Eosinophilic Oesophagitis

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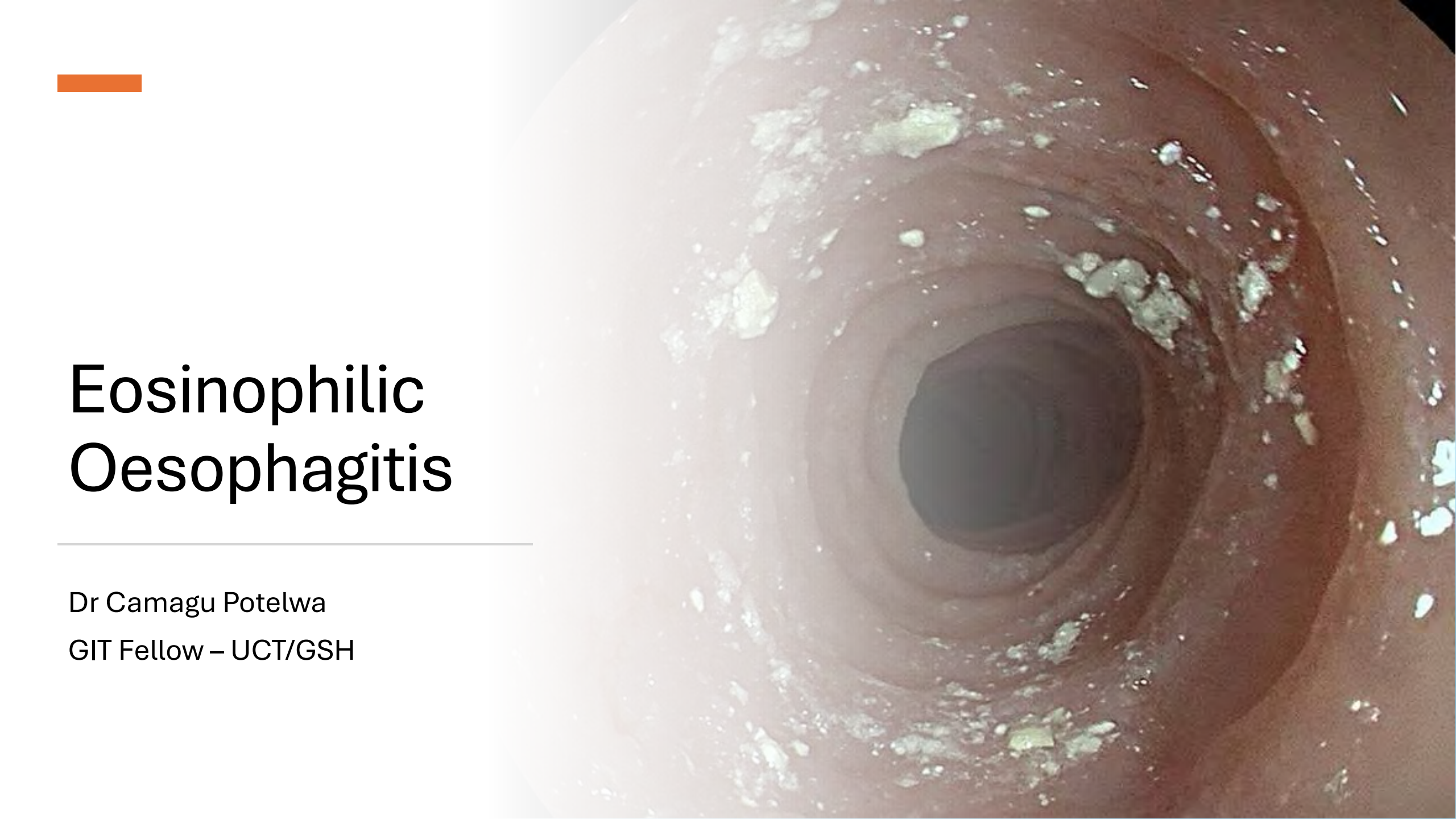


Introduction

- **Eosinophilic Gastrointestinal Diseases (EGIDs):** Chronic, immune-mediated disorders defined by pathologic eosinophil infiltration in the GI tract.
- **EoE (Eosinophilic Oesophagitis):** Restricted specifically to the oesophagus.
- **Non-EoE EGIDs:** Can affect any other GI segment (stomach, small bowel, colon), often with multisegmental overlap.
- Driven by **Type 2 inflammation** and allergen-driven inflammatory process.
- 2022 international consensus established "EGID" as the umbrella term to resolve previous ambiguity (e.g., "eosinophilic gastroenteritis").

Epidemiology, Natural History, and Treatment of Eosinophilic Gastrointestinal Diseases.Visaggi, Pierfrancesco et al. Gastroenterology, Volume 170, Issue 3, 476 - 494

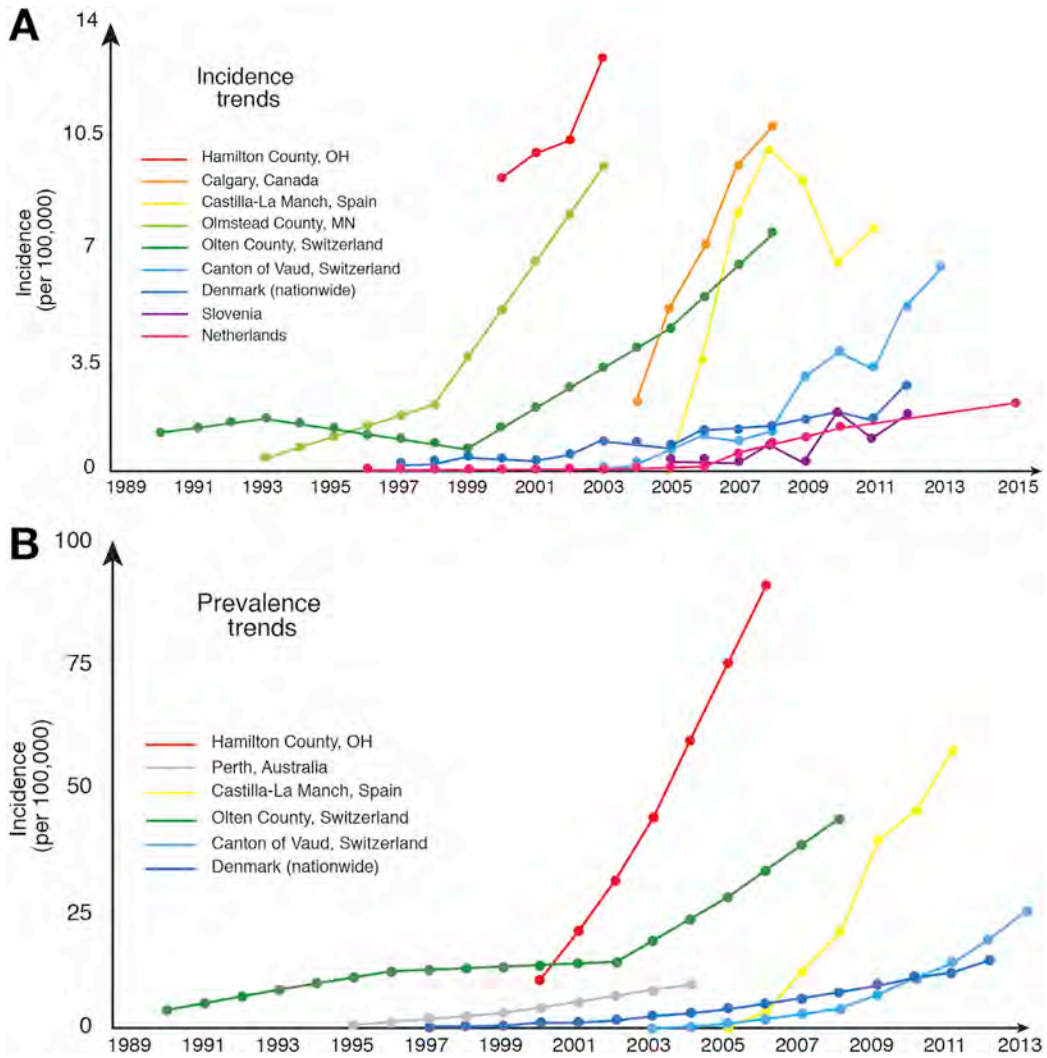
Definition of EoE

- Eosinophilic oesophagitis (EoE) is a chronic allergen-induced, type 2 immune-mediated disease of the oesophagus characterized by symptoms of oesophageal dysfunction and an eosinophilic predominant infiltrate in the oesophagus.
- Eosinophilic oesophagitis is characterised by symptoms of **dysphagia and/or food impaction in adults, and feeding problems, abdominal pain and/or vomiting in children**, with oesophageal **histology showing a peak eosinophil count of ≥15 eosinophils/high power field** (or ≥15 eosinophils/0.3 mm2 or >60 eosinophils/mm2).

A. Dhar, H. N. Haboubi, S. E. Attwood, M. K. H. Auth, J. M. Dunn, R. Sweis, et al. Gut 2022 Vol. 71 Issue 8 Pages 1459

Dellon, Evan SMuir, Amanda B.. ACG Clinical Guideline: Diagnosis and Management of Eosinophilic Esophagitis. The American Journal of Gastroenterology 120(1):p 31-59, January 2025.

Epidemiology


A
Incidence trends
Incidence (per 100,000)
14
10.5
7
3.5
0
Hamilton County, OH
Calgary, Canada
Castilla-La Manch, Spain
Olmstead County, MN
Olten County, Switzerland
Canton of Vaud, Switzerland
Denmark (nationwide)
Slovenia
Netherlands
1989 1991 1993 1995 1997 1999 2001 2003 2005 2007 2009 2011 2013 2015
B
Prevalence trends
Incidence (per 100,000)
100
75
50
25
0
Hamilton County, OH
Perth, Australia
Castilla-La Manch, Spain
Olten County, Switzerland
Canton of Vaud, Switzerland
Denmark (nationwide)
1989 1991 1993 1995 1997 1999 2001 2003 2005 2007 2009 2011 2013

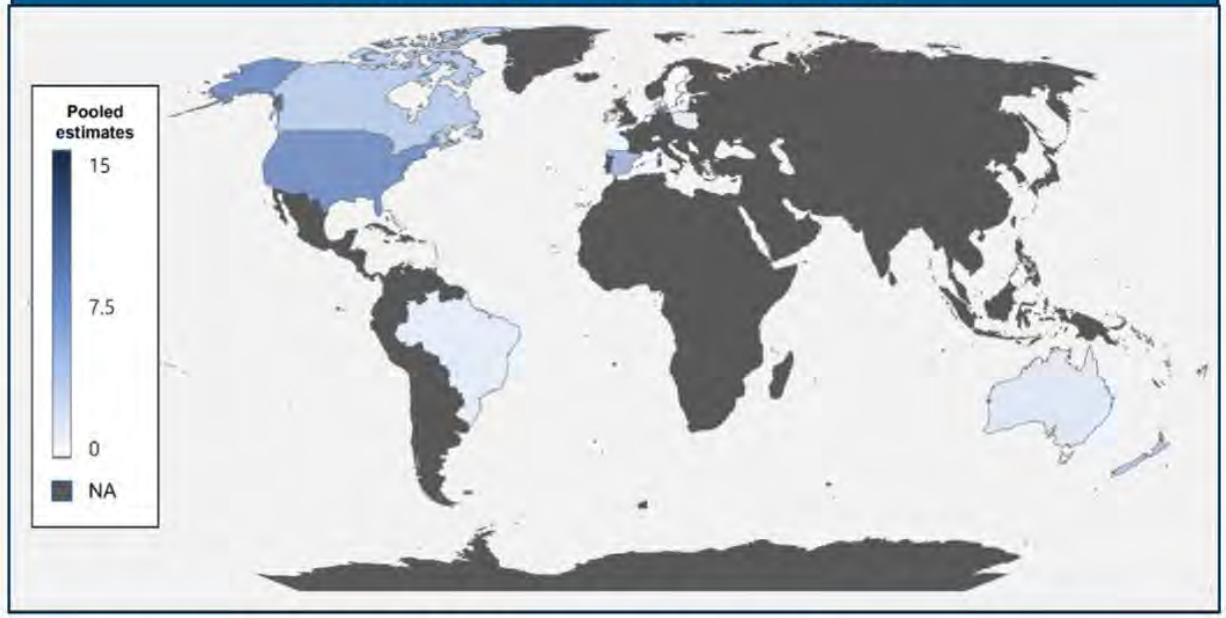
Global incidence and prevalence of eosinophilic esophagitis (EoE), 1976-2022

Systematic review
Meta-analysis

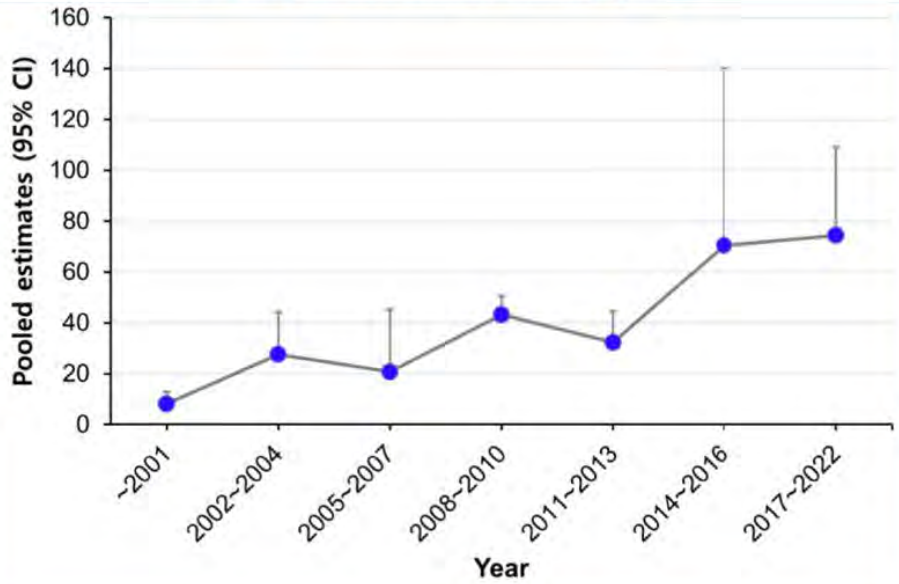
288 million participants

147,668 patients with EoE

Global map
15 countries across the five continents



Time trends of prevalence of EoE
cases per 100,000 inhabitant-years



- **Global incidence of EoE: 5.31 (95% CI, 3.98–6.63)** cases per 100,000 inhabitant-years
- **Global prevalence of EoE: 40.04 (95% CI, 31.10–48.98)** cases per 100,000 inhabitant-years

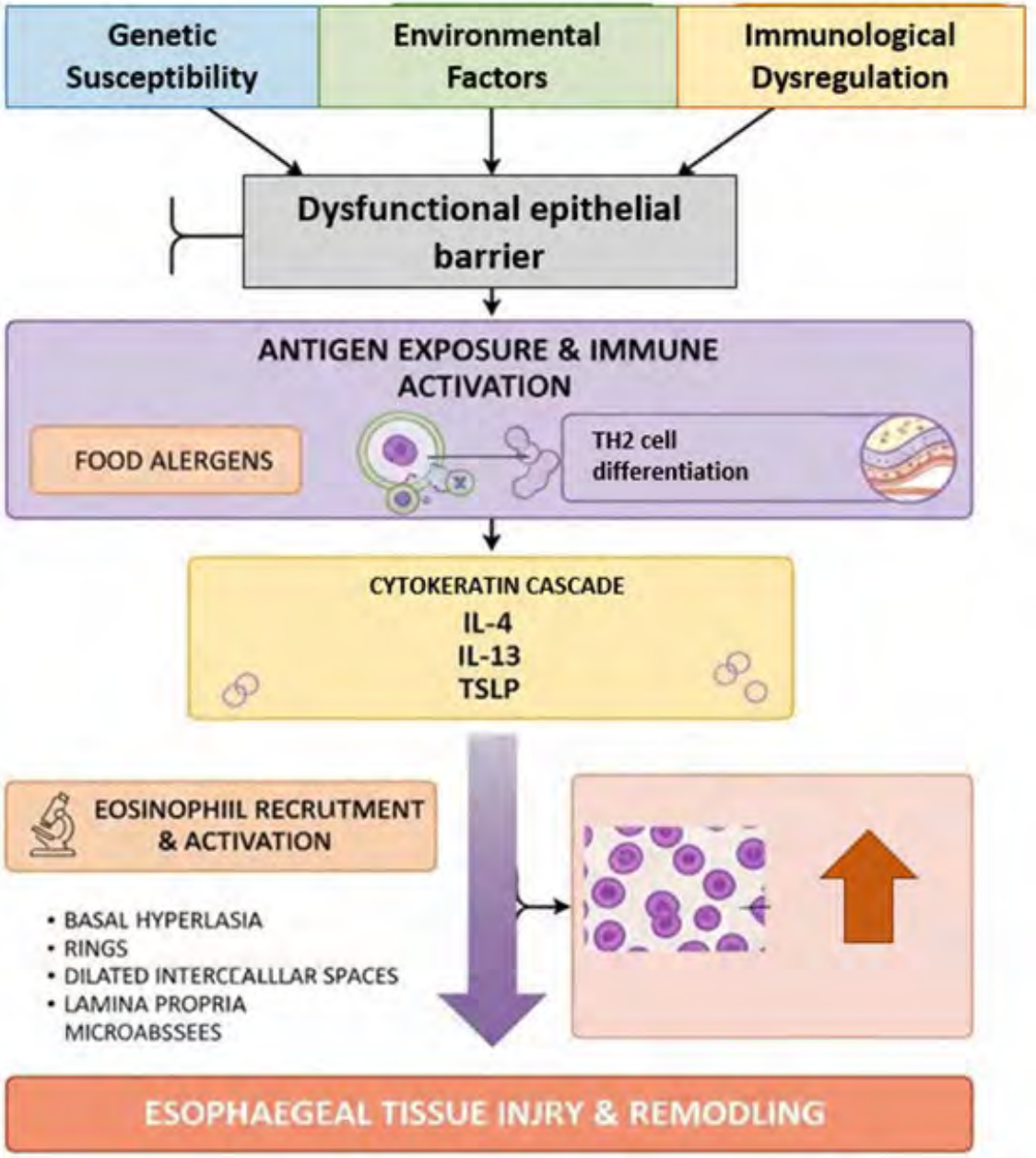
Clinical Gastroenterology and Hepatology

Pathophysiology

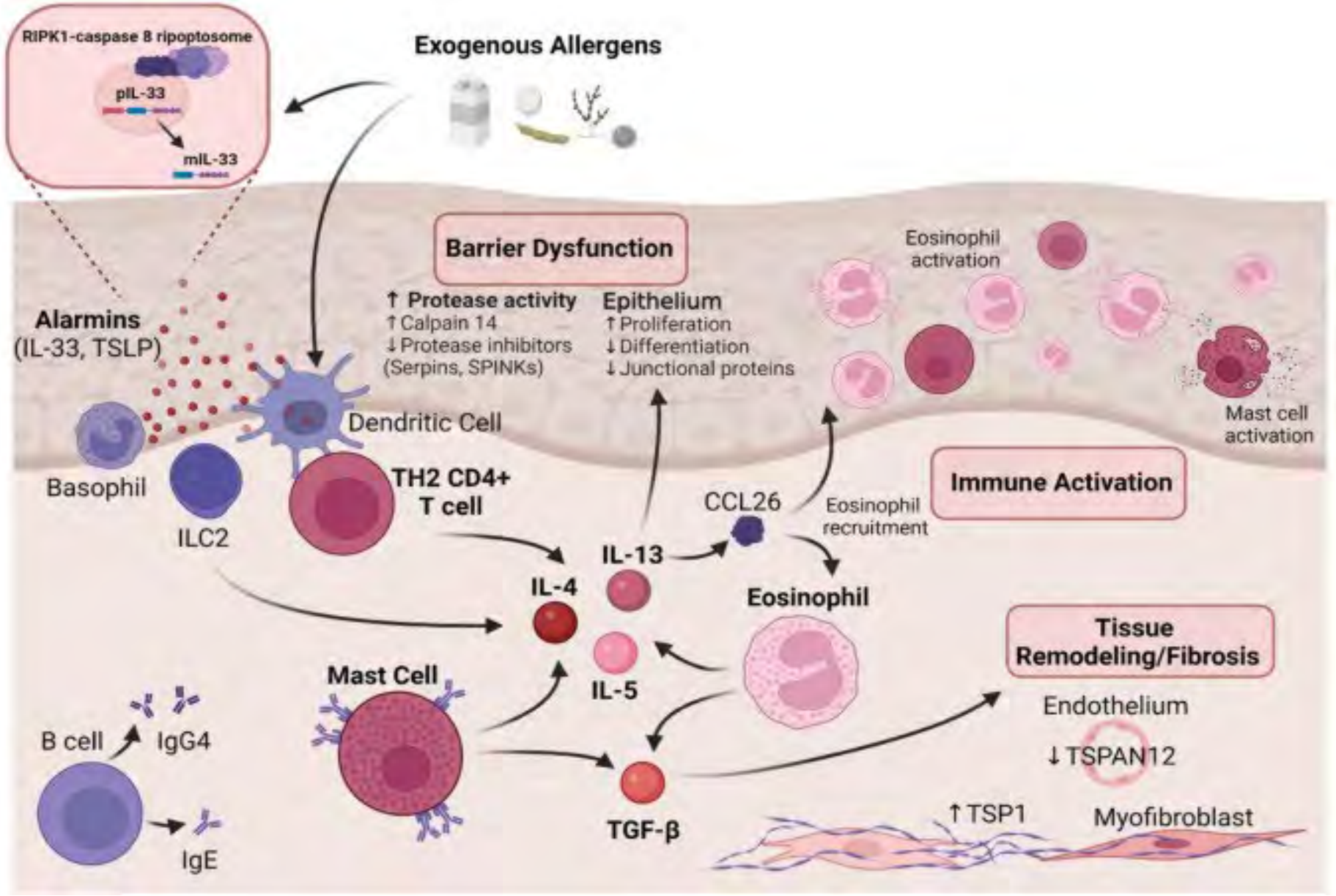
Pathophysiology of EoE

- **Genetic & Epigenetic**
  - Strong genetic susceptibility with several candidate genes identified.
  - **Barrier Dysfunction:** Structural weaknesses in the oesophageal lining allow antigens to penetrate deeper tissues.
- **Environmental Triggers:**
  - Microbiome imbalances and food antigens serve as the primary external drivers of inflammation.
- **The Type 2 Inflammation**
  - Food antigens trigger the release of **TSLP(thymic stromal lymphopoietin)** and **IL-33**.
  - These enhance TH2 inflammation, producing **IL-4, IL-5, and IL-13**.
  - **IL-13** specifically stimulates the release of **eotaxin-3**, the primary chemoattractant that recruits eosinophils to the oesophagus.

Insights into the natural history and disease course of eosinophilic esophagitis .Ketchem, Corey J. et al. Annals of Allergy, Asthma & Immunology, Volume 135, Issue 2, 155 - 161



Salzano, S.; Caltabiano, R.; Zizzo, M.; Fabozzi, M.; Palicelli, A.; Zanelli, M.; Koufopoulos, N.; Troina, G.; Mangiafico, S.; Broggi, G. Eosinophilic Esophagitis: A Review of Histopathological and Diagnostic Aspects. *Diagnostics* **2025**, *15*, 3011

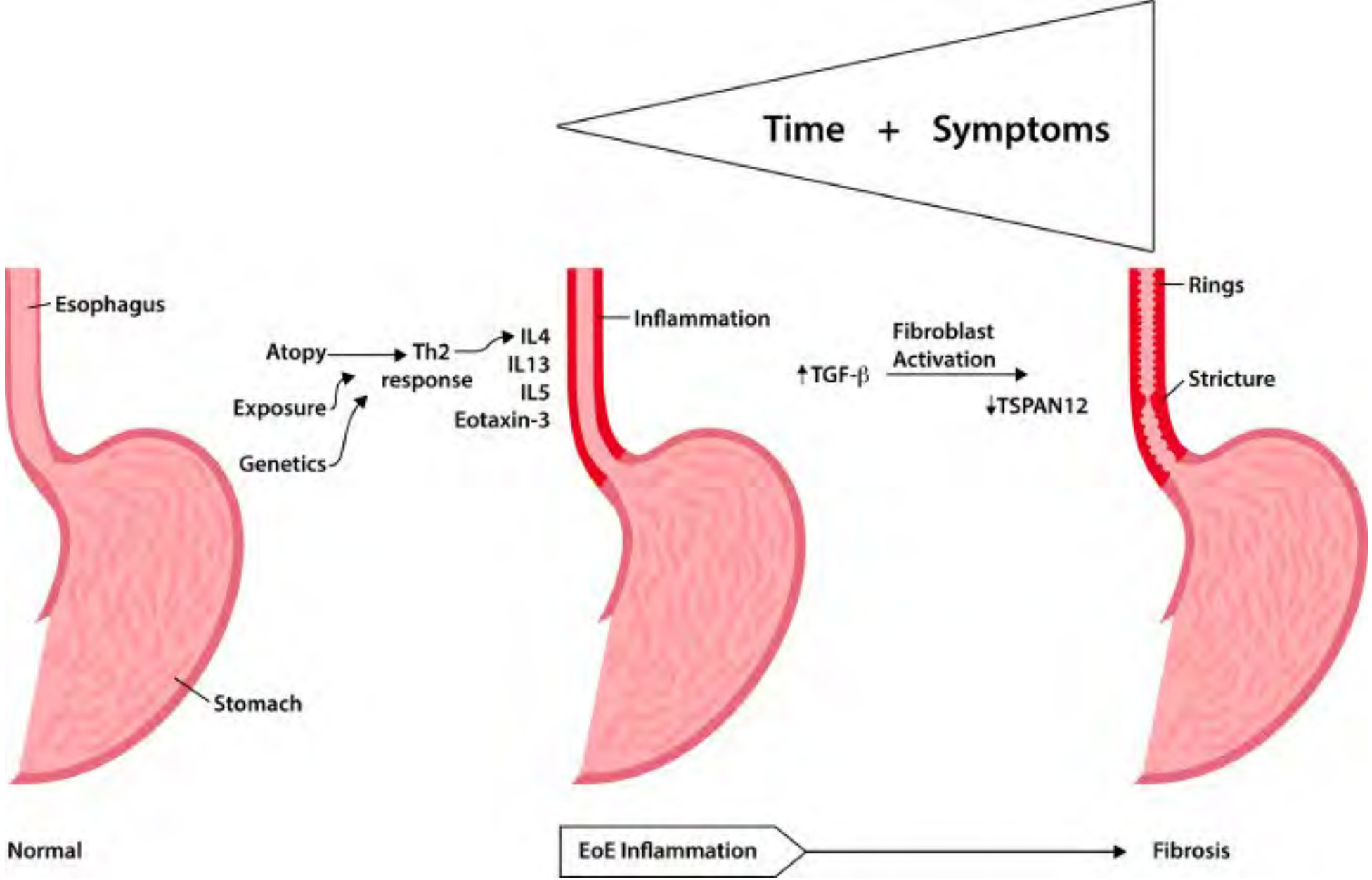


Breaking down the complex pathophysiology of eosinophilic esophagitis.Underwood, Brynne et al. Annals of Allergy, Asthma & Immunology, Volume 130, Issue 1, 28 - 39

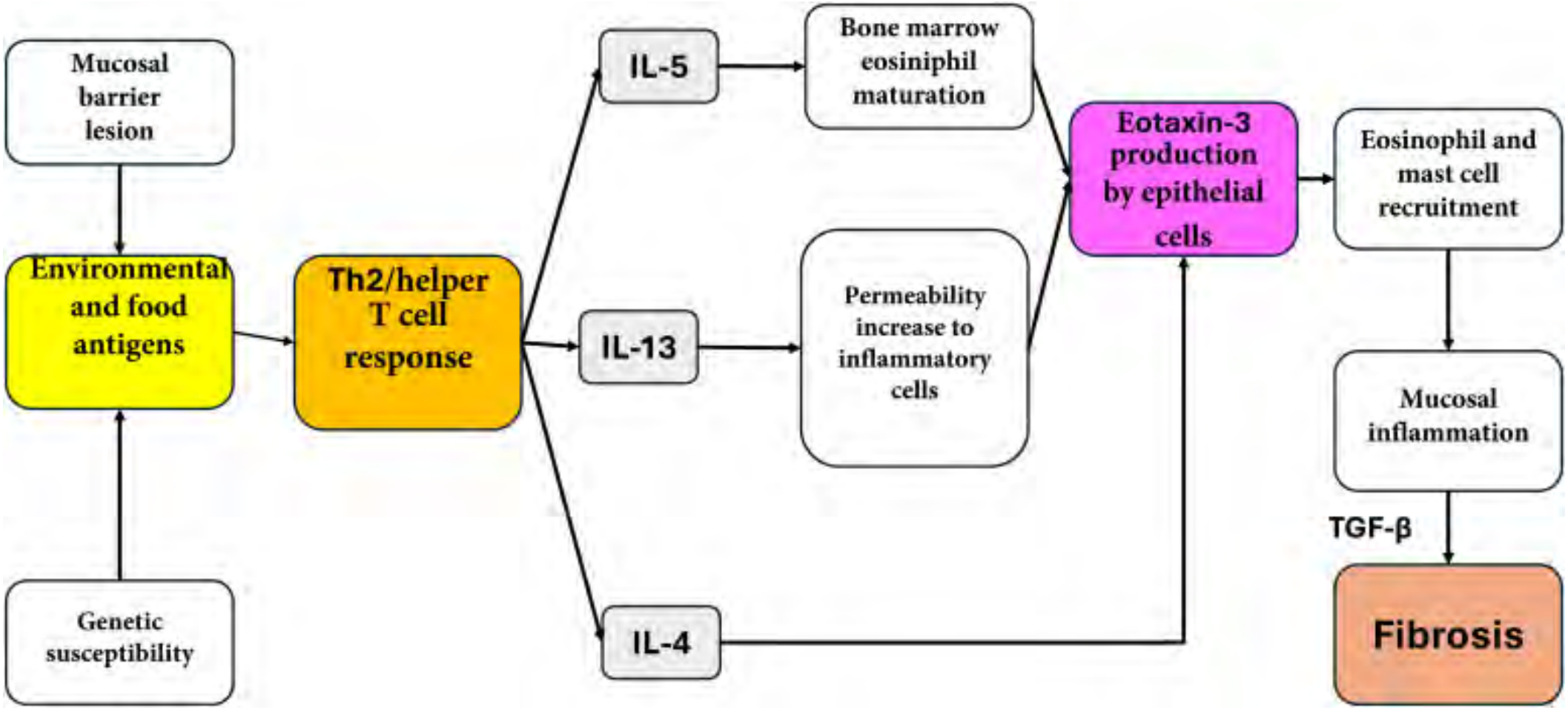
The Mechanism of Oesophageal Remodeling

- **Eosinophil Recruitment:** Recruited eosinophils release potent factors, including **TGF-β**
- **Fibroblast Activation:**
  - Cytokines promote the transition of fibroblasts into **myofibroblasts**.
  - These cells secrete collagen and extracellular matrix components, leading to **tissue remodelling**.
- **The TSPAN12 Factor:**
  - Reduction in **TSPAN12(tetraspanin 12)** expression is linked to higher rates of **fibro-stenosis**.
  - **IL-13** actively decreases TSPAN12, accelerating the scarring process.
- Chronic remodelling results in a non-compliant, stiff oesophagus with impaired motility, directly causing the classic symptoms of dysphagia and food impaction.

Insights into the natural history and disease course of eosinophilic esophagitis .Ketchem, Corey J. et al. Annals of Allergy, Asthma & Immunology, Volume 135, Issue 2, 155 - 161



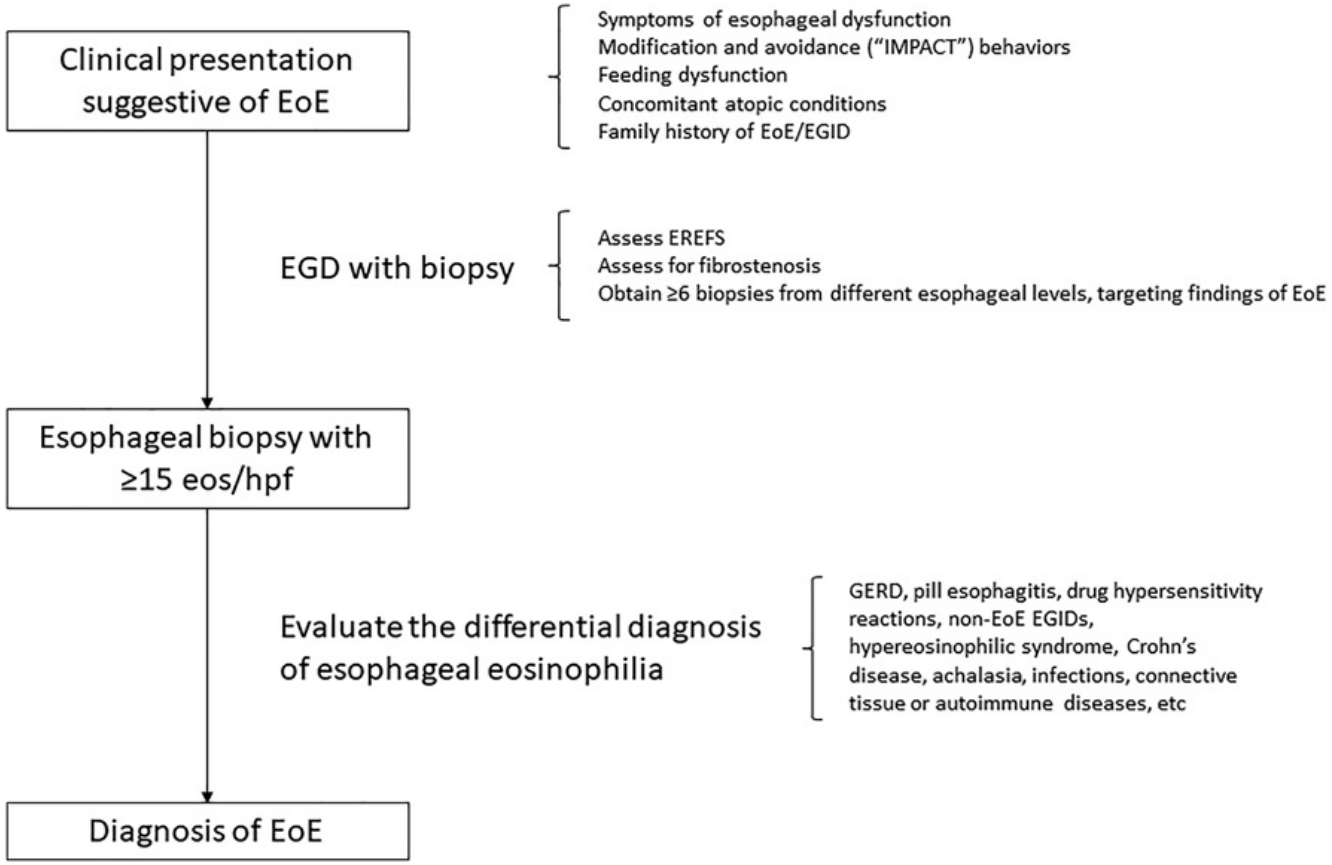
Insights into the natural history and disease course of eosinophilic esophagitis .Ketchem, Corey J. et al. Annals of Allergy, Asthma & Immunology, Volume 135, Issue 2, 155 - 161



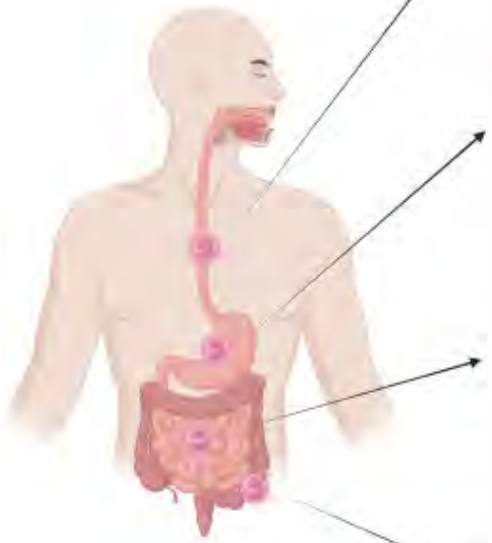
D. García-Compeán, A.R. Jiménez-Rodríguez, C.E. González-Martínez,Eosinophilic esophagitis: Current concepts of pathophysiology, diagnosis, and treatment,Revista de Gastroenterología de México (English Edition),olume 90, Issue 1,2025,

Diagnosis of EOE

Diagnostic Criteria



Symptoms of oesophagus dysfunction



EGIDs	NOMENCLATURE	HISTOLOGY	CARDINAL SYMPTOMS
	Eosinophilic esophagitis (EoE)	≥15 eos/hpf	• Dysphagia • Food impaction • Use of adaptive eating behaviors to cope with dysphagia
	Eosinophilic gastritis (EoG)	≥30-40 eos/hpf	• Recurrent or chronic epigastric pain • Vomiting • Dyspepsia
	Eosinophilic enteritis (EoN)	≥50-60 eos/hpf	• Recurrent or chronic abdominal pain • Diarrhea • Bowel obstruction • Bowel perforation • Ascitis
	Eosinophilic colitis (EoC)	Right colon ≥100 eos/hpf Left colon ≥60 eos/hpf	• Recurrent or chronic abdominal pain • Diarrhea • Bowel obstruction • Bowel perforation • Ascitis

Epidemiology, Natural History, and Treatment of Eosinophilic Gastrointestinal Diseases.Visaggi, Pierfrancesco et al. Gastroenterology, Volume 170, Issue 3, 476 - 494

Modification and Avoidance (IMPACT) Behaviours

Table 4. "IMPACT" behaviors to assess while taking a dysphagia history

Behavior	Description
Imbibe fluids	Drinking a lot of liquids to help get each bite down smoothly
Modify foods	Cutting foods into small pieces or pureeing foods
Prolong meal times	Eating slowly and being the "last one at the table"
Avoid hard texture foods	Meats, crusty breads, and foods with sticky consistencies are often removed from the diet to minimize symptoms
Chew excessively	Thorough chewing to achieve a mush-like consistency to allow easier swallowing
Turn away tablets/pills	Pill dysphagia is a subtle symptom of EoE and may be the only indication of swallowing dysfunction

EoE, eosinophilic esophagitis.
Adapted from Hirano and Furuta. Gastroenterology. 2020;158(4):840–51 (81).

Dellon, Evan S.. ACG Clinical Guideline: Diagnosis and Management of Eosinophilic Esophagitis. The American Journal of Gastroenterology 120(1):p 31-59, January 2025.

Concomitted Atopic Conditions + FHx

- In addition to symptoms, the presence of other atopic diseases, including **immediate-type food allergies**, **asthma, eczema (atopic dermatitis),** and **allergic rhinitis**, should increase the suspicion of EoE.
- At least 60%–80% of patients with EoE will have concomitant allergic conditions.
- The more atopic comorbidities a patient has, the more likely they are to have EoE.
- 1 study showed 1/3 of patients seen in allergy clinics have unrecognized dysphagia or other typical EoE symptoms
- Having a family history of EoE should increase suspicion of EoE

Dellon, Evan S.. ACG Clinical Guideline: Diagnosis and Management of Eosinophilic Esophagitis. The American Journal of Gastroenterology 120(1):p 31-59, January 2025.

Endoscopy with Biopsy

- **Assess EREFS**
- **Assess for fibro-stenosis**
- **Obtain at least 6 oesophageal biopsies from different levels targeting findings of EOE.**

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Endoscopy

- Inspect the entire oesophagus **immediately after intubation**.
- Prevents the scope from accidentally rubbing off or displacing white exudates (plaques) before they are documented.
- **Full Insufflation:** Mandatory to distinguish between transient contractions and fixed structural rings/strictures.
- Gently wash off mucus, saliva, or debris to ensure the mucosal surface is clearly visible.

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Assess EREFS

- **Common Endoscopic Features:**
  - **Edema:** Loss of normal vascular patterns.
  - **Fixed Rings:** "Trachealization" of the esophagus.
  - **Exudates:** White plaques or spots (often mistaken for Candida).
  - **Furrows:** Vertical lines or "tracks" in the mucosa.
  - **Strictures:** Focal narrowing or diffuse luminal reduction.
- **Signs of Advanced Disease:**
  - **Crepe-Paper Mucosa:** Mucosal fragility that tears easily during endoscopy.
  - **The "Tug" or "Pull" Sign:** A firm sensation felt by the endoscopist when taking biopsies, indicating underlying fibrosis.
- While these findings are not pathognomonic, one or more are present in nearly **90%+** of cases. A "normal-looking" oesophagus does NOT rule out EoE; biopsies are still mandatory.

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The EREFS Scoring System

- **What is EREFS?** A validated classification system used to grade the severity of five key features:
  - **E**dema (0–1)
  - **R**ings (0–3)
  - **E**xudates (0–2)
  - **F**urrows (0–2)
  - **S**trictures (0–1)
- Scores range from **0 to 9**. The grade is determined by the "worst appearing area" of the Oesophagus.
  - High accuracy in distinguishing EoE from other disorders.
  - Correlates strongly with treatment response in clinical trials (Goal: EREFS ≤ 2).
- Use of EREFS is **mandatory** for standardizing reporting and tracking disease progression over time.

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Diagnosis and Management of Eosinophilic Esophagitis

Evan S. Dellon, MD MPH FACG; Amanda B. Muir, MD; David A. Katzka, MD FACG; Shailja C. Shah, MD MPH; Bryan G. Sauer, MD MSc FACG; Seema S. Aceves, MD PhD; Glenn T. Furuta, MD; Nirmala Gonsalves, MD FACG; Ikuo Hirano, MD FACG

Concept and Content: Erica Duh, MD | **Reviewer:** Evan S. Dellon, MD, MPH FACG

Diagnosis

EoE is diagnosed based on the presence of:

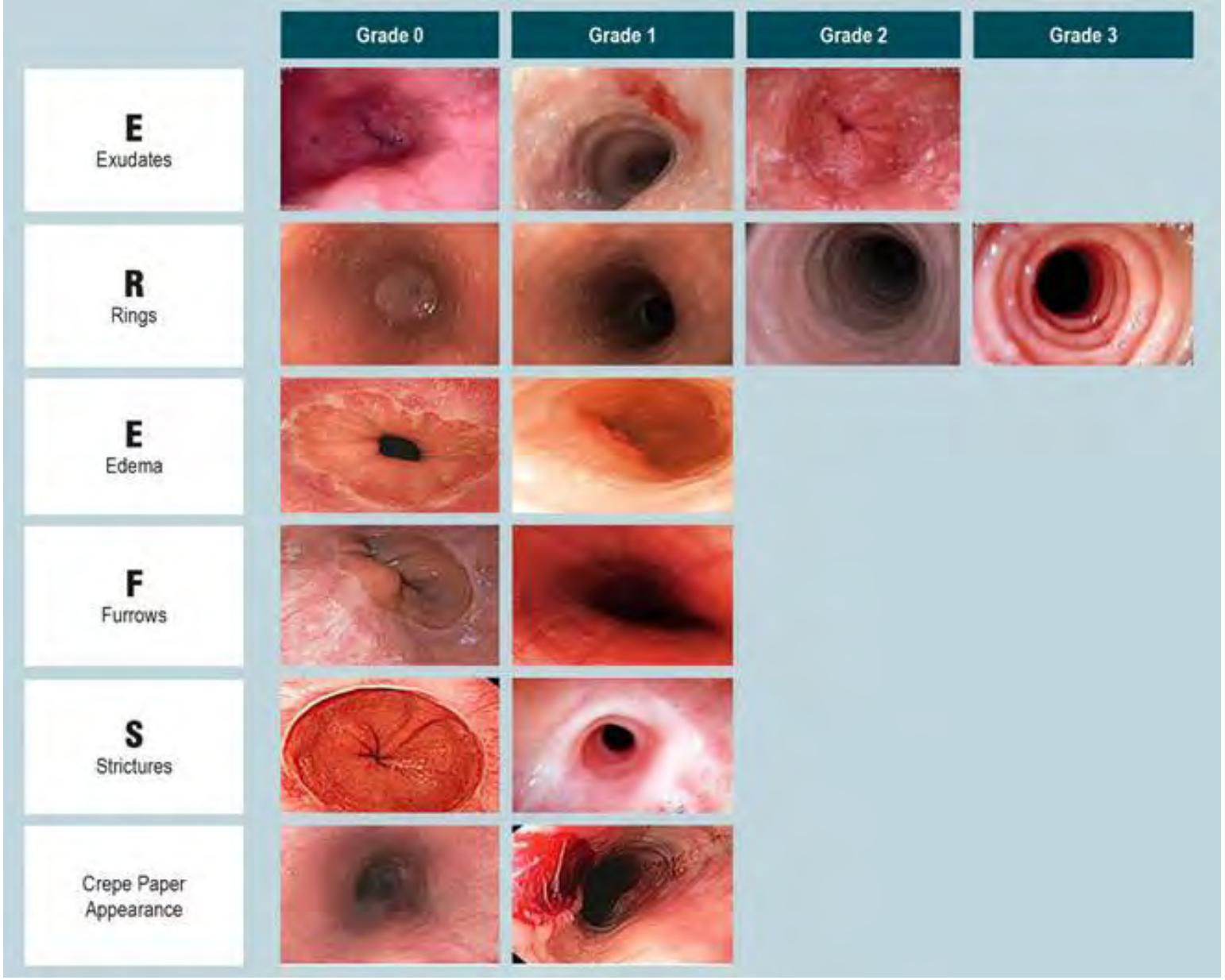
1. Symptoms of esophageal dysfunction
2. ≥15 eosinophils per high-power field on biopsy
3. Evaluation for non-EoE disorders that can contribute to esophageal eosinophilia

Use the EoE Endoscopic Reference Score (EREFS) to systematically assess endoscopic findings of EoE during each endoscopy

Edema	1: Present (decreased vascularity)		
Rings	1: Mild (ridges)	2: Moderate (does not impede scope passage)	3: Severe (standard scope does not pass)
Exudates	1: ≤10% of surface area	2: >10% of surface area	
Furrows	1: Mild	2: Severe (with appreciable depth)	
Stricture	1: Present; also estimate diameter in mm		

Obtain at least 6 targeted biopsies from 2 esophageal levels!

- Quantify number of eosinophils on biopsies from every endoscopy!



CASTANO, Rodrigo et al . Eosinophilic Esophagitis and Clinical, Endoscopic, and Therapeutic Differences Between Adolescents and Adults. **Rev. colomb. Gastroenterol**

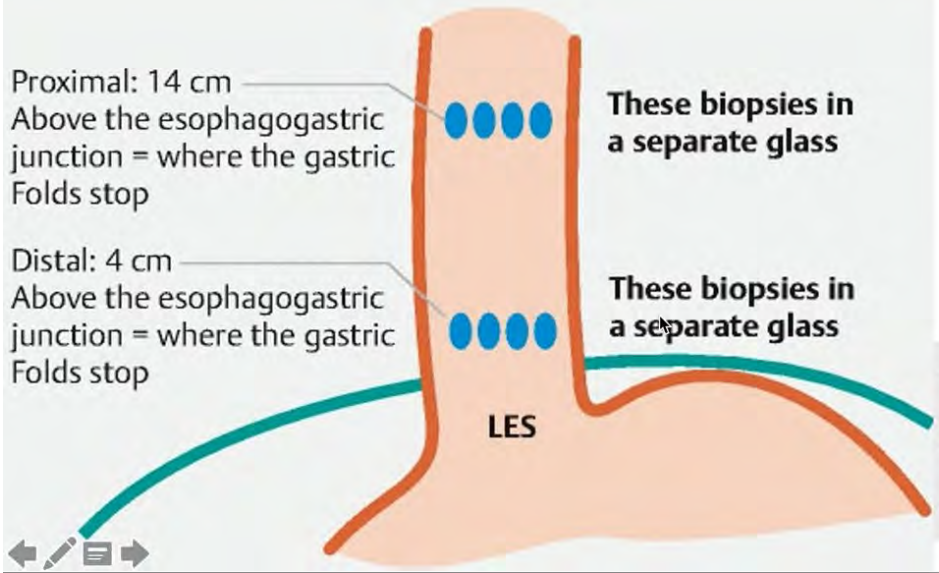
Biopsy Strategy for EoE

- EoE inflammation is non-uniform it can be a patchy disease
  - **6+ biopsies** are required to reach nearly **100% diagnostic sensitivity**.
  - Obtaining only 1–2 biopsies significantly increases the risk of a false negative.
- **Targeting Technique:**
  - Target areas with visual inflammation, specifically **furrows or exudates**, to increase yield.
  - Obtain 2–4 biopsies from at least **two distinct levels** (proximal and distal esophagus).
- **Biopsy at Food Impaction:** * Mandatory to biopsy once the bolus is cleared during emergency endoscopy.
  - This is often the only time these patients interact with GI; failing to biopsy leads to significant delays in diagnosis.

Dellon, Evan S.. ACG Clinical Guideline: Diagnosis and Management of Eosinophilic Esophagitis. The American Journal of Gastroenterology 120(1):p 31-59, January 2025.

Biopsy Protocol

Biopsy protocol for **all** patients with DYSPHAGIA **regardless** of a macroscopic normal mucosa.
REMEMBER 4 – 14 – 4
Take 4 biopsies 14 cm and 4 cm above the esophago-gastric junction.
15 % will have eosinophilic esophagitis regardless of other comorbidity.



The 4-14-4 biopsy protocol for improving the diagnosis of eosinophilic esophagitis.

This strategy is the result of the consensus meeting for the endoscopy leaders in the North Danish Region, September 2011.

Krarup et al. Endoscopy 2021; 53(01): 15-24 DOI: 10.1055/a-1206-0852

Histologic Quantification & Reporting

- Pathologists should report exact peak counts, not just ">15."
  - A drop from 200 to 20 eos/hpf indicates a strong treatment response, whereas 200 to 150 suggests failure. Both technically remain ">15."
- Because microscope field sizes vary, **eosinophil density (60 eos/mm^2)** is more accurate than "per high-power field (hpf)," though hpf remains the current clinical standard.
- Quantification must be performed for **every** endoscopy to accurately gauge the anti-inflammatory effect of therapy.

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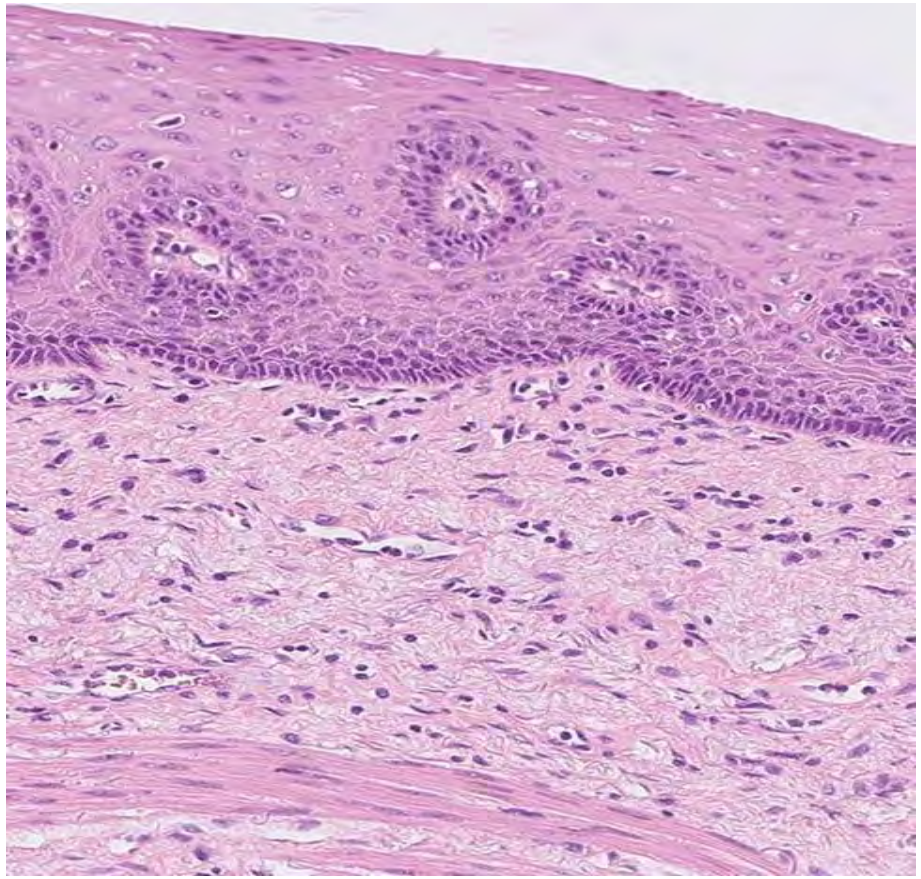
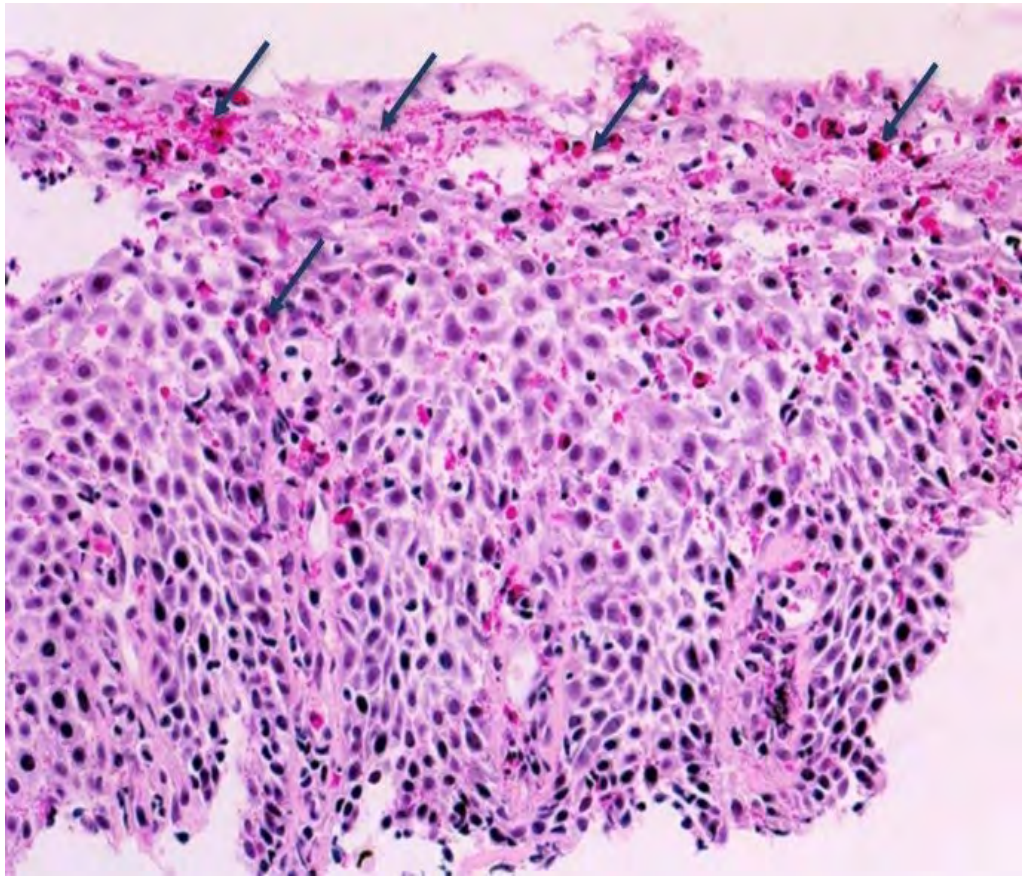
Histology





von Arnim, U. Eosinophilic esophagitis—from definition to therapy. *Allergo J Int* **33**, 1–8 (2024).

Beyond the Eosinophil

- Recent trials show that depleting eosinophils alone does not always resolve symptoms or endoscopic signs.
- **The EoE Histologic Scoring System (EoEHSS):**
  - Evaluates **8 features**, not just eosinophils (e.g., Basal zone hyperplasia, Abscesses, surface Layering).
  - Assesses both **Grade** (severity) and **Stage** (extent).
- **Clinical Drivers:**
  - **Basal Zone Hyperplasia:** Associated with ongoing symptoms.
  - **Lamina Propria Fibrosis:** A critical marker for remodeling and stricture risk.
- Expect a transition from simple eosinophil counting to a more holistic assessment of oesophageal tissue via EoEHSS.

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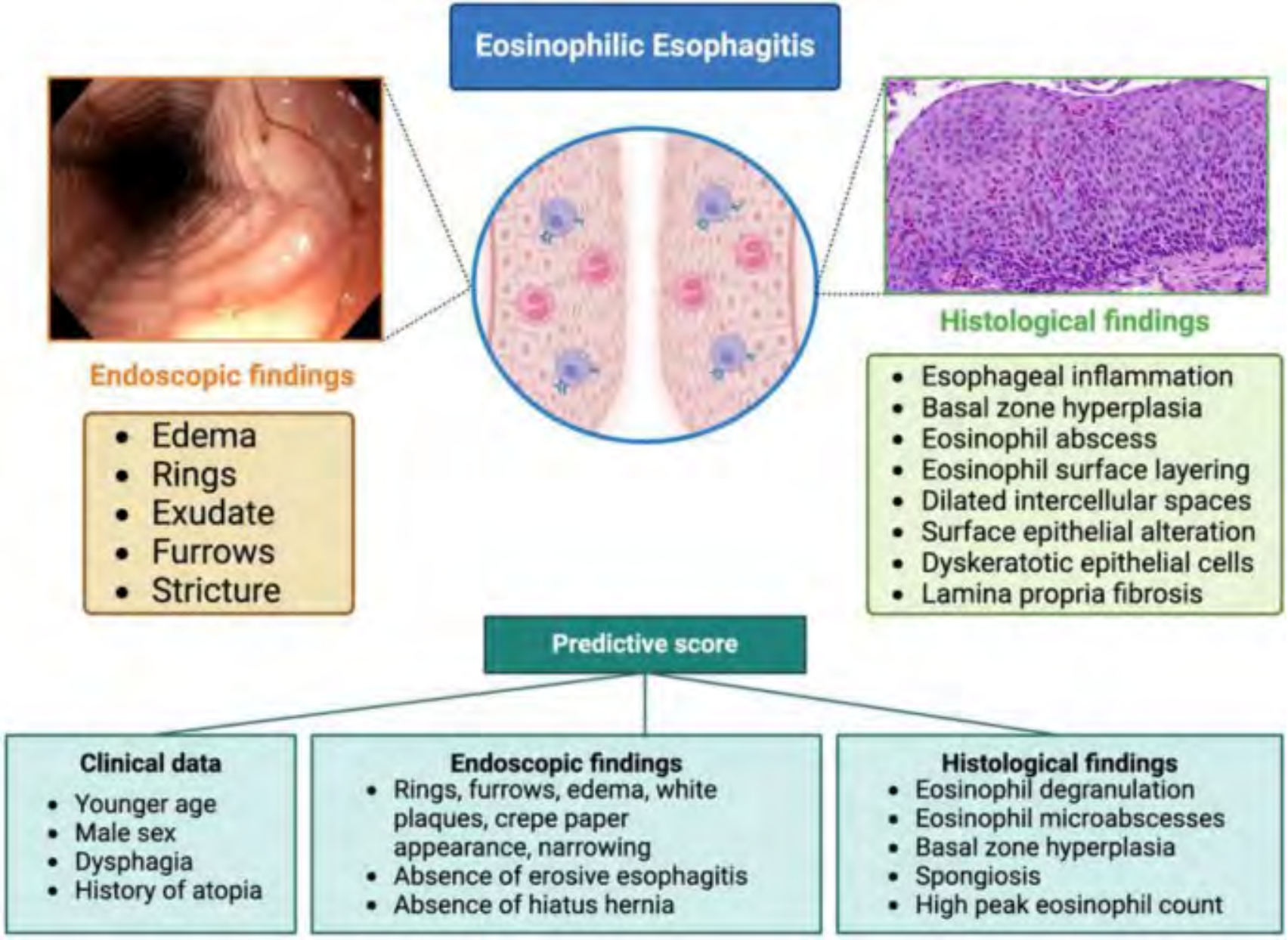
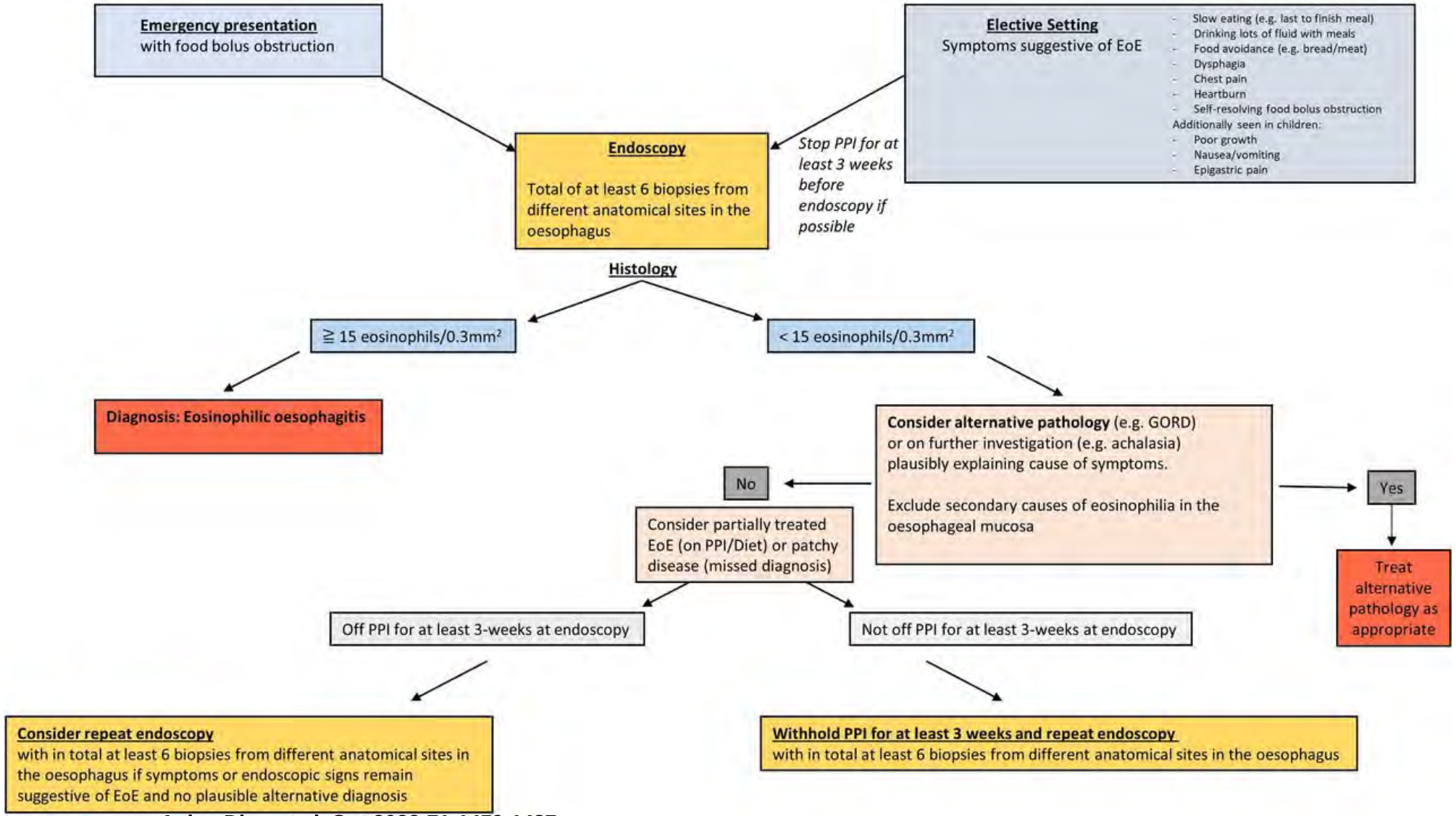


Rossi, C.M., Lenti, M.V., Santacroce, G. *et al.* Eosinophilic oesophagitis in adults: from symptoms to therapeutic options. *Intern Emerg Med* **20**, 655–665 (2025)

Eosinophilic oesophagitis diagnostic algorithm in emergency and elective settings.



Anjan Dhar et al. Gut 2022;71:1459-1487

Management

The Goals of EoE Treatment

- **Quality of Life Goals:**
  - Resolution of symptoms (dysphagia, chest pain).
  - Prevention of emergencies: Food impactions and oesophageal perforations.
  - In children: Ensuring normal growth, development, and adequate nutrition.
- **Biologic & Structural Goals:**
  - **Inflammation:** Normalize endoscopic (EREFS) and histologic (Eos count) appearance.
  - **Fibrosis:** Address and reverse oesophageal stricturing and remodelling.
- **The Dual-Treatment Strategy:**
  - **Anti-inflammatory (Diet/Meds):** Treats the underlying cause and can improve oesophageal calliber over time.
  - **Mechanical (Dilation):** Directly treats strictures and luminal narrowing for immediate symptom relief.

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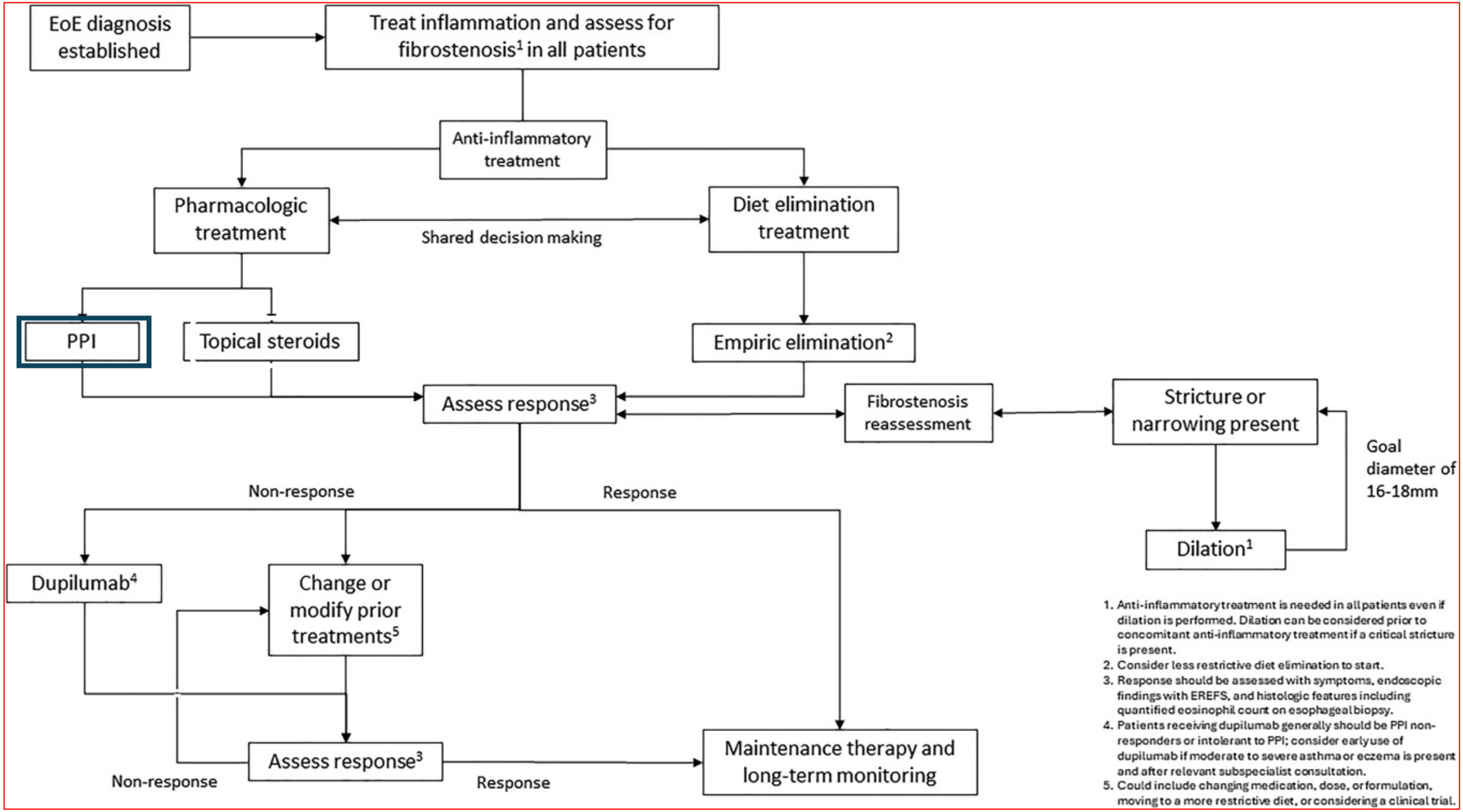
EoE diagnosis established
Treat inflammation and assess for fibrostenosis[1] in all patients
Anti-inflammatory treatment
Pharmacologic treatment
Shared decision making
Diet elimination treatment
PPI
Topical steroids
Empiric elimination[2]
Assess response[3]
Fibrostenosis reassessment
Stricture or narrowing present
Goal diameter of 16-18mm
Dilation[1]
Non-response
Response
Dupilumab[4]
Change or modify prior treatments[5]
Assess response[3]
Non-response
Response
Maintenance therapy and long-term monitoring
1. Anti-inflammatory treatment is needed in all patients even if dilation is performed. Dilation can be considered prior to concomitant anti-inflammatory treatment if a critical stricture is present.
2. Consider less restrictive diet elimination to start.
3. Response should be assessed with symptoms, endoscopic findings with EREFS, and histologic features including quantified eosinophil count on esophageal biopsy.
4. Patients receiving dupilumab generally should be PPI non-responders or intolerant to PPI; consider early use of dupilumab if moderate to severe asthma or eczema is present and after relevant subspecialist consultation.
5. Could include changing medication, dose, or formulation, moving to a more restrictive diet, or considering a clinical trial.

Proton Pump Inhibitors(PPIs)

- **Mechanism:** PPIs do more than block acid; they actively target EoE inflammation by:
  - Decreasing **eotaxin-3** expression (the primary cytokine recruiting eosinophils).
  - Repairing and improving oe**sophageal barrier function**.
  - Maintaining epithelial "homeostasis" (transcriptional balance).
- Patients often associate PPIs only with reflux. It is vital to explain these **anti-inflammatory** roles to ensure adherence, even if the patient has no heartburn symptoms.
- 60.8% of patients show symptomatic improvement.
- **Histologic Remission:** 50.5% achieve <15 eos/hpf.
- Trials show PPIs are effective as topical steroids (fluticasone) in reducing eosinophil counts and dysphagia.

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Treatment for Eosinophilic Esophagitis

Shared Decision Making

Use shared decision making to select first line dietary (empiric elimination) or pharmacologic (PPI or topical steroids) therapy.

Dietary Elimination

An empiric food elimination diet is suggested for treatment of EoE.

- Consider starting with a less restrictive empiric elimination (1FED or 2FED) initially

Allergy testing to direct food elimination diets is not currently suggested

Trials show that 1FED has similar response rates to more restrictive diets

Endoscopic Dilation

Esophageal dilation should be used in parallel with anti-inflammatory therapy in patients with esophageal strictures and dysphagia, and not used as monotherapy.

PHARMACOLOGIC THERAPY

Proton Pump Inhibitors

- Adults: Omeprazole 20 mg BID or 40 mg daily or equivalent
- Children: 2mg/kg/day (or 1mg/kg twice daily)

Swallowed Topical Steroids

Budesonide

- Adults: 2-4 mg/day
- Children: 1-2 mg/day

Fluticasone

- Adults: 1760 mcg/day in a divided dose
- Children 110-880mcg/day in a divided dose

A trial comparing budesonide to fluticasone showed similar efficacy; choice of topical steroid depends on local availability and patient/provider preference

Dupilumab: Consider for patients who are non-responsive to PPI treatment and for step-up therapy in most cases.

- ≥40 kg: 300 mg subq every week
- 30 to <40 kg: 300 mg subq every other week
- 15 to <30 kg: 200 mg subq every other week

Monitoring Response

Assess symptoms, esophageal biopsies for histologic findings, and endoscopic features (EREFS). Symptoms should not be monitored in isolation.

Maintenance Therapy

Continue effective dietary or pharmacologic therapy to prevent recurrence of symptoms, histologic inflammation, and endoscopic abnormalities

Pediatric Considerations

- Dysphagia in a child with EoE? Consider an esophagram
- Consider evaluation by a feeding therapist and/or dietician as an adjunct therapeutic intervention in those with feeding dysfunction

BID = twice a day
EoE = eosinophilic esophagitis
Eos = eosinophils
EREFS = EOE Endoscopic Reference Score
FED = food elimination diet
Hpf = high power field
Subq = subcutaneous

Dosing Strategies & Safety

- **Initial Treatment ("High-Dose"):** Usually double the standard GERD dose).
- Studies suggest **twice-daily** dosing is significantly more effective for inducing remission (up to 54%) compared to once-daily (10–12%) in some cohorts.
    - Once remission is achieved, some patients (up to 80%) can successfully "step down" to once-daily dosing, though 30% may relapse and require dose escalation.
- **Long-Term Safety Profile:** A massive 10-year study of over 17,000 participants found **no increased risk** for: * Chronic kidney disease, dementia, or bone fractures. Pneumonia, COPD, or diabetes.
    - Only a slight increase in *Clostridium difficile* (C. diff) infections was associated with long-term use.

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PCABs and H2RAs in EoE

- **Potassium-Competitive Acid Blockers (PCABs):**
  - Preliminary data available; formal clinical trials are expected.
  - A retrospective analysis of 118 patients compared **Vonoprazan** to standard PPIs (Rabeprazole, Esomeprazole).
- **PCAB Performance vs. PPIs:**
  - 72.7% (comparable to PPIs).
  - Average 2-point reduction in EREFS (endoscopic reference score).
  - **Histologic Remission:** 39.4% achieved complete remission.
- **H2 Receptor Antagonists (H2RAs):**
  - There are currently **no data** to suggest that H2 blockers (e.g., Famotidine) are effective for treating EoE.

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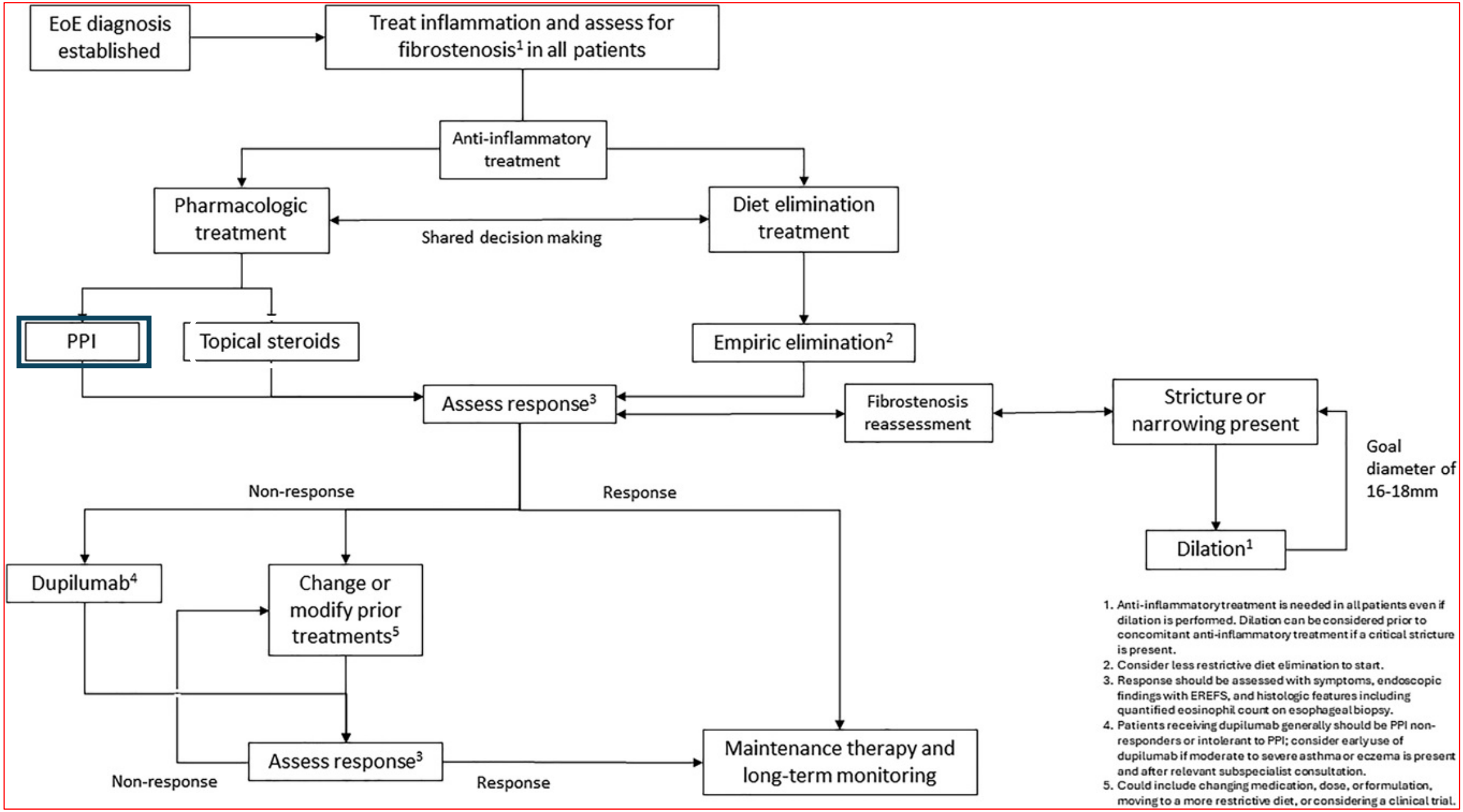
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5. Could include changing medication, dose, or formulation, moving to a more restrictive diet, or considering a clinical trial.

Swallowed Topical Corticosteroids (STCs)

- Designed to "coat" the oesophagus with anti-inflammatory medication, similar to applying steroid cream to atopic dermatitis.
- Over 13 randomized, double-blind trials confirm STCs are superior to placebo.
- **Histologic Response :**
  - Meta-analyses show **60%–70%** response rates.
  - Recent Phase 3 trials for specialized formulations (BOS and BOT) show response rates between **62% and 95%**.
- **Formulations:**
  - **BOS (Budesonide Oral Suspension):** FDA-approved (2024).
  - **BOT (Budesonide Orodispersible Tablet):** EMA-approved (2018).

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Treatment for Eosinophilic Esophagitis

Shared Decision Making

Use shared decision making to select first line dietary (empiric elimination) or pharmacologic (PPI or topical steroids) therapy.

Dietary Elimination

An empiric food elimination diet is suggested for treatment of EoE.

- Consider starting with a less restrictive empiric elimination (1FED or 2FED) initially

Allergy testing to direct food elimination diets is not currently suggested

Trials show that 1FED has similar response rates to more restrictive diets

Endoscopic Dilation

Esophageal dilation should be used in parallel with anti-inflammatory therapy in patients with esophageal strictures and dysphagia, and not used as monotherapy.

PHARMACOLOGIC THERAPY

Proton Pump Inhibitors

- Adults: Omeprazole 20 mg BID or 40 mg daily or equivalent
- Children: 2mg/kg/day (or 1mg/kg twice daily)

Swallowed Topical Steroids

Budesonide

- Adults: 2-4 mg/day
- Children: 1-2 mg/day

Fluticasone

- Adults: 1760 mcg/day in a divided dose
- Children 110-880mcg/day in a divided dose

A trial comparing budesonide to fluticasone showed similar efficacy; choice of topical steroid depends on local availability and patient/provider preference

Dupilumab: Consider for patients who are non-responsive to PPI treatment and for step-up therapy in most cases.

- ≥40 kg: 300 mg subq every week
- 30 to <40 kg: 300 mg subq every other week
- 15 to <30 kg: 200 mg subq every other week

Monitoring Response

Assess symptoms, esophageal biopsies for histologic findings, and endoscopic features (EREFS). Symptoms should not be monitored in isolation.

Maintenance Therapy

Continue effective dietary or pharmacologic therapy to prevent recurrence of symptoms, histologic inflammation, and endoscopic abnormalities

Pediatric Considerations

- Dysphagia in a child with EoE? Consider an esophagram
- Consider evaluation by a feeding therapist and/or dietician as an adjunct therapeutic intervention in those with feeding dysfunction

BID = twice a day
EoE = eosinophilic esophagitis
Eos = eosinophils
EREFS = EOE Endoscopic Reference Score
FED = food elimination diet
Hpf = high power field
Subq = subcutaneous

Clinical Outcomes and Safety

- **Symptom Relief:** Most trials show significant improvement in dysphagia, though results vary due to different measurement tools (PROs).
- Uniformly improves EREFS (Endoscopic Reference Score) across all Phase 2 and 3 trials.
- **Off-Label vs. Dedicated Preparations:** Asthma preparations (MDI inhalers) have shown comparable histologic efficacy to the newer, oesophageal-specific products.
- **Candidiasis :**The most common side effect.
  - Rates range from **3.8% (BOS) to 23.7% (BOT)**.
  - Most cases are asymptomatic and can be managed with antifungals or dose reduction.

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Practical Considerations & Recommendations

- Use either **Fluticasone propionate** or **Budesonide**
- A head-to-head trial showed no significant difference between Budesonide slurry (OVB) and Fluticasone MDI:
  - Histologic response: 71% (Budesonide) vs. 64% (Fluticasone).
- **Non-Responders:** Predictors of poor response include:
  - Oesophageal dilation history.
  - "Extremely narrow caliber" esophagus phenotype.

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Best Practices for STC Administration

The "30-Minute Rule": * **Nothing by mouth** (food, water, or gum) for 30 minutes post-dose.

- Ensures maximum contact time between the medication and the esophageal mucosa.

- **Swallowed Fluticasone (MDI) Technique:**
  - Must **not** use a spacer; Must **not** inhale into the lungs.
  - Actuate the inhaler into the mouth while performing a **dry swallow**.
- **Oral Viscous Budesonide (Slurry) Preparation:**
  - Mix budesonide respules with a thick vehicle (e.g., 5 packets of sucralose or 1–2 tsp of honey/syrup).
  - The goal is a "maple syrup" consistency to slow the transit time.
- **Candidiasis Prevention:**
  - After the 30-minute waiting period, patients should **rinse and spit** with water to clear residual steroid from the oral cavity

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Swallowed Topical Corticosteroids (STC)

- **Comparative Efficacy:**
  - **Budesonide:** 71% Histologic Remission.
  - **Fluticasone:** 64% Histologic Remission.
- **The Candida Paradox:**
  - Esophageal candidiasis (thrush) is the most common side effect.
  - **Clinical Marker:** Patients with candidiasis are **6x more likely** to achieve histologic remission.
  - **Significance:** Serves as a surrogate marker for high drug exposure and good patient adherence.
- **Systemic Steroids:** Explicitly **not indicated** as first-line therapy for inducing remission in EoE.

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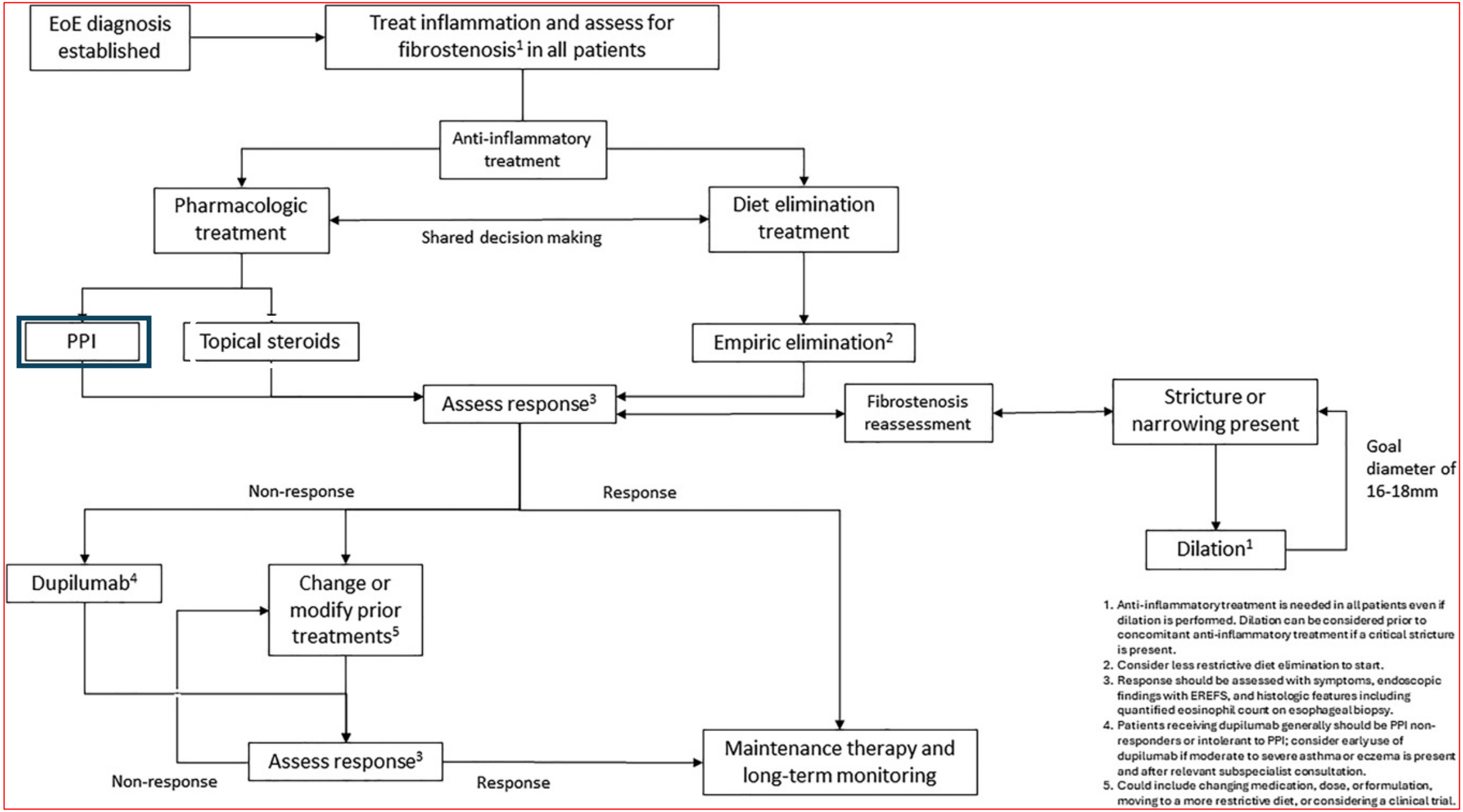
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Dietary Elimination Therapy

- First proven effective in 1995; 10/10 peadiatric patients responded to elemental formula, confirming EoE is triggered by food antigens.
- **Histologic Response:** 90–94% (highest of all interventions).
  - **Adult Outcomes:** 72% histologic response, though symptoms and strictures may persist.
- **Significant Barriers:**
  - **Palatability:** Poor taste often leads to non-adherence (38% failure in adults).
  - **Logistics:** High cost, limited insurance coverage, and potential need for feeding tubes (G-tubes).
  - **Quality of Life:** Extremely restrictive; requires intensive dietitian monitoring for nutritional deficits.

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Empiric Elimination Diets (6FED)

- **The Six-Food Elimination Diet (6FED):** Removes animal milk (dairy), wheat, egg, soy, nuts/peanuts, and fish/shellfish.
- **Clinical Success:**
  - **Histologic Remission:** 70% across multiple meta-analyses.
  - **Symptom Improvement:** Up to 94% of patients report reduced symptoms.
- **Milk (Dairy)** is the most common trigger (50–62%).
  - **Wheat** is the second most common (29–60%).
- Better patient acceptance, lower cost, and improved adherence compared to liquid-only diets.

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Step-Up Approach of Elimination Diets

- **The "Step-Up" Method:** * Starts with a **2-food elimination (2FED)**: Dairy and Wheat.
  - **43% success rate**; non-responders move to 4FED, then 6FED.
  - **Efficiency:** Reduces endoscopies and trigger identification time by 20%.
- **(1FED vs. 4FED/6FED):**
  - Single-food elimination (Milk only) shows histologic response rates of 34–44%.
  - While 6FED achieves "complete" remission more often, 1FED is often easier for families to maintain.
- Choice depends on patient resources, family lifestyle, and adherence capability.
  - **Shared Decision Making:** Providers must discuss the trade-off between diet restrictiveness and the number of required follow-up endoscopies.

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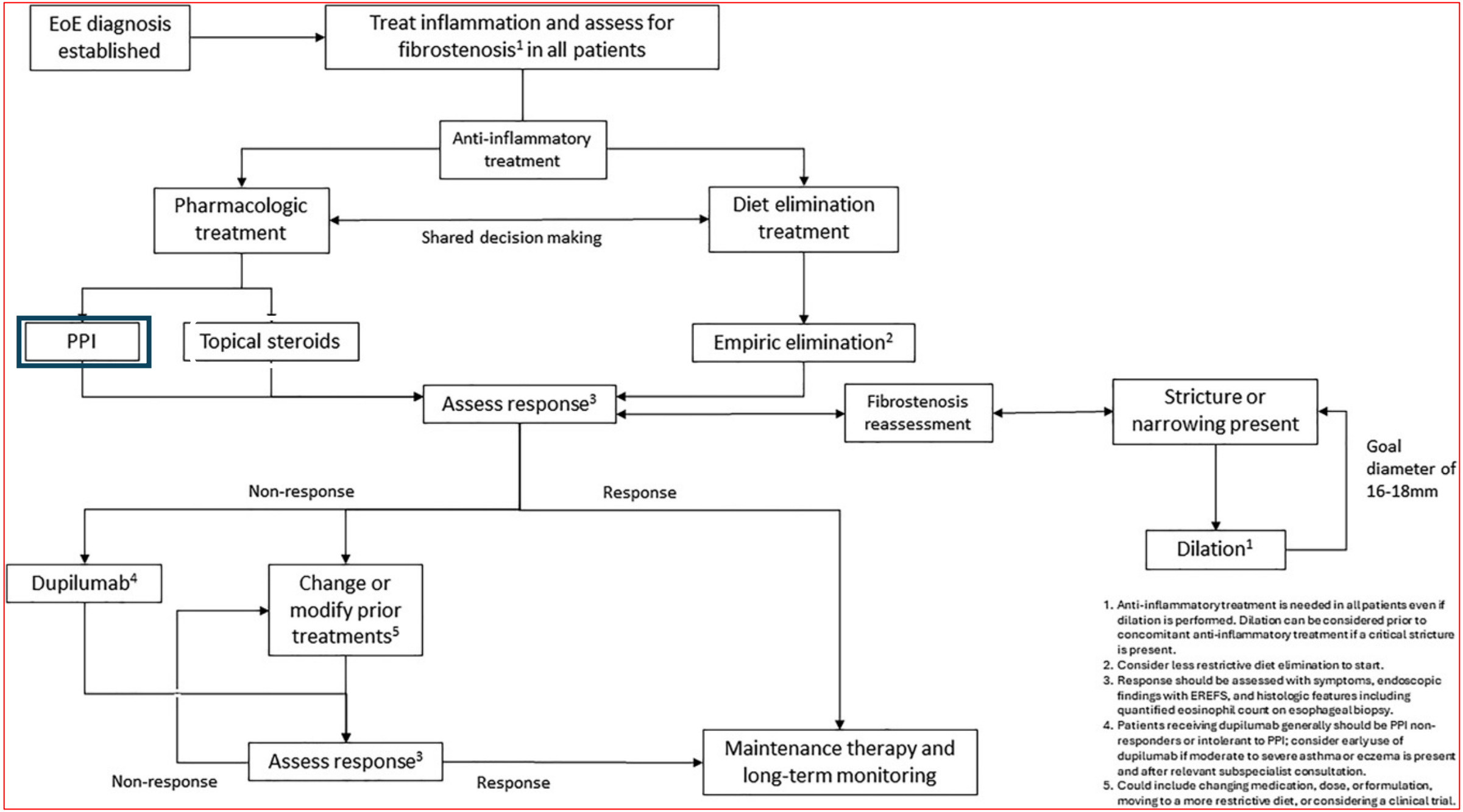
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Biologics

Dupilumab (Anti-IL-4rα)

- **The First FDA-Approved Biologic for EoE**
- **Mechanism:** Monoclonal antibody targeting the IL-4 receptor alpha; blocks **IL-4 and IL-13**, the primary drivers of Type 2 inflammation.
- **Dosing:**
  - **Adults/Adolescents (≥12 yrs, ≥40kg):** 300 mg subcutaneous injection **weekly**.
  - **Children (1–11 yrs, ≥15kg):** Weight-based dosing every **two weeks**.
- **Clinical Efficacy (Phase 3 Trials):**
  - **Histologic Remission (≤6 eos/hpf):** ~60% in adults/adolescents; ~68% in children (higher-dose group).

  Significant reduction in Dysphagia Symptom Questionnaire (DSQ) scores.
  - Improved EREFS and oesophageal caliber (increased diameter).
- Well-tolerated; most common side effect is **injection site reaction**.

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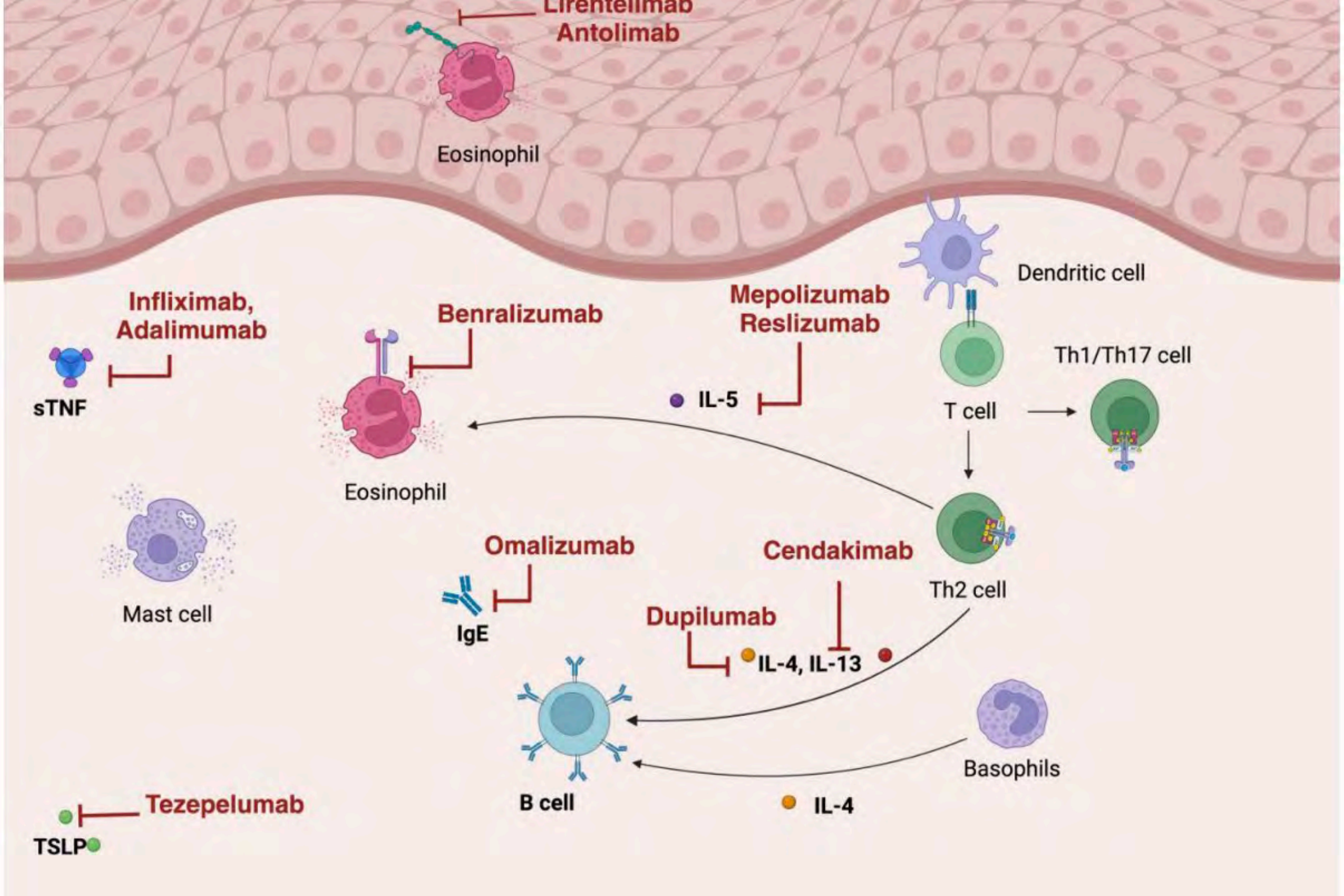
Lirentelimab
Antolimab
Eosinophil
Dendritic cell
Infliximab,
Adalimumab
sTNF
Benralizumab
Mepolizumab
Reslizumab
IL-5
T cell
Th1/Th17 cell
Eosinophil
Mast cell
Omalizumab
IgE
Cendakimab
Th2 cell
Dupilumab
IL-4, IL-13
Basophils
B cell
IL-4
Tezepelumab
TSLP

Clinical Considerations for Biologics

- **Who is the Ideal Candidate?**
- **Patient Profile:** Primarily recommended for patients who are **nonresponsive to PPI therapy** or have refractory/severe disease.
- **Generalizability:** Pivotal trials focused on moderate-to-severe patients (mean disease duration of 5 years; 40% required prior dilation).
- **Special Considerations:**
  - **Real-World Success:** Effective even in patients with "critical strictures" who were excluded from initial clinical trials.
  - **Cost & Access:** Remains a significant barrier; recommendations are "conditional" partly due to high cost and insurance hurdles.
  - **Atopic Patients:** Excellent choice for patients with comorbid asthma, atopic dermatitis, or nasal polyps.

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Investigational & Ineffective Biologics

- **Cendakimab (Anti-IL-13):**
  - Phase 3 trials ongoing.
  - Phase 2 showed significant reduction in eosinophil counts and improved endoscopic appearance.
- **Eosinophil-Depleting Agents (Anti-IL-5 / Anti-Siglec-8):**
  - **Meds:** Benralizumab, Lirentelimab, Mepolizumab, Reslizumab.
  - **The Paradox:** These achieve **near-complete eosinophil depletion** histologically, but often **fail to improve symptoms** significantly better than placebo.
  - **Clinical Note:** Raises questions about whether eosinophils are the *only* driver of symptoms.
- **Omalizumab (Anti-IgE):**
  - **Recommendation: Suggested AGAINST** for EoE.
  - **Rationale:** Trials showed no clinical benefit. Confirms EoE is *not* an IgE-mediated disease.

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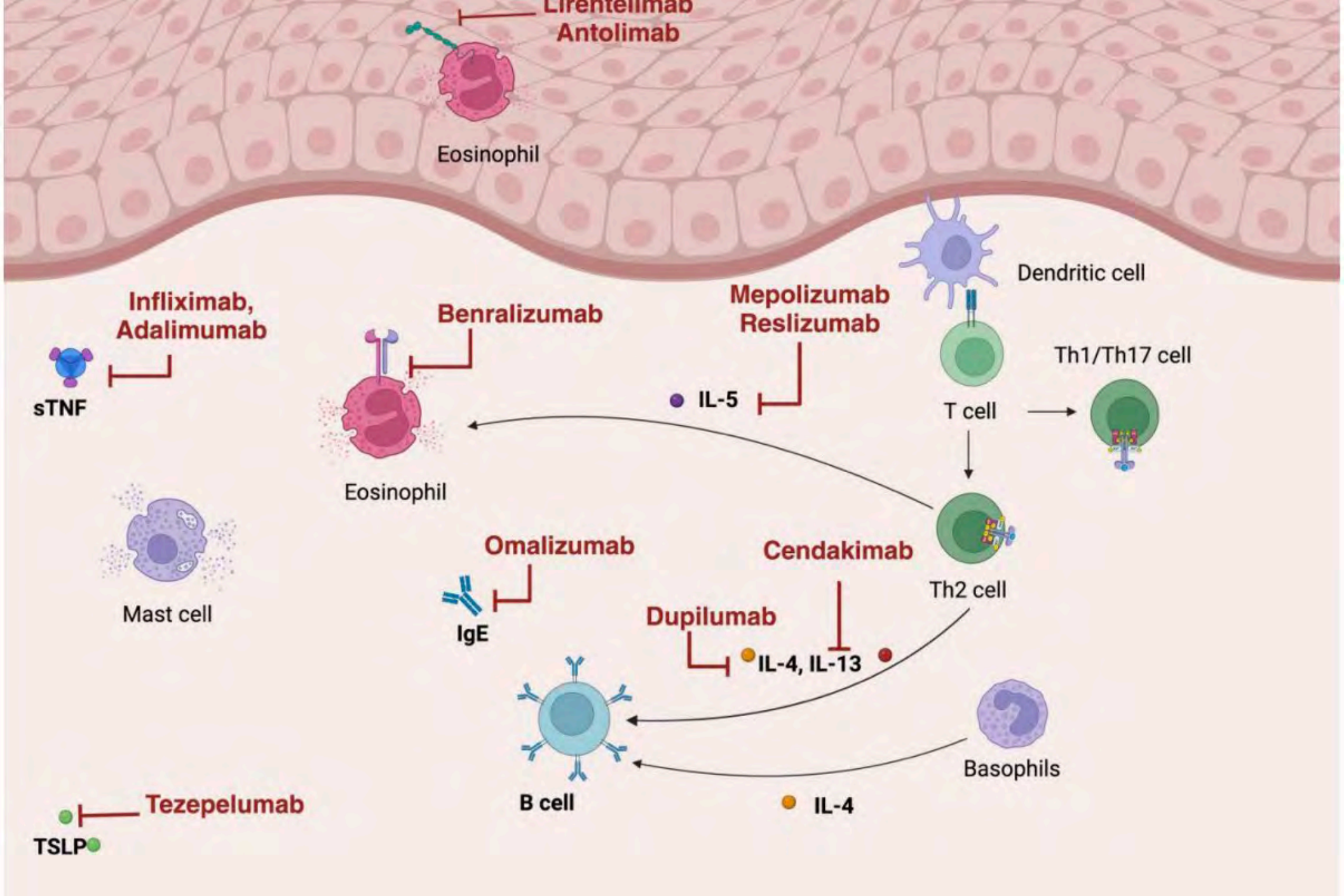
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sTNF
Benralizumab
Mepolizumab
Reslizumab
IL-5
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Th1/Th17 cell
Eosinophil
Mast cell
Omalizumab
IgE
Cendakimab
Th2 cell
Dupilumab
IL-4, IL-13
Basophils
B cell
IL-4
Tezepelumab
TSLP

Small Molecules in EoE

Limited Evidence and Recommendations Against Use

- **Montelukast (Leukotriene Receptor Antagonist):**
  - Targets leukotrienes responsible for eosinophil infiltration and vascular permeability.
  - A blinded, placebo-controlled trial randomized patients to Montelukast vs. Placebo after steroid induction.
  - No significant difference in dysphagia symptoms compared to placebo over 24 weeks.
- **Cromolyn Sodium (Mast Cell Stabilizer):**
  - Aimed at stabilizing mast cells, which are part of the mixed inflammatory infiltrate in EoE.
  - Small randomized trials (n=16) failed to show significant reduction in either symptoms or oesophageal eosinophilia.

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Endoscopic Dilation in EoE

- EoE involves both inflammation and fibrosis. Chronic inflammation leads to **strictures** (focal) and **narrow-caliber oesophagus** (diffuse).
- Endoscopic dilation is suggested as an **adjunct** to medical therapy for patients with dysphagia caused by strictures.
  - Dilation improves symptoms in **95%** of cases.
  - Highly safe when performed by experienced endoscopists.
    - Perforation risk: <0.5%
    - Hospitalization: <1%
- Improves caliber but does **not** treat the underlying inflammatory disease.

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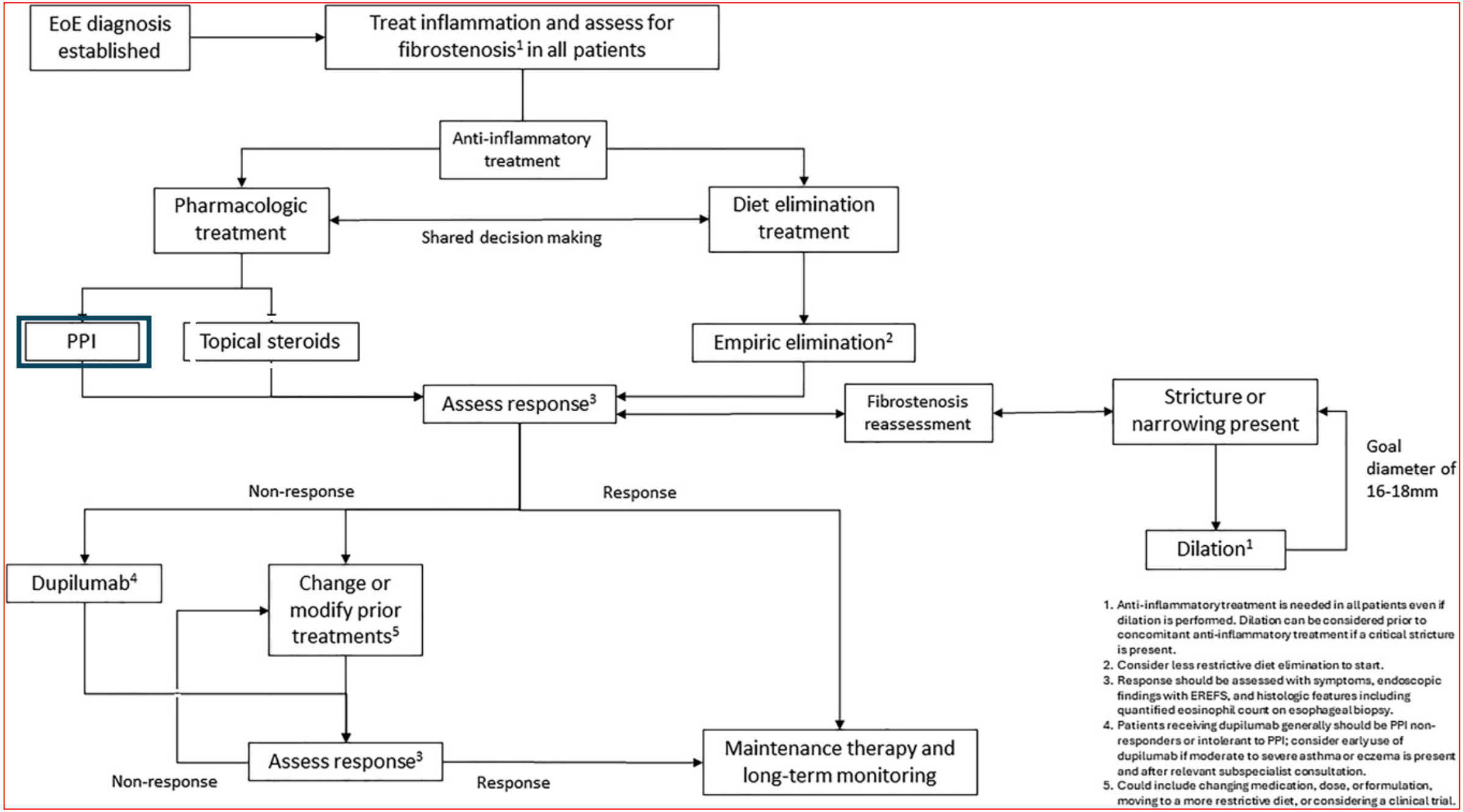
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Clinical approach to dilation

- Dilation should **not** be used as monotherapy.
  - Effective medical/dietary therapy reduces the long-term need for repeated dilations by controlling subepithelial inflammation.
- ASGE Consensus Guidelines:
  - Start with a conservative "Rule of 3" (do not dilate more than 3mm in a single session).
  - Aim for a final diameter of **15–18 mm** for symptomatic relief.
  - Small-caliber scopes may be necessary for initial passage in severe cases.

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Maintenance Therapy

- Unlike some childhood allergies, patients do **not** "grow out" of EoE. It is considered a final, chronic stage of the allergic march.
- When treatment is stopped, disease activity (histologic and symptomatic) nearly **universally recurs**, typically within 3 to 8 months.
- Untreated or interrupted therapy leads to progressive esophageal stiffening and strictures in most patients.
- Long-term treatment is associated with "deep remission," which may modify the disease course, decrease food impactions, and reduce the need for future dilations.

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Maintenance with Pharmacotherapy

- **Topical Steroids (STC):**
  - Randomized trials of Budesonide (BOT and BOS) show that ~75% of patients maintain remission on long-term therapy compared to <5% on placebo.
  - It is reasonable to titrate to the **lowest effective dose** (e.g., reducing from 1 mg bd to 0.5 mg bd), though every-other-day dosing may be ineffective.
- **PPI Therapy:**
  - 70–85% of patients maintain their response at 1 year.
  - Studies show maintenance of response in >60% of adults even after 3.6 years of follow-up.
- **Biologics (Dupilumab/Cendakimab):**
  - Responses are maintained—and often improve—through 52 weeks of continuous treatment.

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Maintenance with Dietary Therapy

- While highly effective, approximately **50% of patients** struggle to maintain strict elimination diets long-term.
- **The "Diet Holiday" Strategy:**
  - Allow patients to relax dietary restrictions during vacations, holidays, or high-stress periods.
  - Use medical therapy (PPIs or Steroids) to "bridge" these gaps and prevent symptom flares.
  - To prevent total burnout and improve the long-term feasibility of dietary management.

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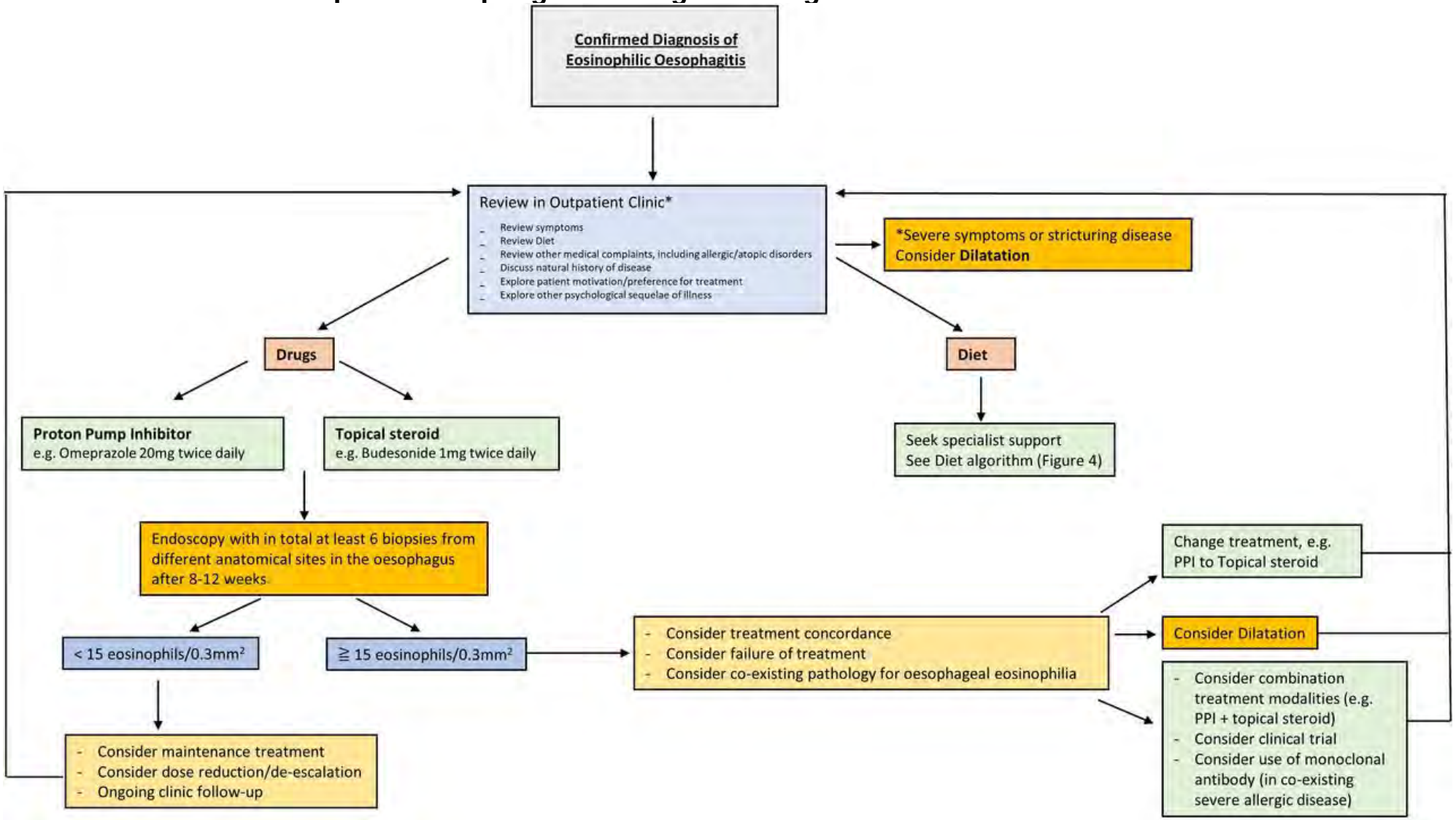
Eosinophilic oesophagitis management algorithm in adults and children.



Anjan Dhar et al. Gut 2022;71:1459-1487

Monitoring and Evaluation of Response

- **Why Clinical Evaluation Alone is Insufficient:**
  - Symptoms do not always match inflammation levels.
  - **IMPACT Behaviors:** Patients often "self-manage" symptoms by avoiding tough foods, chewing excessively, or eating slowly, which can mask ongoing disease.
  - Symptoms can improve while fibrostenosis (scarring) continues to worsen.
- **3 Levels of monitoring**
  - **Symptomatic:** Assessing dysphagia and modified eating behaviors.
  - **Endoscopic:** Using the **EREFS** score (Goal: ≤2).
  - **Histologic:** Measuring eosinophil counts (Goal: **<15 eos/hpf**).

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Follow-up & Evaluation

- **Initial Re-evaluation:**
  - **Diet/PPI/Steroids:** Repeat endoscopy with biopsies **8–12 weeks** after starting or changing therapy.
  - **Dupilumab:** Re-evaluate between **12–24 weeks**.
- **Deep Remission:**
  - Borrowed from IBD; defined as complete resolution in all three levels(Symptoms + Endoscopy + Histology).
  - Ideal, but only achieved by 9.4% of patients. Relapse is common if therapy stops.
- **The Risk of Gaps in Care:**
  - Patients who have no clinical follow-up for **2+ years** are at significantly higher risk for progression to fibro-stenosis.
- If a dose is reduced, a repeat endoscopy is necessary to confirm that remission is maintained at the lower dose.

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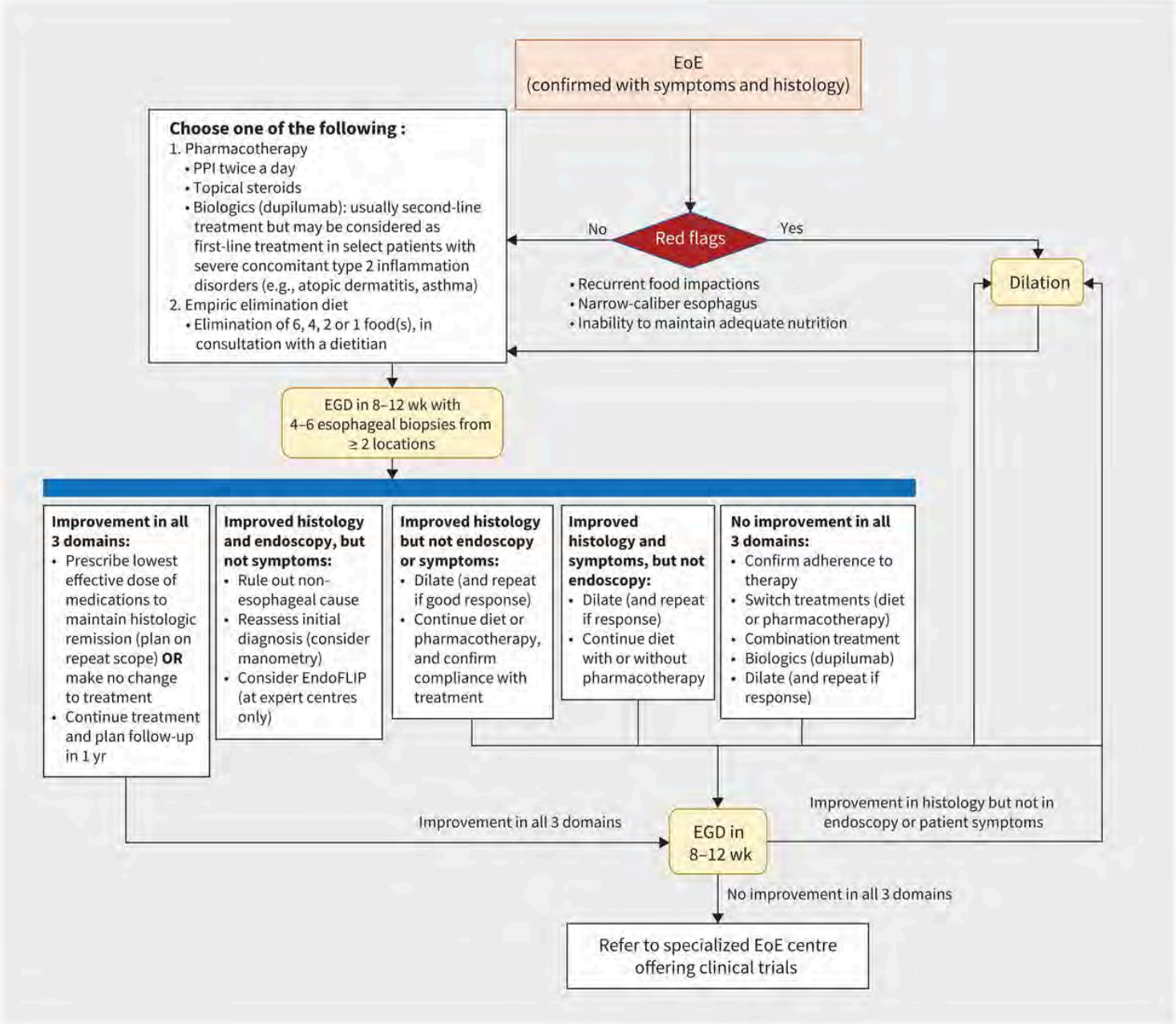

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CMAJ Feb 2024, 196 (4) E121-E128;

Thankyou