

Navigating non-IgE-mediated food allergy

Dr. Moshe Ben-Shoshan MD, MSc

Jennifer Gerds, Executive Director,
Food Allergy Canada



Palais des congrès
de Montréal



THE COLLEGE OF
FAMILY PHYSICIANS
OF CANADA



LE COLLÈGE DES
MÉDECINS DE FAMILLE
DU CANADA

Presenter Disclosure

Presenter: Moshe Ben-Shoshan MD, MSc

Relationships with financial sponsors:

- Any direct financial relationships, including receipt of honoraria: Humber River Hospital, Sanofi
- Membership on advisory boards or speakers' bureaus: Food Allergy Canada, Pfizer Canada, Novartis, Sanofi
- Patents for drugs or devices: N/A
- Other: Novartis, Sanofi clinical trials

Presenter Disclosure

Presenter: Jennifer Gerdt

Relationships with financial sponsors:

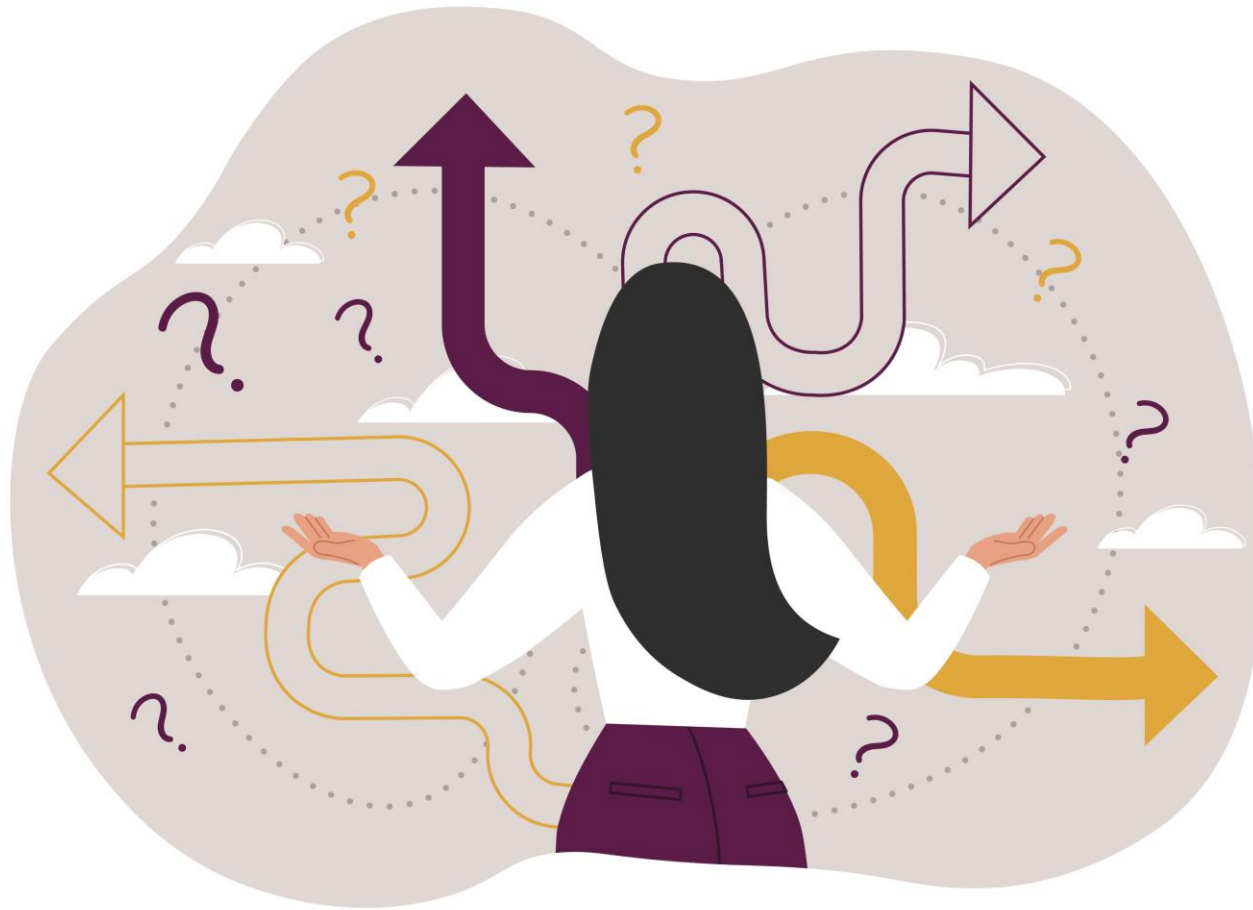
- Any direct financial relationships, including receipt of honoraria: Humber River Hospital
- Membership on advisory boards or speakers' bureaus: N/A
- Patents for drugs or devices: N/A
- Other: N/A

Disclosure of Financial Support

Potential for conflict(s) of interest:

- Dr. Moshe Ben-Shoshan has received honorariums for advisory board meetings from Novartis whose Xolair[®] (omalizumab) product and from Sanofi whose Dupixent[®] (dupilumab) product are being discussed in this program.
- Food Allergy Canada receives funds from Novartis for consulting services and funds from Sanofi which support educational and awareness initiatives. Their products, Xolair[®] and Dupixent[®], respectively, are being discussed in this program.

Patient journey: non-IgE-mediated food allergy



Learning objectives



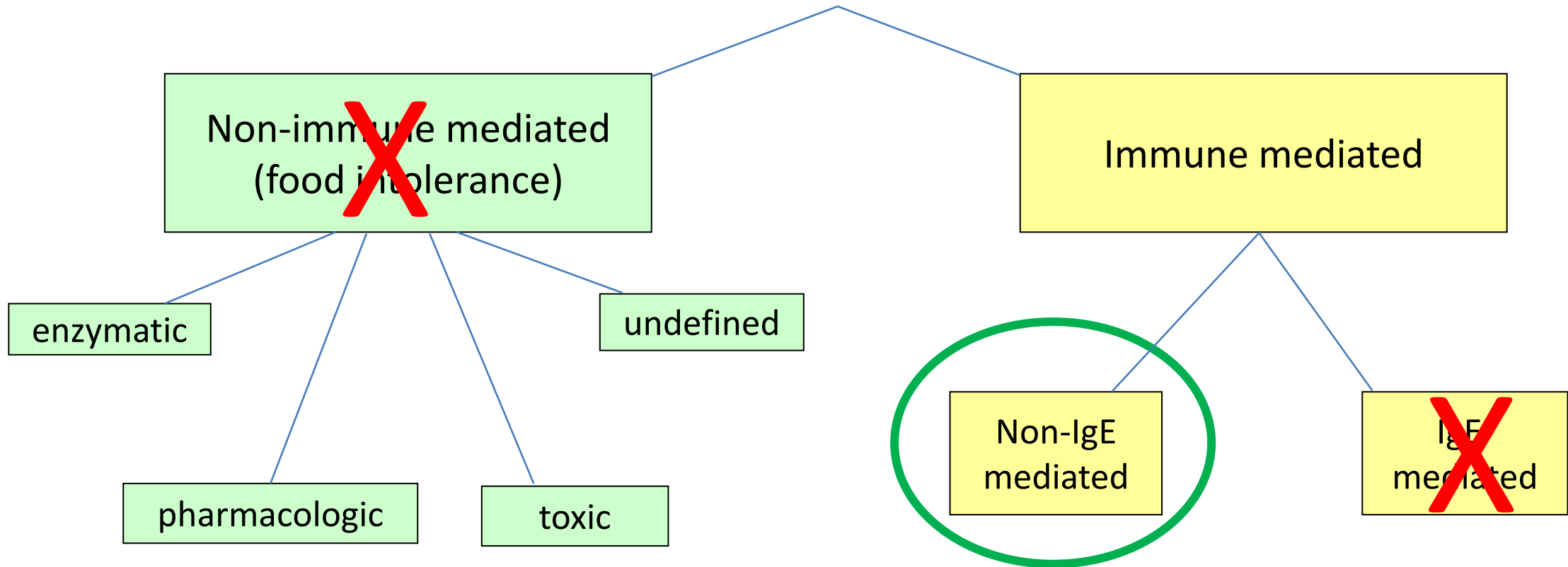
- Explain the differences between IgE- and non-IgE-mediated food allergies
- Differentiate the various medical conditions involving non-IgE-mediated food allergy
- Identify opportunities to improve outcomes for patients managing these conditions

Today's session

- Classifications of food allergy
- For the more common non-IgE-mediated food allergy conditions:
 - Pathogenesis, clinical picture, confirmatory tests, management approaches for these conditions
- Revisiting the patient journey
- Resources available to support your patients



Adverse reactions to foods



Non-IgE-mediated food allergy conditions

Food protein-induced allergic proctocolitis (FPIAP)

Food protein-induced enterocolitis syndrome (FPIES)

Eosinophilic esophagitis (EoE)

Case #1

- 3-month-old with history of streaks of blood in stool
- Only breastfed (mother consumes dairy)
- Very fussy when eats
- No constipation, stool not hard

- Are **additional investigations** needed?
- How would you **induce remission**?
- What is the **probability for resolution**?

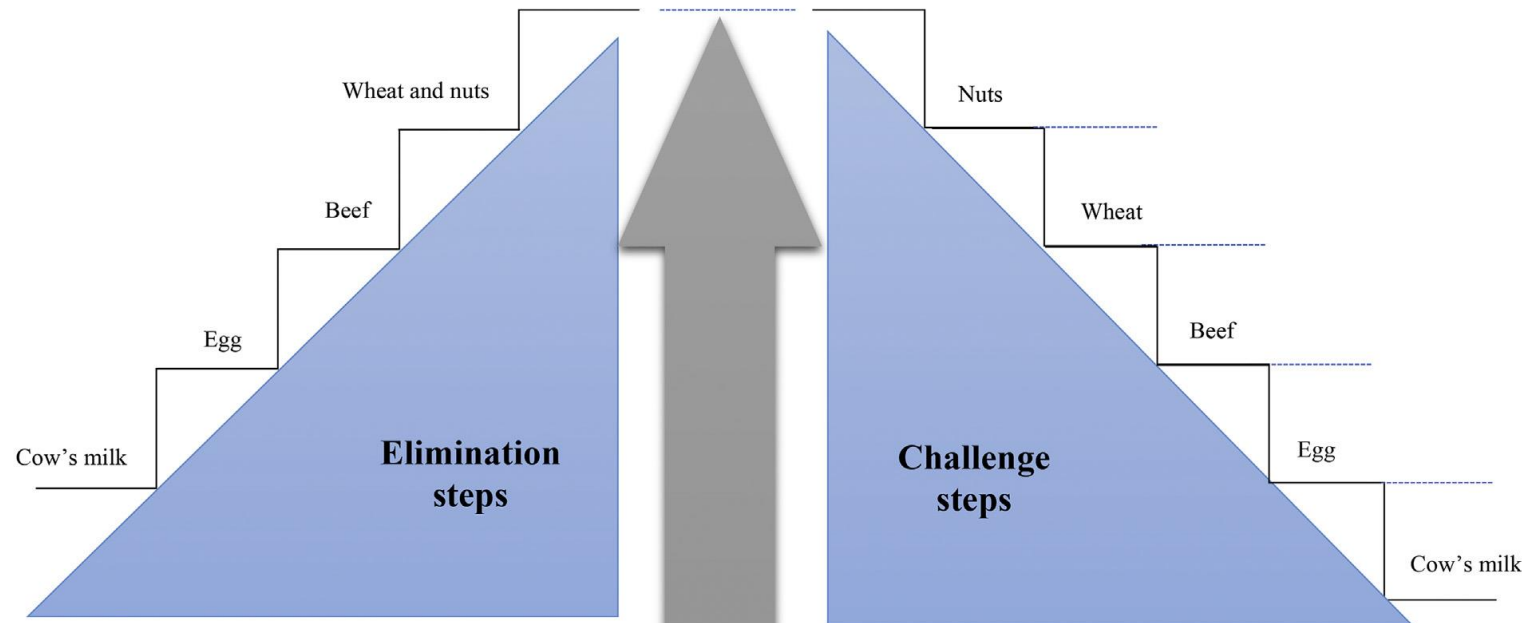


FPIAP: prevalence, risk factors, triggers, symptoms

- Prevalence in infants: varies from 0.16% to 17%
- Risk factors: eczema, first degree relative with food allergy
- Common triggers: cow's milk protein, soy protein
- Symptoms: bloody and mucous stools

FPIAP: diagnosis and management

- Diagnosis
 - Convincing history and resolution of symptoms with food avoidance
 - Confirmatory diagnostic testing (other than OFC) is lacking
 - Most guidelines require gross blood for diagnosis
 - Some guidelines suggest reintroduction or challenge to confirm symptom recurrence after symptoms resolve with elimination
- Management
 - Avoidance of the suspected food with interval challenge to assess for resolution (usually occurs in the first years of life)



Cow's milk was the first food eliminated from diet.*

In patients with no resolution of visible blood in stool within two weeks with cow's milk elimination, egg and beef were sequentially added to the elimination diet at two-week intervals.

If visible blood in stool persisted after beef elimination in the subsequent two weeks, wheat and nuts were eliminated together, in order to shorten the elimination period, which might otherwise be stressful for the family.

Challenges were started with the food which was eliminated last. If elimination diets were extended to wheat and nuts, these foods were challenged separately:

a) If visible blood in stool recurred, the relevant food was re-eliminated, and two weeks after symptom resolution, the challenge step was continued with the other foods in line.

b) If visible blood in stool did not recur, the patient continued to consume that food regularly and the OFC was performed after two weeks with the other foods in line.

OFCs were performed four weeks after disappearance of blood in stool. In patients with atopic dermatitis, the elimination diet, moisturizer and topical steroids were applied first. Topical steroids were prescribed for seven days. A decrease of 10 scoring atopic dermatitis (SCORAD) points was considered to represent remission. After cessation of topical steroids, the OFCs were performed in patients who were able to maintain a 10-point reduction for 30 days while continuing the elimination diet and moisturizer application.

Structured elimination and challenge steps

FPIAP: resolution

- Atopic dermatitis (AD) (OR 3.02, 95% CI 1.2-7.6, p=0.019) and an eosinophil count ≥ 300 cells/ μ L (OR 3.32, 95% CI 1.32-8.33, p=0.01) identified as risk factors for multiple food allergens causing FPIAP
- Blood and mucus in stool disappeared in a median three days (IQR: 1-14.5 days) and 30 days (IQR: 8-75 days), respectively
- A two-week duration of elimination for blood in stool is sufficient to reach a judgment of suspected foods for FPIAP
- Resolution
 - Breastfed: majority resolve with maternal elimination diet (no milk - 50%, no milk/soy - 40%, no milk/soy/egg - 10%)
 - Formula-fed: 80% resolved on extensively hydrolyzed formulas, 20% on amino acid-based formulas
- Often successful reintroduction after 6 months elimination diet

Case #2

- 6-month-old male
- Tried oat cereal, 2h later he experienced severe emesis and diarrhea
- Assessed in the ER and found to be dehydrated
- Treated with oral rehydration (intravenous access was difficult)
- A small amount of oat was introduced again into the diet a few days later. After an hour, he began vomiting with bloody, profuse diarrhea
- He was evaluated in the ER and treated with intravenous fluids

- Are **additional investigations** needed?
- How would you **induce remission**?
- What is the **probability for resolution**?

FPIES: incidence, triggers, symptoms

- Incidence: 15.4 / 100,000 infants less than 2 years old
- Increase in total FPIES cases noted (possibly greater awareness)
- Most frequently reported triggers in children: cow's milk, fish, egg, grains, soy
- 65-80% of children have FPIES to a single food, most commonly cow's milk
- Most infants do not react to food allergens present in maternal breast milk
- Symptoms: severe vomiting and diarrhea
 - Sometimes accompanied by dehydration, lethargy, changes in blood pressure and body temperature, failure to thrive (in some cases)
 - Usually presenting 1-4 hours after ingestion

Caubet J-C, Clin Exp Allergy 2019;49(9):1178-1190

Prattico C, Mule P and Ben-Shoshan M, Int Arch Allergy Immunol 2023;184:567-575

Nowak-Węgrzyn A et al, JACI 2017;139(4):1111-1126.e4

FPIES classification: Acute

Intermittent / low dose allergen ingestion

- Mainly **infants**
- **Severe symptoms**
- **1 major \geq 3 minor**

Major diagnostic criteria:

- Vomiting 1-4h after ingestion and no symptoms consistent with IgE mediated allergy

Minor diagnostic criteria:

- At least 2x vomiting
- Repetitive vomiting 1-4h after another food
- Extreme lethargy • Pallor • Need for ER visit
- Need for IV fluids • Diarrhea within 24h
- Hypotension • Hypothermia

FPIES classification: Chronic

Frequent / high dose ingestion

- Mainly **neonates**
- **Mild symptoms, intermittent vomiting, failure to thrive**
- Resolution of symptoms within days of elimination and acute recurrence with re-introduction (vomiting within 1-4h and diarrhea within 24h)

Severe chronic: intermittent but progressive vomiting(+/- metabolic acidosis / dehydration)

Mild chronic (lower quantity): intermittent diarrhea, poor weight gain

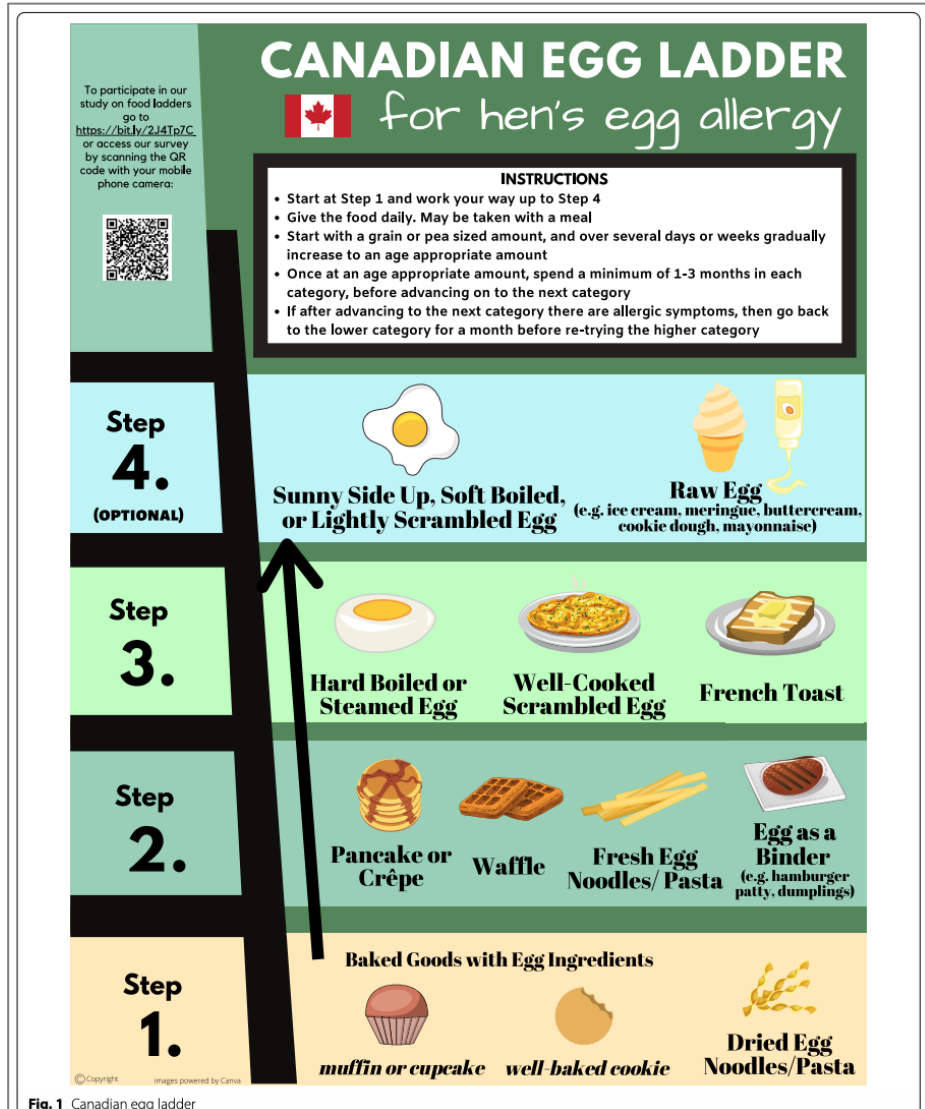
FPIES can also affect adults

- Some patients experience symptoms in adulthood (no symptoms in childhood)
- Most common trigger in adolescents and adults: crustaceans

FPIES: diagnosis and management

- Diagnosis
 - Convincing history and resolution of symptoms with food avoidance
 - Confirmatory diagnostic testing (other than OFC) is lacking
- Management
 - Avoidance of the suspected food with interval challenge to assess for resolution (usually occurs in the first years of life)

Could we apply a food ladder for FPIES?



- 21 patients with mild-to-moderate FPIES to egg (no history of lethargy or intravenous fluid administration)
- Started on the Canadian Egg Ladder
- 19 patients (90.5%) completed the ladder, tolerating a serving size amount of cooked egg, over a median duration of 7 months

Management of acute FPIES

- Acute FPIES reactions can be expected to resolve in 4-12 hours after onset (vs 3-10 days after avoiding the trigger for chronic FPIES reactions)
- Mild reactions typically resolve with oral rehydration
- Moderate to severe reactions can require aggressive fluid resuscitations with repeated saline boluses
- Corticosteroids have also been recommended for patients with severe symptoms
- Ondansetron (Zofran[®]), a serotonin 5-HT₃ receptor antagonist, has been approved in pediatric populations to prevent nausea and vomiting

Long-term FPIES management

- Elimination of the trigger food(s)
- Plans for dietary advancement
- Treatment of symptoms at presentation or on re-exposure
- Monitoring for FPIES resolution

In the United States:

Diagnostic challenges are usually attempted within 12-18 months after the most recent reaction

FPIES: resolution

Patients	Development of tolerance
Patients with CM-induced FPIES, soy-induced FPIES, or both	Average = 1 year
Patients with grain-induced FPIES	Average = 3 years
Patients with other solid food-induced FPIES	Average = 3.5 years

Case #3

- 10-month-old referred due to suspected cow's milk allergy
- This infant was fed with a cow's milk-based formula for the first 2 months of age
- Due to symptoms of infantile colic (episodes of crying or fussing most frequently after a feeding), he was switched to a cow's milk hydrolysate-based formula at the age of 2 months
- At the age of 5 months, he was reintroduced twice to cereals with cow's milk-based formula
- Within minutes afterwards, he developed facial flushing, hives and angioedema of the wrists and ankles

- Was the **use of milk hydrolysate** justified?
- Could the use of hydrolysate **contribute** to an IgE-mediated allergy?



Some facts

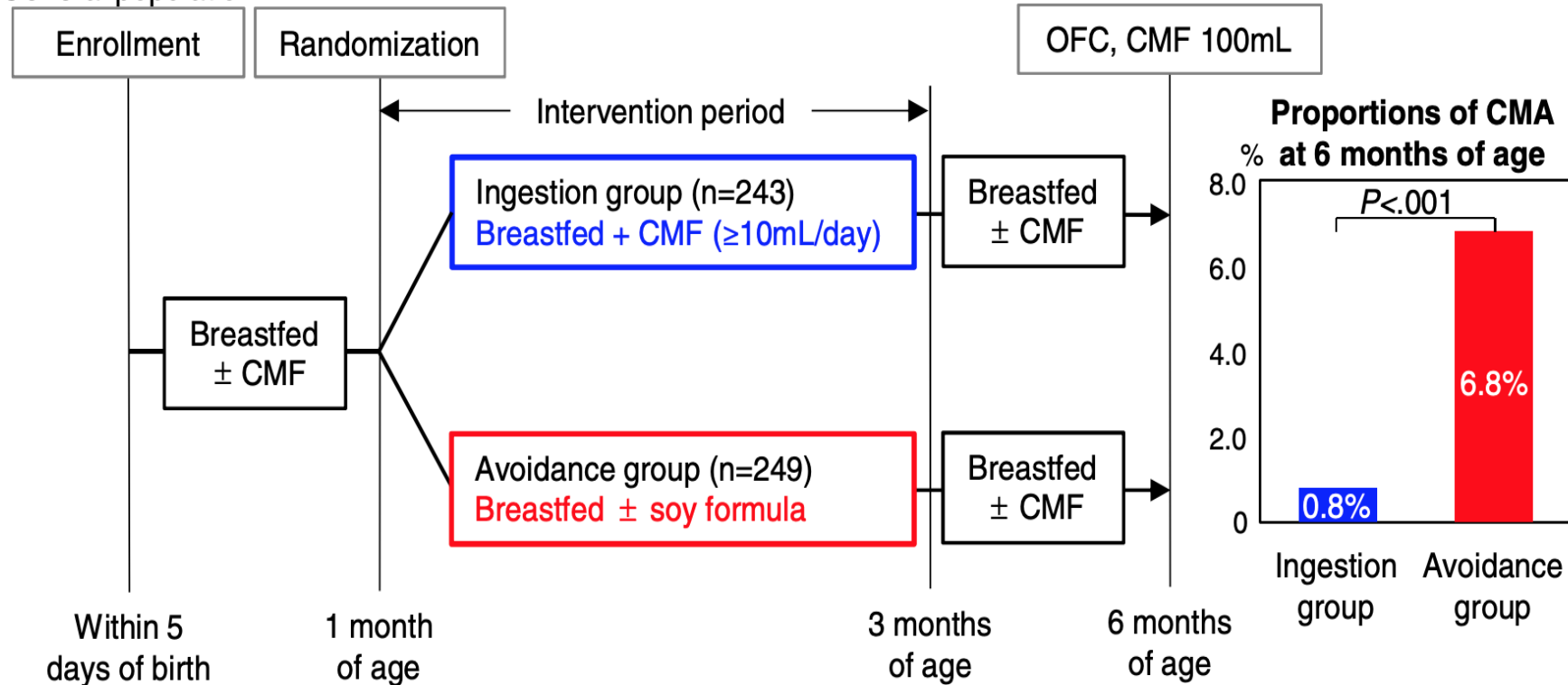
- Many lactation consultants, paediatricians and family physicians advocate maternal elimination diets to maintain breastfeeding benefits in infants with colic
- Colic and fussiness: not likely to be isolated manifestations of cow's milk allergy
- Infantile colic: benign clinical course and usually resolves by 3 months of age
- Recent studies: food elimination may increase the risk of IgE-mediated food allergy



Randomized trial of early infant formula introduction to prevent cow's milk allergy

Overview of the SPADE study

General population



SPADE: Strategy for Prevention of Milk Allergy by Daily Ingestion of Infant Formula in Early Infancy

CMF: Cow's milk formula

OFC: Oral food challenge

CMA: Cow's milk allergy

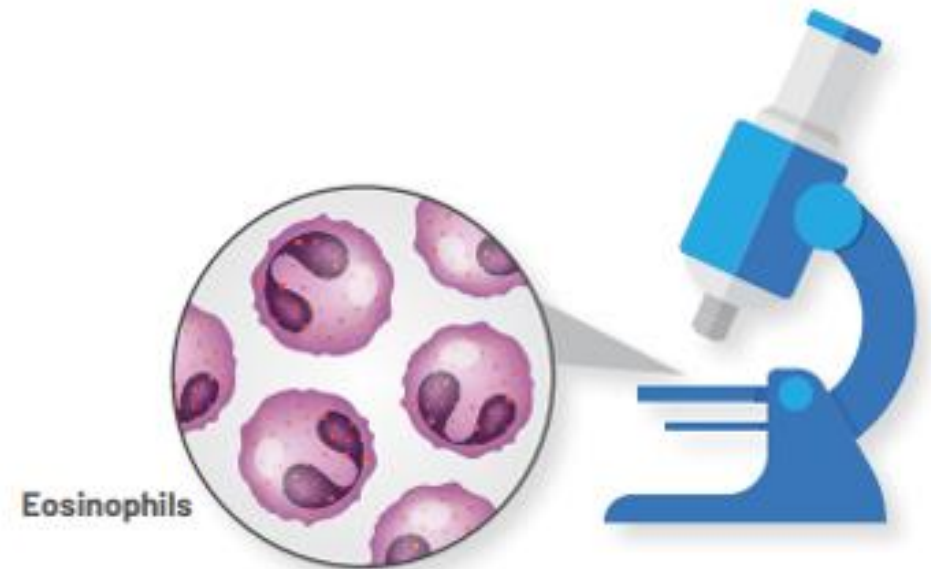


Case #4

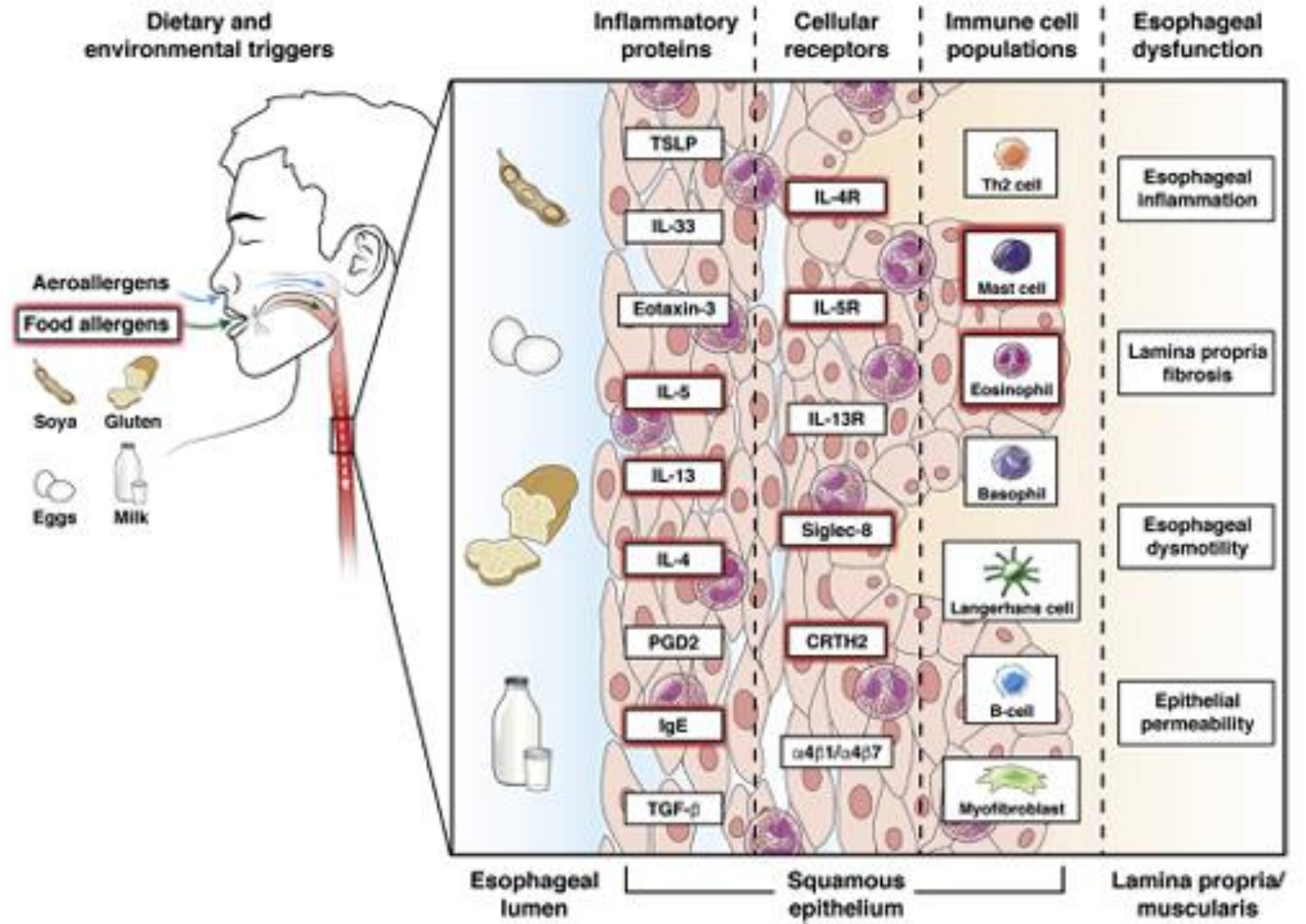
- 18-year-old male with known peanut allergy undergoing oral immunotherapy for peanut for the last 2 years
 - In last year, symptoms of severe food impaction
 - Sensation of choking that exacerbated after starting peanut OIT
 - Active despite topical steroids and high dose PPI
 - Significant progressive eosinophilia (AEC 2.11)
 - Signs of extensive disease (lower GI Sx, weight loss)
 - Severe atopic history (AR, AD, asthma, food allergies)
-
- Are **additional investigations** needed?
 - How would you **induce remission**?
 - Would you consider **biologic therapy**? If so, which one?

EoE: definition and triggers

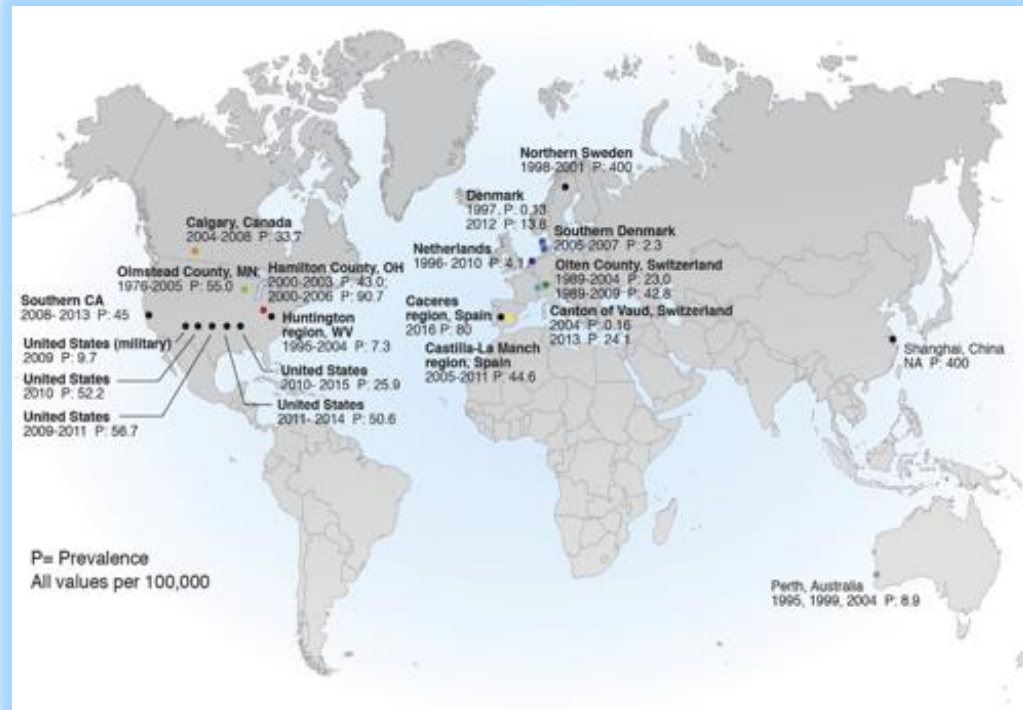
- EoE is a chronic immune-mediated esophageal disease
- With EoE, large numbers of eosinophils (white blood cell) collect in the esophagus
- Too many eosinophils in the esophagus is not normal
- Dietary and environmental triggers (foods most commonly associated with EoE are milk, wheat, egg, soy)



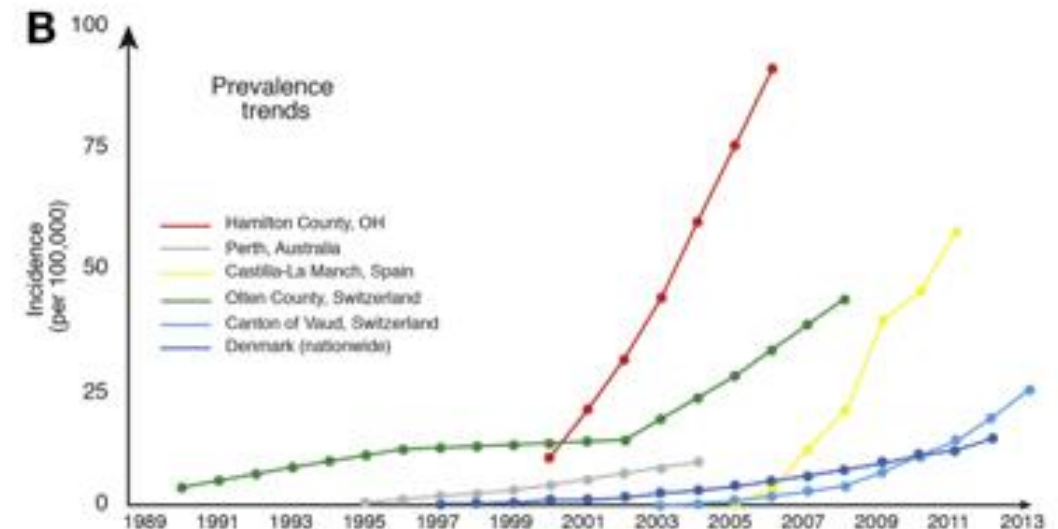
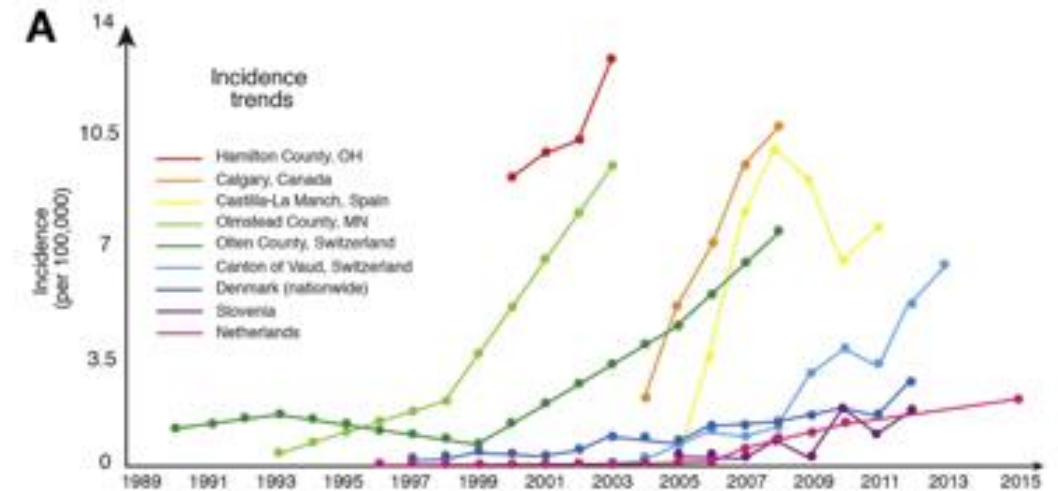
Type 2 inflammation and EoE development



Rising trends of EoE: incidence and prevalence



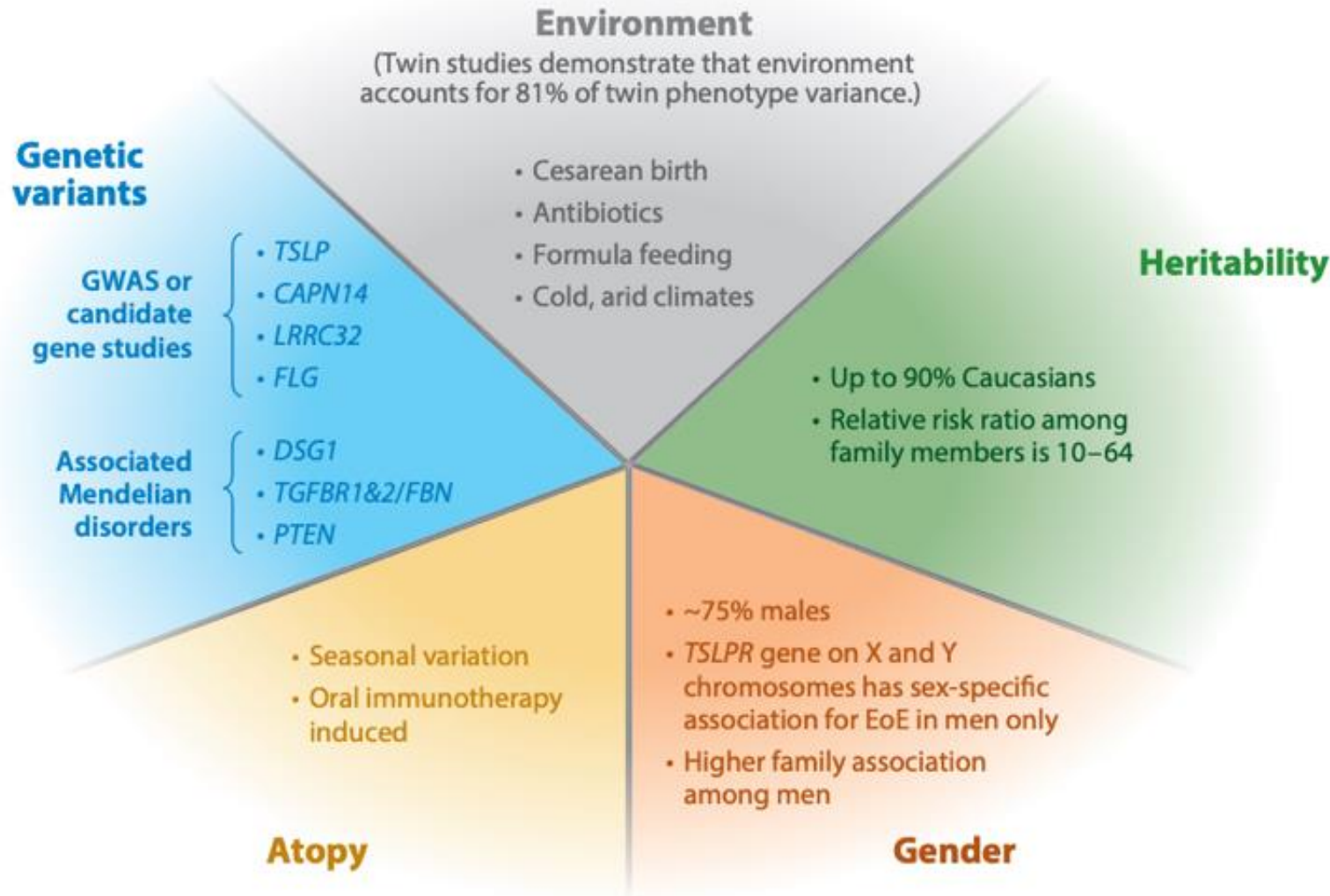
Prevalence = $\sim 1 / 2000$ (US)



Dellon ES and Hirano I, Gastroenterology 2018;154(2):319-332.e3

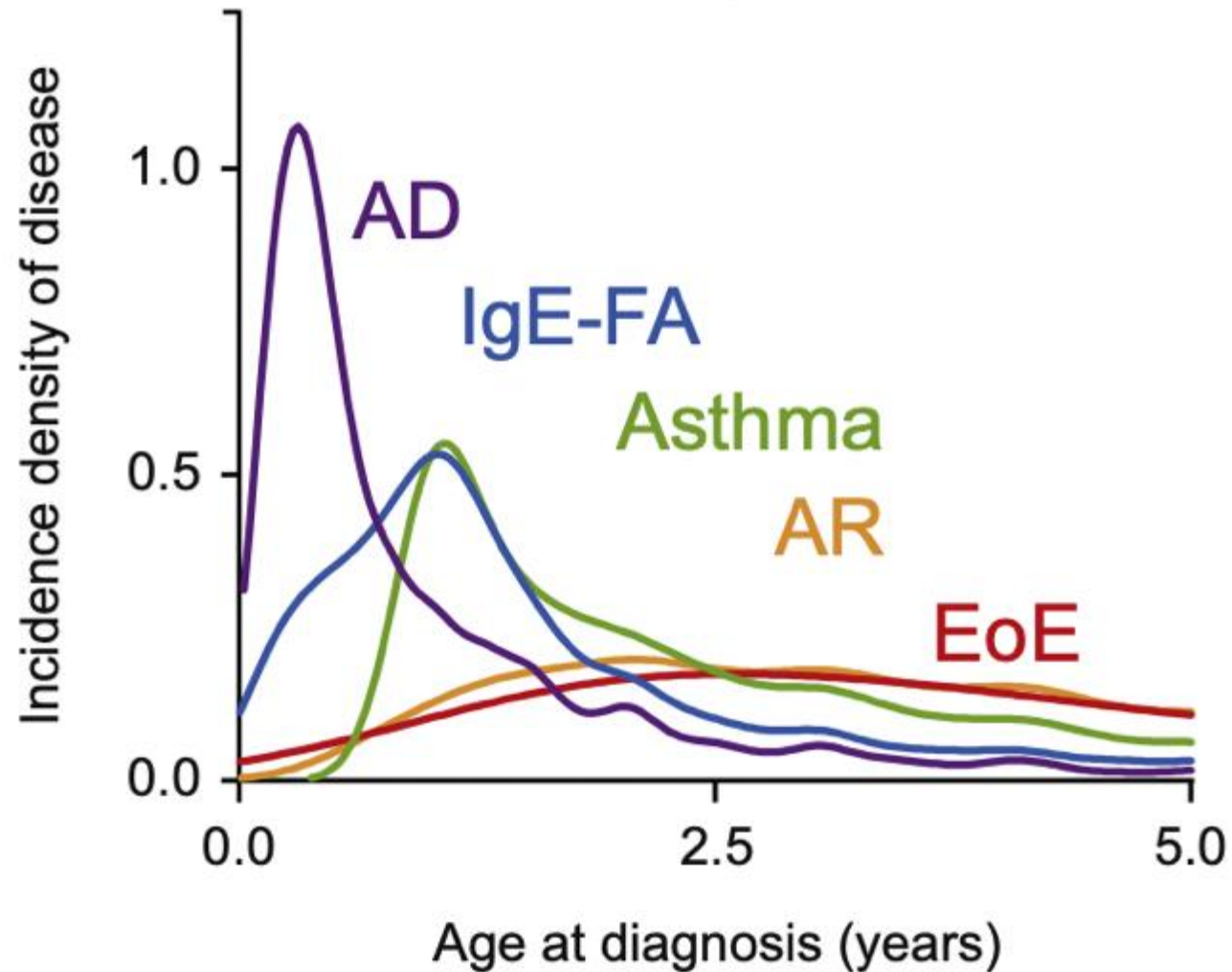
Arias A et al, Aliment Pharmacol Ther 2016;43(1):3-15

EoE: demographics



- EoE affects both children and adults
- Can develop at any age, including infancy
- Affects mostly males

EoE: late manifestation of the atopic march?



Co-occurrence of EoE and food allergy (FA)

- EoE in general population: 0.04%
- EoE in patients with FA: 4.7% (100X increase)
- > 2/3 of EoE patients have an IgE-mediated FA

Allergic march hazard ratios

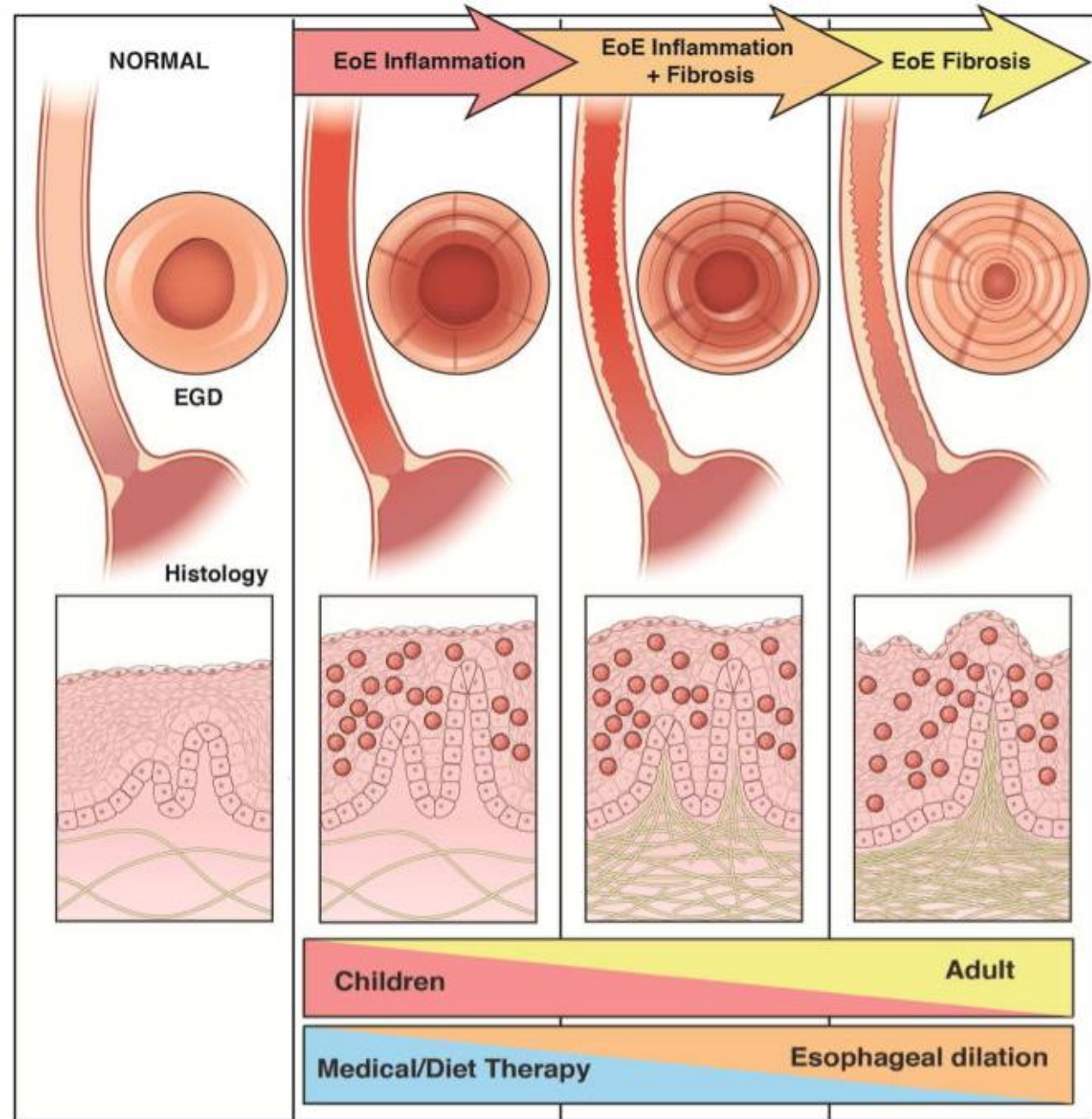
		Secondary Diagnosis				
Primary Diagnosis	AD	AD	IgE-FA	Asthma	EoE	AR
	AD	-	2.5	1.5	3.2	1.9
	IgE-FA		-	1.5	9.1	1.7
	Asthma			-	1.9	1.7
	EoE				-	2.5
	AR				2.8	-

EoE: symptoms vary with age

Common Symptoms	Who Is Affected		
	Infant	Child	Adult
	✓	✓	✓
	✗	✓	✓
	✗	✓	✓
	✓	✓	✓
	✓	✓	Rarely
	✗	✓	Uncommon
	✓	✓	✗
	✓	✓	✗

Patients may form adaptive eating habits (e.g., chewing excessively, drinking lots of fluids) to deal with symptoms

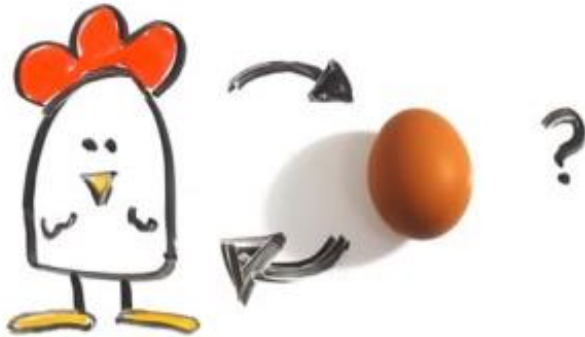
EoE progression from inflammation to fibrosis



EoE: diagnosis

- Symptoms of esophageal dysfunction
- ≥ 15 eos/HPF
 - ≥ 1 biopsy specimen
 - 2-4 biopsies taken from proximal, medium and distal esophagus (5 biopsies = 100% Sn vs 1 = 50% Sn)
- Exclusion of other causes of esophageal eosinophilia

Back to case 4: oral immunotherapy (OIT) and EoE

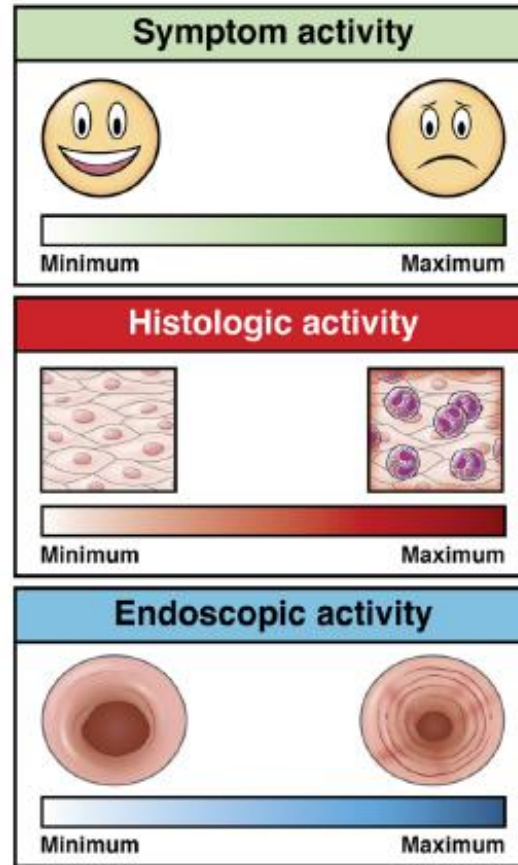
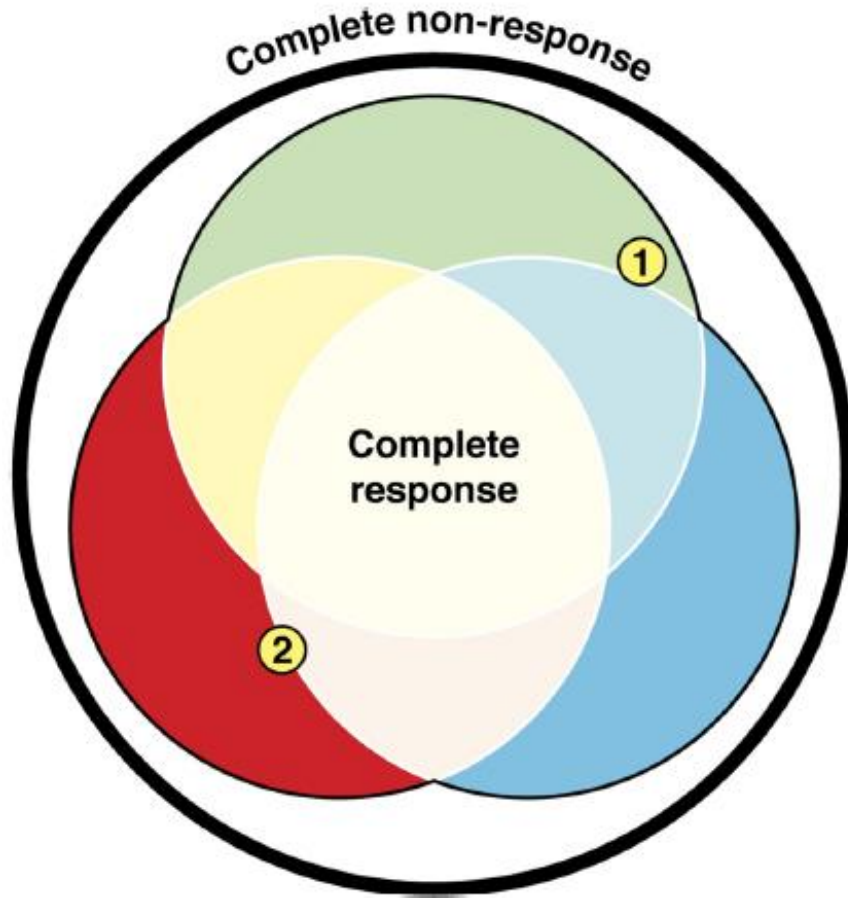


- 10-30% have EoE-like symptoms
- 5% diagnosed with EoE
- Chicken or the egg?

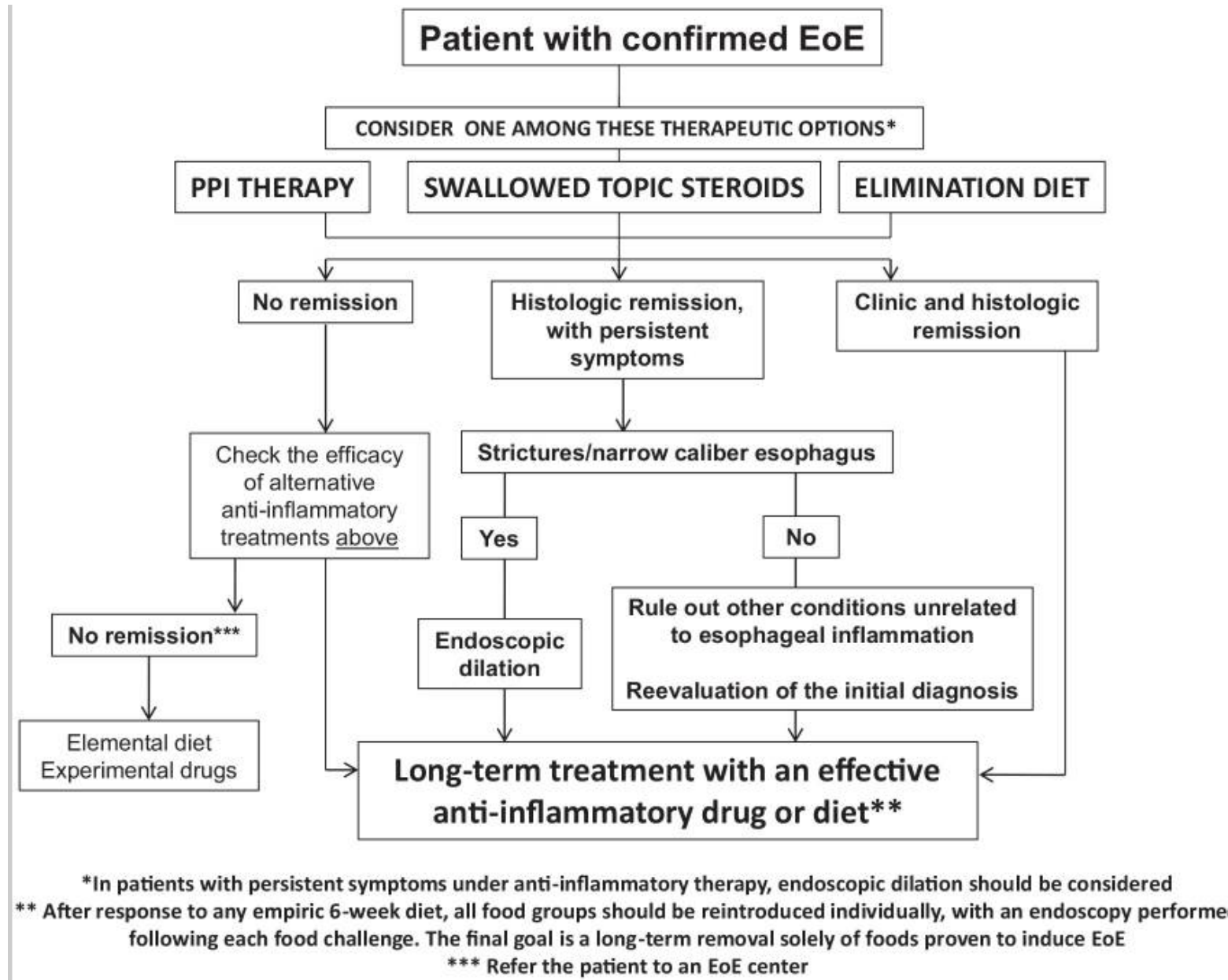
Table 1
Summary of Safety Data From OIT Studies of Patients With Egg, Milk, or Peanut Allergy^a

Rate	Discontinuation (any reason), %	SPR-EoE, %			EoE (biopsy), %	Discontinuation cause, %	
		Organ system	Specific symptom			SPR-EoE	EoE or SPR-EoE
		GI symptoms	Abdominal pain	Vomiting			
Overall	14	34	32	12	5.3	4.7	5.6
Egg	11	ND ^b	28	17	4.2	2.7	3.1
Milk	12	18	30	1	5.4	3.9	4.6
Peanut	16	56	40	20	5.2	6.7	8.5

EoE: goals of treatment



- **Minimal symptoms**
(complete absence of dysphagia without any dietary avoidance based on food texture)
- **Minimal histologic activity**
(0 eos/hpf)
- **Minimal endoscopy activity**
(absence of endoscopic features of inflammation - furrows, exudate, or edema - and an esophageal diameter > 20 mm)



**Proposed
algorithm
for EoE in
clinical
practice**

EoE: summary of recommendations

Gastroenterology 2020;158:1776–1786

CLINICAL PRACTICE GUIDELINES

AGA Institute and the Joint Task Force on Allergy-Immunology
Practice Parameters Clinical Guidelines for the Management of
Eosinophilic Esophagitis



Recommendation	Strength	Quality of evidence
Topical steroids	Strong	Moderate
PPIs in symptomatic EoE	Conditional	Very low
Topical steroids over systemic steroids	Conditional	Moderate
Elemental diet	Conditional	Moderate
6-FED	Conditional	Low quality
Allergy testing based - FED	Conditional	Very low quality
Maintenance with topical steroids	Conditional	Very low quality
Dilation if stricture present	Conditional	Very low quality

EoE: management

Which option is best?

Factor in:

- Consideration of EoE severity and patient ability to start treatment
- Shared decision making
- Response evaluated by repeat endoscopy

Medical therapy

- Proton pump inhibitors
- Topical corticosteroids
- Monoclonal antibodies

Diet therapy

- Elemental
- Empiric (food elimination diet)
 - 1,2,4,6-FED
 - Step-up vs step-down approach
- Allergy testing directed

Dilation

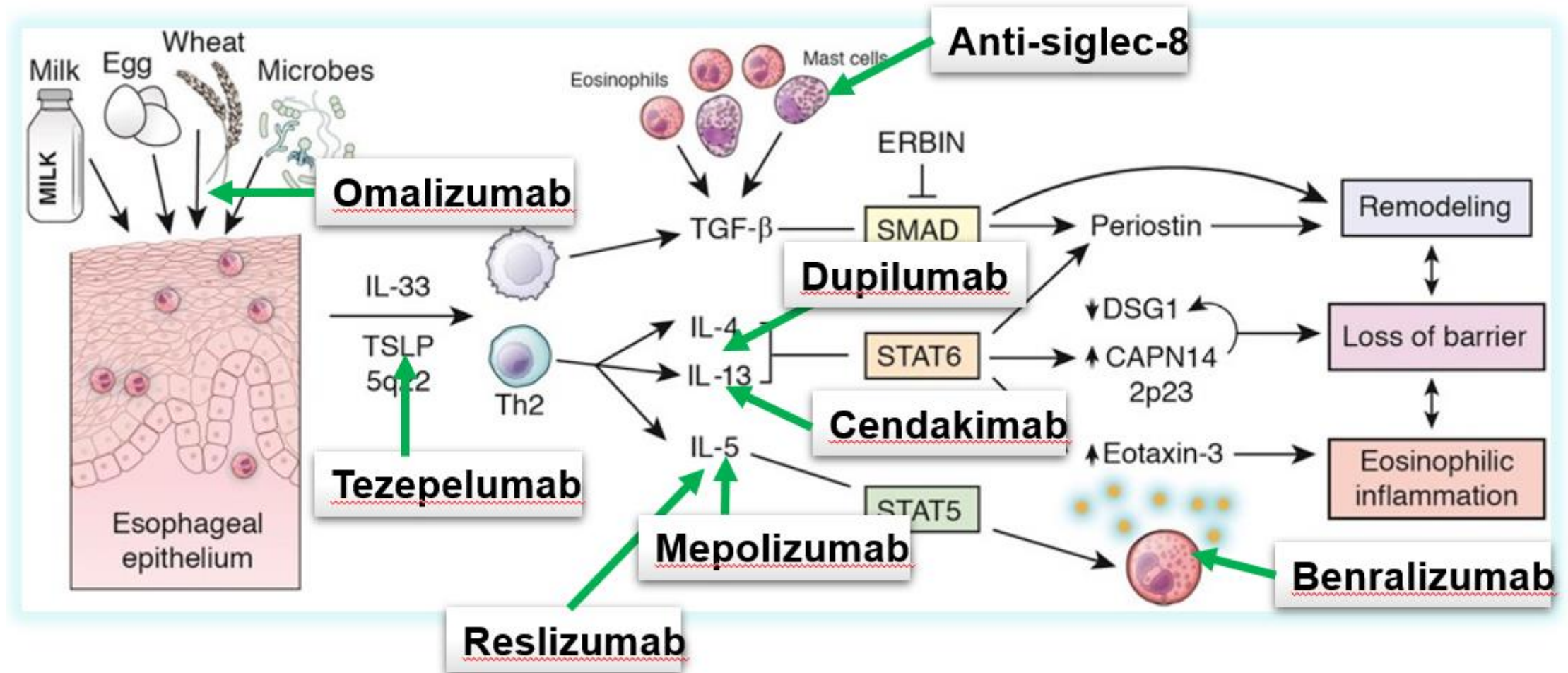
- Endoscopic procedure widens the esophagus to allow food to pass more comfortably

EoE: therapies indicated for use

- Budesonide orodispersable tablets (BOT)
 - Canada & Europe
 - Trials: EOS-1 (remission) & EOS-2 (maintenance)
- Dupilumab
 - US (2022)
 - Canada (2023)
- All other therapies are off-label
 - PPI
 - Swallowed fluticasone
 - Budesonide slurry



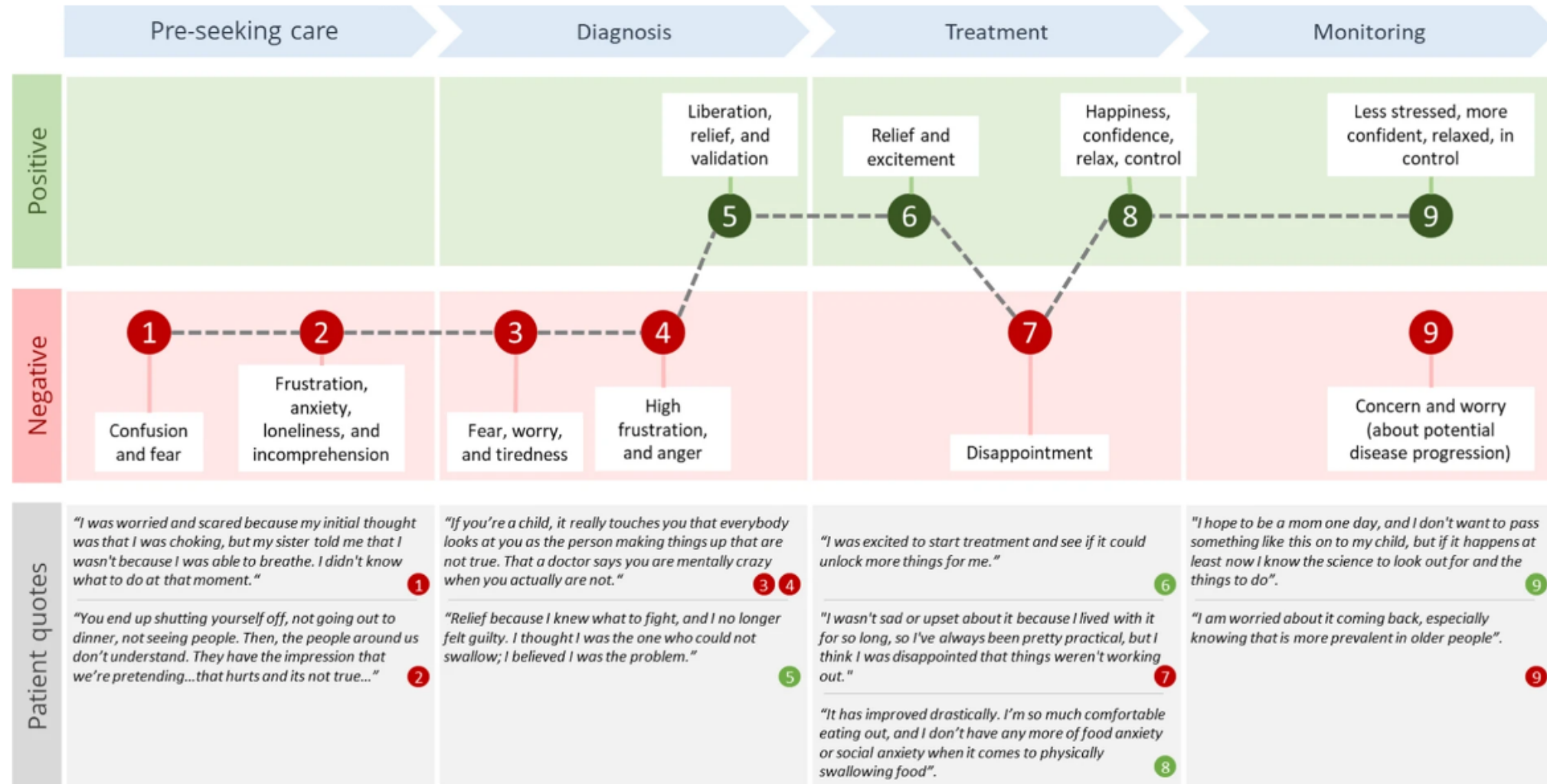
EoE: biologic therapies targeting T2 inflammation



Conclusion and key points

- Non-IgE-mediated food allergies can be associated with severe clinical manifestations
- Studies suggest increased prevalence
- Diagnosis is challenging and does not rely on skin tests / IgE levels
- Main pathogenic mechanisms unclear although likely a chronic, T2-inflammatory, allergic disease (mainly in the case of EoE)
- Unlike EOE, FPIAP and FPIES often resolve spontaneously with age
- Multiple potential targets for novel EoE treatments with role of biologics in algorithms to be defined

Emotional journey of patients with EoE



EoE resources at foodallergycanada.ca/EoE

Œsophagite éosinophilique (OE) :
Diagnostic et traitement

Allergies Alimentaires Canada

Qu'est-ce que l'œsophagite éosinophilique (EoE) ?

L'œsophagite éosinophilique (EoE) est une gastro-intestinale chronique qui affecte le tube qui relie la bouche à l'estomac. Elle est caractérisée par une inflammation de l'œsophage due à l'accumulation de cellules éosinophiles.

Quels sont les symptômes ?

Les symptômes de l'EoE peuvent varier selon l'âge et la gravité de la condition. Ils peuvent inclure :

- Difficulté à avaler
- Aliments qui restent coincés
- Douleur à la poitrine
- Douleur abdominale
- Rejets plus fréquents
- Quantité accrue de vomissements
- Évitement de certains aliments (viandes sèches, légumes secs)
- Bruyères d'estomac
- Impaction alimentaire
- Refus de manger
- Faible gain de poids
- Vomissements
- Régurgitation
- Refus de manger

Le diagnostic de l'EoE est basé sur des tests de laboratoire et une endoscopie avec biopsies.

Eosinophilic esophagitis (EoE):
Diagnosis and treatment

Food Allergy Canada

What is eosinophilic esophagitis?

Eosinophilic esophagitis (EoE) is a chronic gastrointestinal condition that affects the esophagus, the tube that carries food from the mouth to the stomach. With EoE, large numbers of eosinophils (type of white blood cell) collect in the esophagus due to inflammation, leading to symptoms.

What are the symptoms?

EoE symptoms can vary by person and age. The symptoms can range from mild discomfort with little or no pain to very painful and distressing.

Symptoms (in order of most to least frequently reported)	Children <5 years of age	Children 5-17 years of age	Adolescents	Adults
Difficulty swallowing (dysphagia)	✓	✓	✓	✓
Food sticking	✓	✓	✓	✓
Chest pain	✓	✓	✓	✓
Abdominal pain	✓	✓	✓	✓
Prolonged meal times	✓	✓	✓	✓
Excessive amounts of fluid intake with meals	✓	✓	✓	✓
Avoidance of certain food textures (such as dry meats, bread, rice, harder foods)	✓	✓	✓	✓
Heartburn		✓	✓	✓
Food impaction (when food becomes stuck in the esophagus) - this is a medical emergency	Rare	Infrequent	✓	✓
Poor weight gain/growth	✓	✓	✓	✓
Vomiting	✓	✓	✓	✓
Regurgitation	✓	✓	✓	✓
Food refusal (fussy eaters)	✓			

Most commonly, there is **difficulty swallowing** (dysphagia) when eating. Food may feel like it is travelling slowly down the esophagus or sticking in the chest. It can happen only sometimes or every time a person eats.

foodallergycanada.ca

f t i in y

patient sheets



EoE in adults: From diagnosis to treatment

Webinar with Dr. Milli Gupta
October 11, 2023

Food Allergy Canada

recorded webinar:
adult focus



Understanding EoE

Webinar with Dr. Vishal Avinashi and Kirstin Wingate
October 21, 2020

Food Allergy Canada

recorded webinar:
pediatric focus

More topics at foodallergycanada.ca/webinars



recorded webinar:
non-IgE-mediated cow's milk allergy



recorded webinar:
IgE-mediated cow's milk allergy

Free FPIES webinar this month

What is FPIES and how do you manage it?

November 27, 2023 at 12pm EST

Expert speaker: Dr. Anna Nowak-Wegrzyn

Visit foodallergycanada.ca/events to register



Thank you for participating in
today's session!



Visit our booth #706 for free resources!

Please fill out your session evaluation now!

Click this button in the
agenda!

SESSION EVALUATION | ÉVALUATION DE SÉANCE



FamilyMedicineForum



@FamilyMedForum



FamilyMedForum

#myfmf