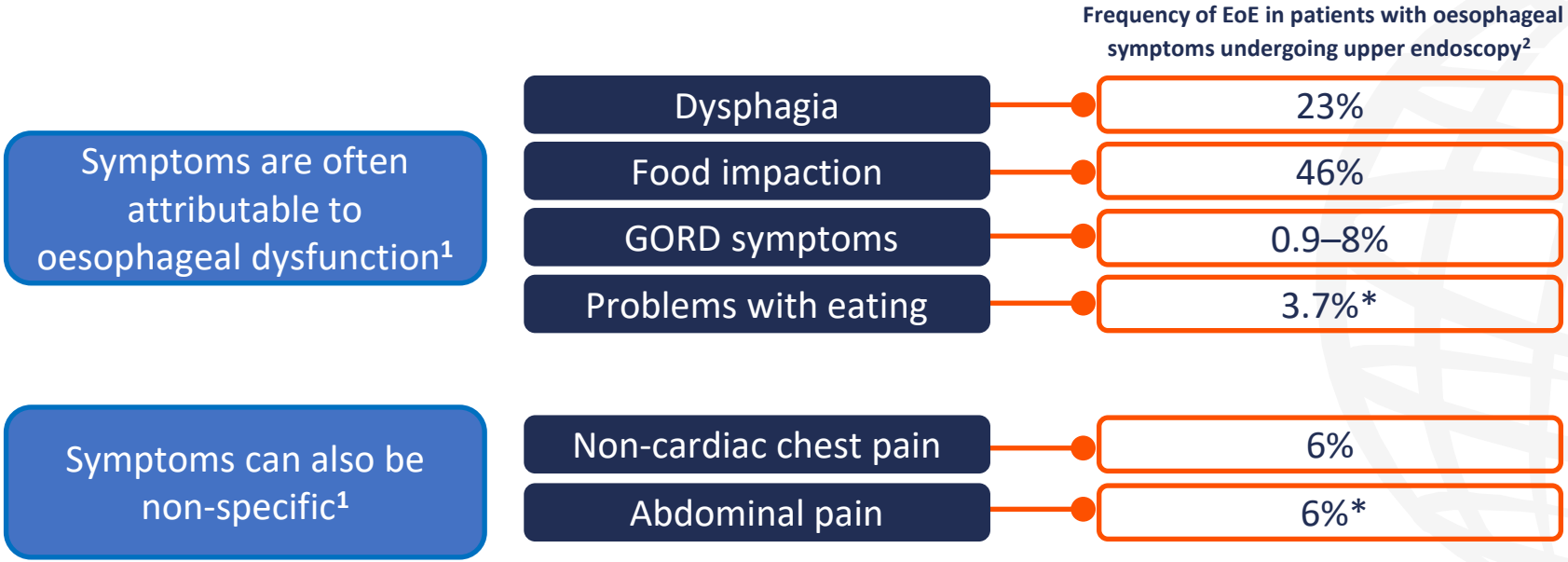
Environmental factors[1]

Neonatal ICU admission; pre-term labour; Caesarean delivery; supplemented breastfeeding; antibiotic/anti-secretive drug use in infancy;[3] *Helicobacter pylori*[6]

EoE, eosinophilic oesophagitis; ICU, intensive care unit; Th2, type 2 helper T cell.

1. Carr S, et al. *Allergy Asthma Clin Immunol.* 2018;14(Suppl. 2):58; 2. Chehade M, et al. *J Allergy Clin Immunol Pract*. 2018;6:1534–44;
3. Lucendo AJ, et al. *Therap Adv Gastroenterol*. 2022;15:1–16; 4. Lyles J, Rothenberg M. *Curr Opin Immunol*. 2019;60:46–53; 5. Muir A, Falk GW. *JAMA*. 2021;326:1310–8;
6. Jensen ET, Dellon ES. *J Allergy Clin Immunol*. 2018;142:32–40.

Clinical manifestations of EoE



*In children under 18 years of age undergoing upper endoscopy for abdominal pain.
EoE, eosinophilic oesophagitis; GORD, gastro-oesophageal reflux disease.
1. Dellon ES, et al. *Gastroenterology*. 2022;163:59–76; 2. Lucendo AJ, et al. *United European Gastroenterol J.* 2017;5:335–58.

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How do eosinophilic oesophagitis symptoms vary with age?

Clinical manifestations of EoE vary with age

Infants and toddlers[1]

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

Children[1]

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

Adolescents/adults[2]

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

EoE, eosinophilic oesophagitis.

1. Carr S, et al. *Allergy Asthma Clin Immunol.* 2018;14:58; 2. Barni S, et al. *Ital J Pediatr*. 2021;47:230.

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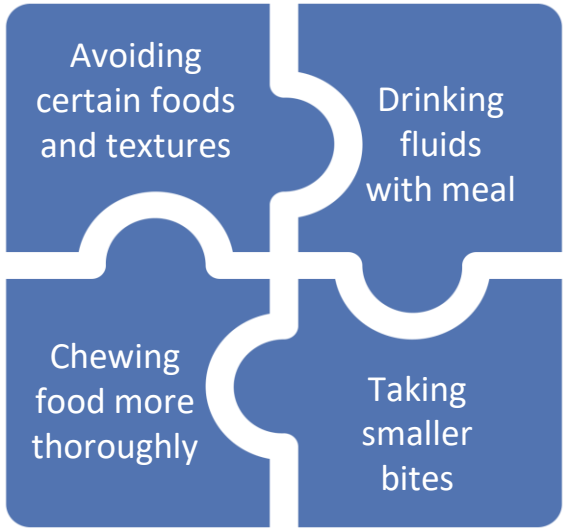
Some patients may be asymptomatic or have adapted to long-standing disease.

What is the best approach to detect eosinophilic oesophagitis in these patients?

Adaptive behaviours and consequences of delayed diagnosis in patients with EoE

Compensatory feeding mechanisms:[1]



EoE symptoms may not always correlate with disease activity[2,3]

Increased interval between symptom onset and endoscopic diagnosis may lead to an increasing stricture rate[2]

Diagnosis: <2 years
Stricture rate: 17%

Diagnosis: >20 years
Stricture rate: 71%

EoE, eosinophilic oesophagitis.

1. Dellon ES, et al. *Gastroenterology*. 2022;163:59–76; 2. Dhar A, et al. *Gut*. 2022;71:1459–87; 3. Muir A, et al. *Ann Allergy Asthma Immunol* 2019;122:572–3.

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What are the key differential diagnoses to consider based on presenting symptoms?

Differential diagnostic features for EoE and GORD

	Feature	EoE	GORD
	**Dominant symptom**	Dysphagia	Heartburn, regurgitation
	**Food impaction**	Common	Uncommon
	**Sex**	Male predominance	Male = female
	**Associated atopic conditions**	Allergic asthma, atopic dermatitis and allergic rhinitis	No association with atopic conditions

EoE, eosinophilic oesophagitis; GORD, gastro-oesophageal reflux disease.
Attwood SE. *Br J Hosp Med (Lond).* 2019;80:132–8.

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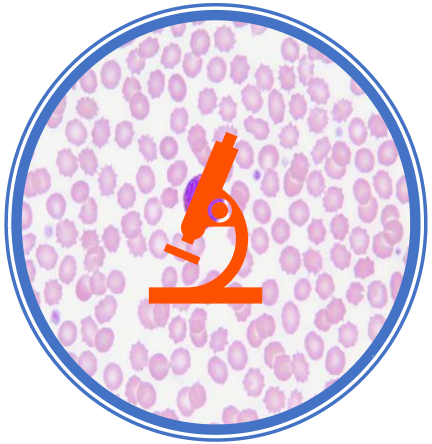
Differential diagnosis of EoE

- 1 in 17 people will develop dysphagia in their lifetime[1]
- Differential diagnosis for dysphagia is varied and includes nervous system, brain and muscle disorders, infection, narrowing, blockages and structural abnormalities in the throat[2]

Other causes of eosinophilia on biopsy in patients with dysphagia[3]

- Gastro-oesophageal reflux disease
- Inflammatory bowel disease
- Connective tissue disease



- Parasitic and fungal infections
- Allergic vasculitis
- Drugs

EoE, eosinophilic oesophagitis.

1. World Gastroenterology Organisation. 2014. Available at: https://www.worldgastroenterology.org/guidelines/dysphagia/dysphagia-english (accessed 9 January 2024);
2. Cleveland Clinic. 2023. Available at: https://my.clevelandclinic.org/health/symptoms/21195-dysphagia-difficulty-swallowing (accessed 8 December 2023);
3. Gonsalves NP, et al. *J Allergy Clin Immunol.* 2020;145:1–7.

Diagnosing eosinophilic oesophagitis

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What are the roles of endoscopy and histology in confirming a diagnosis of eosinophilic oesophagitis?

Endoscopy and histology workup[1]

Adults with:
Dysphagia and/or
bolus impaction and/or
upper GI symptoms

Children with:
Decreased appetite and/or
food refusal and/or
abdominal pain and/or
chew foods finely

Upper endoscopy

Normal
Random oesophageal biopsies 6–8

EREFS
Targeted oesophageal biopsies 6–8
(consider dilation when a stricture is present)

Histology: >15 eos/HPF in oesophageal mucosa

Yes → **EoE**

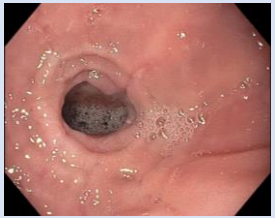
No → Consider other aetiologies (primary and secondary)*[2]

*Primary disorders associated with eosinophilia other than EoE include gastro-oesophageal reflux disease, achalasia, Crohn's disease, fungal or viral infections and pill oesophagitis; secondary disorders include hyper-eosinophilic syndrome; drug hypersensitivity reactions and connective tissue diseases.
EoE, eosinophilic oesophagitis; eos/HPF, eosinophils per high-power field; EREFS, endoscopic reference score; GI, gastrointestinal.
1. Visaggi P, et al. *Therap Adv Gastroenterol.* 2021;14:1–17. 2. Sorge A, et al. *Curr Treat Options Gastroenterol* 2023;21:256–71.

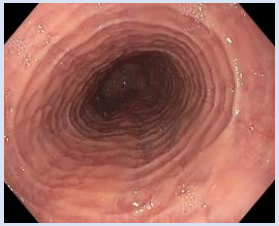
What endoscopic and histological features indicate eosinophilic oesophagitis?

Endoscopic findings: Components of the EREFS

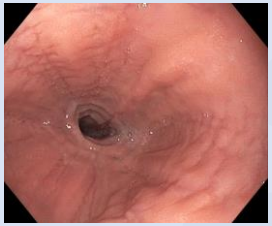
Endoscopy findings (EREFS)[1]



Grade 3 ring/ stricture and oedema



Grade 2 rings; Grade 2 furrows



Grade 3 ring/stricture; Grade 2 furrows, oedema

OEdema	
Absent	0
Mild: Loss of clarity of vascularity	1
Severe: Absent vascularity	2

Concentric Rings	
Absent	0
Mild: Visible on insufflation only	1
Moderate: Visible without insufflation; allows passage of adult endoscope	2
Severe: Inability to pass adult endoscope	3

White Exudates	
Absent	0
Mild: White exudate <10% of oesophageal surface area	1
Severe: White exudate >10% of oesophageal surface area	2

Longitudinal Furrows	
Absent	0
Mild: Vertical lines without visible depth	1
Severe: Vertical lines with mucosal depth (indentation)	2

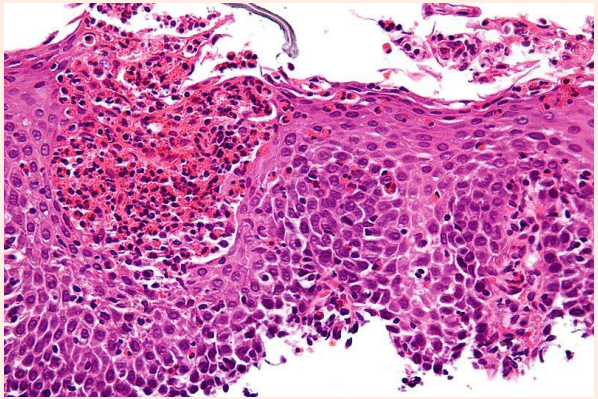
Strictures	
Absent	0
Present	1

The prevalence of endoscopic findings varies by age[2]

Images provided by Dr Nirmala Gonsalves.
EREFS, endoscopic reference score.
1. Hirano I, et al. *Gut*. 2013;62:489–95; 2. Visaggi P, et al. *Therap Adv Gastroenterol.* 2021;14:1–17.

Histopathological manifestations of EoE

Histopathological findings



≥15 eos/hpf[1]
(required for diagnosis)

Other features include:

- Eosinophilic micro-abscesses (clusters of ≥4 eosinophils)[2]
- Eosinophil degranulation[2]
- Subepithelial fibrosis[2]
- Basal cell hyperplasia[1]
- Prominent dilated intracellular spaces with disruption of tight junctions[1]

Use of the **EoEHSS composite grade and stage scores** and **VAS assessment** of overall histopathological disease severity may provide the most consistent and uniform scoring of histological features in adult EoE patients[1]

Image from Nephron/Wikimedia Commons. Available at: https://commons.wikimedia.org/wiki/File:Eosinophilic_esophagitis_-_very_high_mag.jpg.

EoE, eosinophilic oesophagitis; EoEHSS, Eosinophilic Esophagitis Histologic Scoring System; eos/hpf, eosinophils per high-power field; VAS, Visual Analogue Scale.
1. Warners MJ, et al. *Aliment Pharmacol Ther*. 2018;47:940–50; 2. Gonsalves NP, Aceves SS. *J Allergy Clin Immunol.* 2020;145:1–7.

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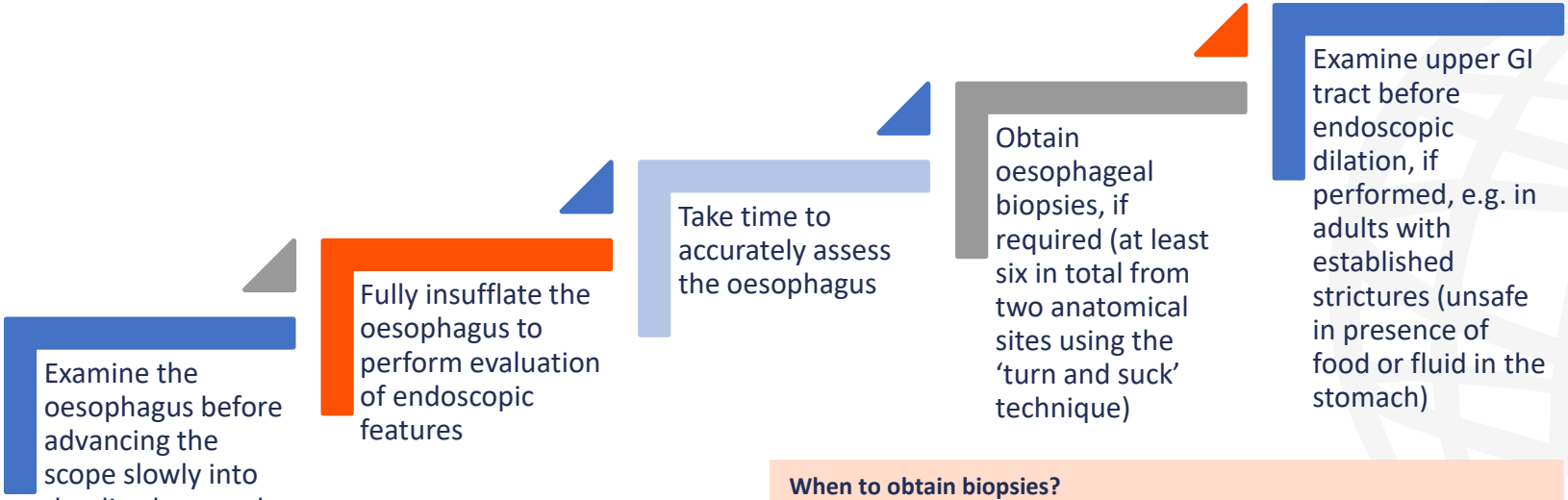
How can we optimize endoscopy in patients with suspected eosinophilic oesophagitis?

Best endoscopic examination practice for EoE



When to obtain biopsies?

- All adults with endoscopic signs of EoE, or with symptoms of dysphagia and/or food impaction, even with a normal-appearing oesophagus
- During the EGD performed for food bolus impaction in patients without a known diagnosis of EoE

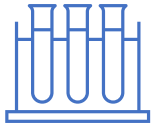
EGD, esophagogastroduodenoscopy; EoE, eosinophilic oesophagitis; GI, gastrointestinal.

Sorge A, et al. *Curr Treat Options Gastroenterol.* 2023;21:256–71.

Since endoscopy is invasive and expensive, what is the potential for minimally invasive tools for diagnosis and monitoring?

Can minimally invasive tools replace endoscopy?

Biomarkers[1,2]



- **Blood/serum** (AEC)
- **Plasma** (CLC/GAL-10, ECP, EDN, Eotaxin-3 and MBP-1)
- **Urine** (OPN and MMP-9)
- EoE diagnostic panel (EDP)

The presence of concomitant atopies makes it difficult to identify specific biomarkers[3]

Histological techniques[4]

- Oesophageal string test (EST)
- Cytosponge (capsule technology)
- Unsedated transnasal endoscopy with biopsy

Promising for assessing inflammation without the use of standard endoscopy

Functional imaging[4,5]

- Tethered confocal microscopy
- Endoluminal functional lumen imaging probe (EndoFLIP)

EndoFLIP should not be used to diagnose EoE; potential role in severity assessment and therapeutic monitoring

AEC, absolute eosinophil count; CLC/GAL-10, galectin-10; ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; EoE, eosinophilic oesophagitis; MBP-1, major basic protein-1; MMP-9, matrix metalloproteinase-9; OPN, osteopontin.

1. Wechsler JB, et al. *Allergy* 2021;76:3755–65; 2. Min S, et al. *J Allergy Clin Immunol.* 2022;149:782–7.e1; 3. Grueso-Navarro E. *Int J Mol Sci* 2023;24:3669;
4. Barni S, et al. *Ital J Pediatr*. 2021;47:230; 5. Hirano I, et al. *Clin Gastroenterol Hepatol.* 2017;15:325–34.

Treating patients with eosinophilic oesophagitis

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What is the current role of biologics in the treatment of eosinophilic oesophagitis?

Current role of biologics in the treatment of EoE

EoE treatment goals[1]

- Improvement in clinical symptoms
- Resolution of oesophageal eosinophilia and other histological abnormalities
- Endoscopic improvement
- Improved quality of life
- Improved oesophageal function
- Minimized adverse effects of treatment
- Prevention of disease progression and subsequent complications

PPIs[2] | STCs[2] | Diet[2] | Dupilumab[3]* | Endoscopic dilation[2]

Treatments should be evaluated periodically and adjusted, when necessary, on the basis of the response[2]

When to consider biologic therapy[3]

First line:

- Patients with multiple comorbid atopic conditions

Step up therapy:

- Difficult-to-treat EoE
- Patients with failure to thrive, poor growth or significant weight loss
- Frequent use of rescue therapies
- Patients with severe diet restriction/amino acid formula
- Patients with clinically significant oesophageal strictures
- Patients who are refractory to or have adverse events to current therapy

*Indicated for the treatment of EoE in adults and adolescents (aged ≥12 years) weighing at least 40 kg[4] and children aged 1 to 11 years.[5]

EoE, eosinophilic oesophagitis; PPI, proton pump inhibitor; STC, swallowed topical corticosteroid.

1. Franciosi JP, et al. *Cochrane Database Syst Rev.* 2023;7:CD004065; 2. Feo-Ortega S, Lucendo AJ. *Therap Adv Gastroenterol.* 2022;15:17562848211068665; 3. Aceves SS, et al. *Ann Allergy Asthma Immunol.* 2023;130:371–8; 4. Rothenberg ME, et al. *Lancet Gastroenterol Hepatol.* 2023;8:990–1004; 5. Joszt L. *The American Journal of Managed Care*. 2024. Available at: www.ajmc.com/view/fda-approves-dupilumab-to-treat-eoe-for-children-under-12-years (accessed 26 January 2024).

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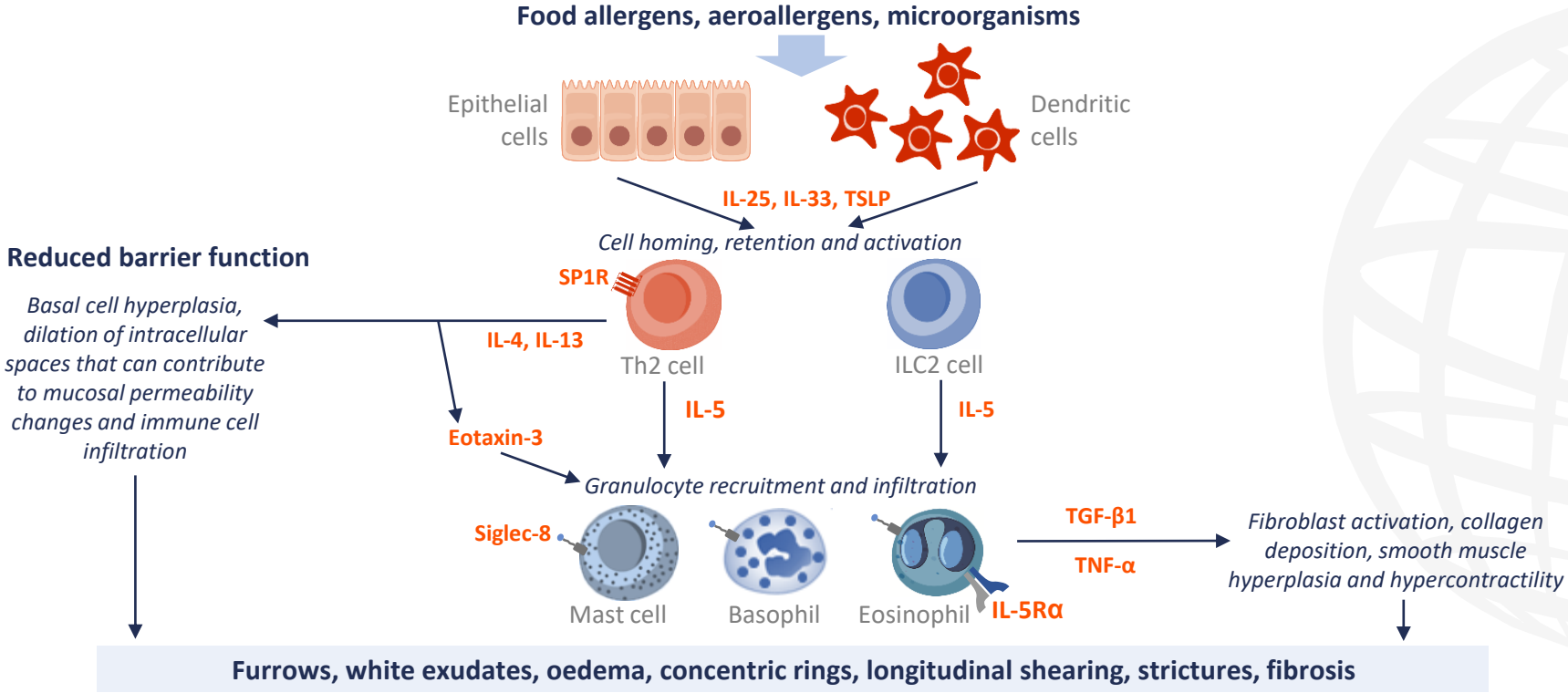
What are the other emerging therapies for eosinophilic oesophagitis and how do they target the underlying pathophysiology?

EoE pathophysiology overview[1–5]



EoE, eosinophilic oesophagitis; IL, interleukin; IL-5Rα, IL-5 receptor alpha subunit; ILC2, type 2 innate lymphoid cells; Siglec-8, sialic acid-binding immunoglobulin-like lectin 8; SP1R, sphingosine-1-phosphate receptor; TGF-β1, transforming growth factor beta 1; Th2, type 2 T-helper cell; TNF-α, 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.

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Selected agents in development for EoE

Studies that did not meet all primary endpoints:

IL-5Rα

Benralizumab[1,2]
Phase III: NCT04543409 (MESSINA) February 2023 Age 12–65 years

Siglec-8

Lirentelimab[1–3]
Phase II/III: NCT04322708 (KRYPTOS) January 2022 Age 12–80 years

IL-5

Mepolizumab[1,2,4]
Phase II: NCT03656380 December 2022 Age 16–75 years

Reslizumab[1,2,5]
Phase III: NCT00635089 January 2012 Age 5 years and older

Studies that are ongoing or that met primary endpoints:

IL-13

Cendakimab[1,2]
Phase II/III: NCT02098473 January 2017 Age 18–65 years, NCT04753697 October 2024, NCT04991935 September 2026 Age 12–75 years

SP1R

Th2 cell

Etrasimod[1,2]
Phase II: NCT04682639 (VOYAGE) June 2023 Age 18–65 years

TSLP

Tezepelumab[1,2]
Phase III: NCT05583227 (CROSSING) January 2027 Age 12–80 years

EoE, eosinophilic oesophagitis; IL, interleukin; IL-5Rα, IL-5 receptor alpha subunit; Siglec-8, sialic acid-binding immunoglobulin-like lectin 8; SP1R, sphingosine-1-phosphate receptor; Th2, type 2 T-helper cell; TSLP, thymic stromal lymphopoietin.
1. Racca F, et al. *Front Physiol*. 2022;12:815842; 2. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ all clinical trials searchable by NCT number (accessed 19 December 2023); 3. Dellon ES, et al. Presented at: American College of Gastroenterology 2022 Annual Scientific Meeting, Charlotte, NC, USA. 21–26 October 2022. Poster 0201; 4. Dellon ES, et al. *Gut*. 2023;72:1828–37; 5. Spergel JM, et al. *J Allergy Clin Immunol.* 2012;129:456–63.

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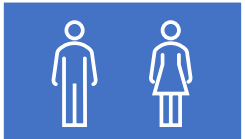
What can we learn from clinical trial data about the efficacy of biologics in the management of eosinophilic oesophagitis?

Latest EoE efficacy data for biologic therapies

Phase II: Cendakimab (RPC4046) NCT02098473[1]



N=99

- Patients with active EoE
- Aged 18–65 years
- Dysphagia symptoms and histological evidence of EoE

- RPC4046 180 mg or 360 mg treatment for 16 weeks (IV loading dose then SC)

Primary endpoint:

- Mean changes from baseline in oesophageal eos count in 5 hpfs with the highest level of inflammation

Results: Phase III ongoing

- Placebo (n=34): **–4.4** ±59.9
- 180 mg dose (n=31): **–94.8** ±67.3 (p<0.0001)
- 360 mg dose (n=34): **–99.9** ±79.5 (p<0.0001)

Phase II: Etrasimod NCT04682639[2]

N=108

- Adults with active EoE
- Aged 18–65 years

- Oral etrasimod 1 mg or 2 mg QD vs placebo for 24 weeks; 28-week extension ongoing

Primary endpoint:

- Percentage change from baseline in oesophageal peak eos count at week 16

Results:

- 2 mg QD (n=41): **46.1%** decrease vs placebo (p=0.0103)
- 1 mg QD (n=39) **32.5%** decrease vs placebo (p=0.2861)

EoE, eosinophilic oesophagitis; eos, eosinophil; hpf, high-power field; IV, intravenous; QD, once a day; SC, subcutaneous.

1. Hirano I, et al. *Gastroenterology.* 2019;156:592–603; 2. Dellon ES, et al. Presented at: American College of Gastroenterology 2022 Annual Scientific Meeting, Vancouver, Canada. October 20–25, 2023. Abstract 25.

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Latest EoE efficacy data for biologic therapies

Phase III: Dupilumab (three parts) NCT03633617

Part A: N=81
Part B: N=240

- Patients with active EoE
- Aged ≥12 years
- All the patients had a score of ≥10 on the DSQ at baseline

- SC dupilumab 300 mg weekly dose or placebo (**part A**)
- Dupilumab 300 mg either weekly or every 2 weeks OR weekly placebo (**part B**) up to week 24
- Eligible patients who completed part A or part B continued the trial in part C

Primary endpoints (parts A and B):

- Histological remission (peak oesophageal intraepithelial eos count of ≤6 per hpf)
- Absolute change from baseline in the DSQ score

DSQ, Dysphagia Symptom Questionnaire; EoE, eosinophilic oesophagitis; eos, eosinophil; hpf, high-power field; SC, subcutaneous.

Dellon ES, et al. *N Engl J Med.* 2022;387:2317–30.

Latest EoE efficacy data for biologic therapies

Phase III: Dupilumab (three parts) NCT03633617

Part A and B results at 24 weeks:[1]

Histological remission (peak oesophageal intraepithelial eos count of ≤6 per hpf)

- Part A: **60%** (25/42) dupilumab QW vs **5%** (2/39) placebo (p<0.001)
- Part B: **59%** (47/80) dupilumab QW; **60%** (49/81) dupilumab Q2W; **6%** (5/79) placebo (p<0.001)

Absolute change from baseline in DSQ score

- Part A difference: **–12.32** points (p<0.001)
- Part B difference: **–9.92** points (p<0.001)

LIBERTY EoE TREET: Long-term efficacy results at 52 weeks (part C):[2]

Treatment arm	Histological remission	Mean absolute change from baseline in DSQ score
Placebo Q2W/dupilumab Q2W	**72%** (23/32)	**–23.7** points
Dupilumab Q2W/dupilumab Q2W	**68%** (25/37)	**–27.3** points
Placebo QW/dupilumab QW	**74%** (54/73)	**–20.9** points
Dupilumab QW/dupilumab QW	**85%** (55/65)	**–30.3** points

Findings reinforce the importance of weekly dupilumab, rather than every 2 weeks

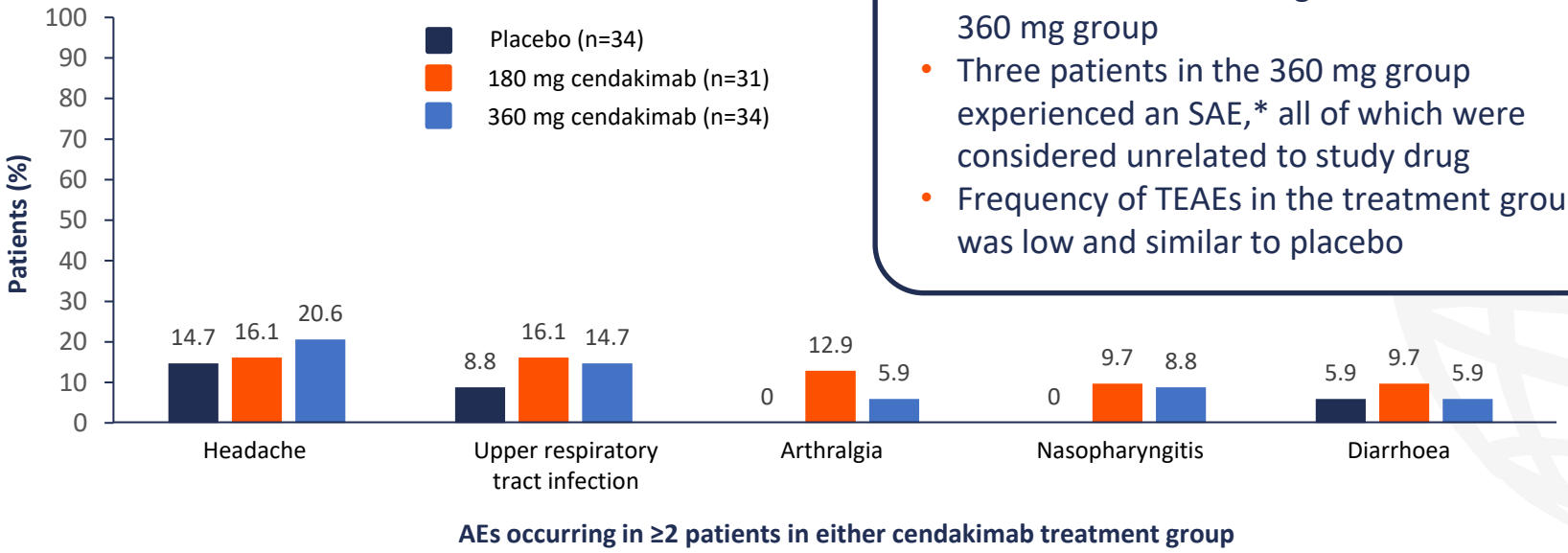
DSQ, Dysphagia Symptom Questionnaire; EoE, eosinophilic oesophagitis; eos, eosinophil; hpf, high-power fields; Q2W, every 2 weeks; QW, once a week.

1. Dellon ES, et al. *N Engl J Med.* 2022;387:2317–30; 2. Rothenberg ME, et al. *Lancet Gastroenterol Hepatol*. 2023;8:990–1004.

What do the clinical trials tell us about the safety profiles of current and emerging biologic therapies?

Safety data for biologic therapies for EoE

Cendakimab (RPC4046) NCT02098473



AEs occurring in ≥2 patients in either cendakimab treatment group

Safety

- Incidence of AEs was higher in the 360 mg group
- Three patients in the 360 mg group experienced an SAE,* all of which were considered unrelated to study drug
- Frequency of TEAEs in the treatment groups was low and similar to placebo

*An SAE was defined as any untoward medical occurrence that resulted in death, was life-threatening (has an immediate risk of death), required admission to a hospital or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, or resulted in a congenital anomaly or birth defect.

AE, adverse event; EoE, eosinophilic oesophagitis; SAE, serious AE; TEAE, treatment-emergent AE.

Hirano I, et al. *Gastroenterology.* 2019;156:592–603.

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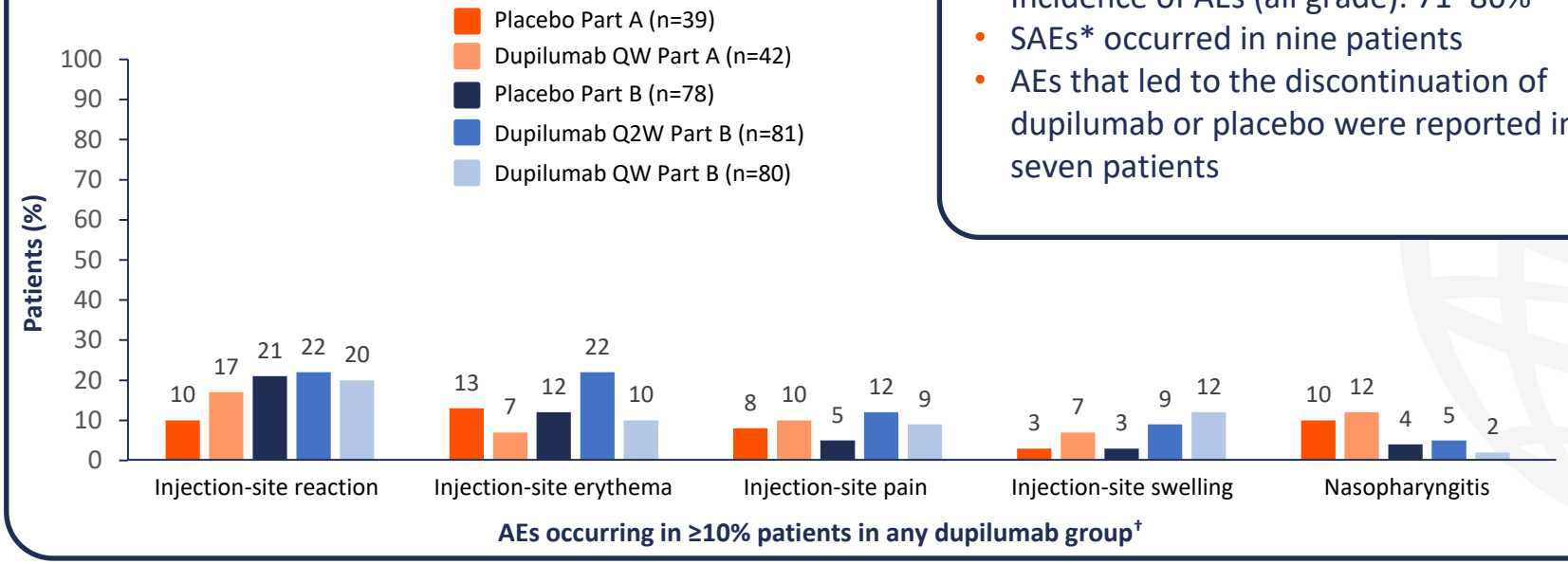
Safety data for biologic therapies for EoE

Dupilumab NCT03633617



Safety (parts A and B)

- Incidence of AEs (all grade): 71–86%
- SAEs* occurred in nine patients
- AEs that led to the discontinuation of dupilumab or placebo were reported in seven patients

*None of the AEs or SAEs that were assessed were considered by the trial investigators to be related to the trial regimen, with the exception of one SAE of systemic inflammatory response syndrome; the patient with this event was continued to be followed in the trial, and the event did not recur.

†AEs in this category were reported according to the preferred terms in the Medical Dictionary for Regulatory Activities, version 23.0.

AE, adverse event; EoE, eosinophilic oesophagitis; Q2W, every 2 weeks; QW, once a week; SAE, serious AE.

Dellon ES, et al. *N Engl J Med.* 2022;387:2317–30.

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What are the future directions for the treatment of eosinophilic oesophagitis?