Overview of diagnosis and management of Eosinophilic Esophagitis

New Frontiers In Eosinophilic Esophagitis management January 12 2022

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Learning Objectives:

- Described the current understanding of EoE
- Discuss the current guideline in the management of EoE

2

1st reported cases of EoE

Case report

Eosinophilic esophagitis in a patient with vigorous achalasia

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Abstract

A patient with vigorous achalasia is presented who had marked smooth muscle hypertrophy and eosinophilic infiltration of the esophagus identical to that seen in patients with eosinophilic gastroenteritis. Eosinophilic infiltration of the esophagus probably represents a variant of the eosinophilic gastroenteritis syndrome and may predispose to an esophageal motor disorder.

Gastroenterology 1978

The American Journal of Surgical Pathology
9(7): 475–479, July

Randall G. Lee, M.D.

Marked eosinophilia in esophageal mucosal biopsies

ABSTRACT The significance of marked eosinophilic infiltration in esophageal mucosal biopsy specimens was evaluated in 11 patients. The patients were generally young, with an average age of 14.6 years; all had diffuse intraepithelial eosinophilia in several biopsies. Ten patients (91%) had evidence for reflux esophagitis, which was associated with esophageal stricture in three of the six patients older than 1 year. Marked esophageal eosinophilia might therefore indicate prolonged or severe gastroesophageal reflux. One patient with peripheral eosinophilia, a history of asthma, and concurrent idiopathic eosinophilic gastroenteritis lacked evidence of reflux and represents a case of idiopathic eosinophilic esophagitis. Critical review of the literature establishes three additional cases. Idiopathic eosinophilic esophagitis is an unusual variant of idiopathic, but presumably allergic, eosinophilic infiltration of the gastrointestinal tract.

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Eosinophilic infiltrate and GERD

- Children with reflux esophagitis

Table III. Frequency of histologic abnormalities

Finding	*Patients (%)*
Intraepithelial eosinophils	71
Intraepithelial neutrophils	28
Basal zone hyperplasia or papillary lengthening	46
Ulceration	9
Barrett epithelium	4

Data for 113 patients in whom histologic abnormalities were noted.

J. pediatrics 1983

- Children with presumed GERD treated with amino acid formula

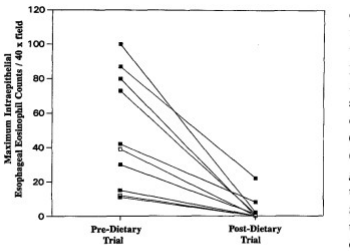

Figure 2. Maximal intraepithelial esophageal eosinophil counts predietary and postdietary trial with an amino acid–based formula. ■, The 8 patients who reported complete resolution of symptoms; □, the 2 patients who reported improvement. The difference between the predietary and postdietary trial maximal intraepithelial eosinophil counts was significant ($P = 0.005$, Wilcoxon signed rank test).

Kelly et al. Gastroenterology 1995

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Updated consensus recommendations for children and adults (2011)

- 2007 Definition: Chronic immune/antigen-mediated Esophageal disease characterized by esophageal dysfunction and eosinophil-predominant inflammation (≥ 15 eosinophils per high powered field) following exclusion of other causes of eosinophilia. Esophageal eosinophilia alone is insufficient to make the diagnosis and unresponsive to PPI.
- 2011 definition: As above plus at least one other histologic feature of eosinophilic inflammation (eosinophilic microabscesses, superficial layering, or extracellular eosinophil granules)
- Endoscopic findings are not part of the definition

Liacouras C et al. J Allergy Clin Immunol 2011

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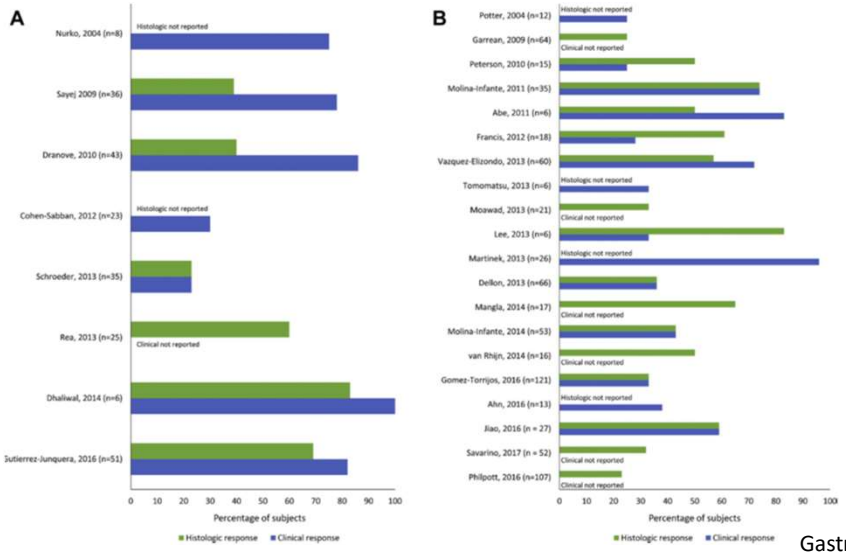
PPI and clinical and histologic response EoE



Gastroenterology 2018

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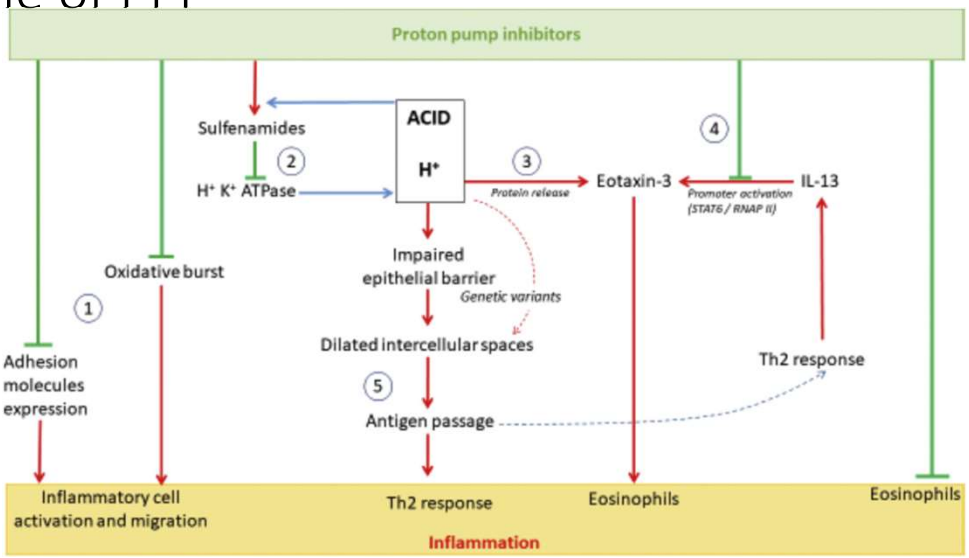
Role of PPI



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AGREE conference
(A Working Group on PPI-REE)

Table 2. EoE Diagnostic Criteria

- Symptoms of esophageal dysfunction
  - Concomitant atopic conditions should increase suspicion for EoE.
  - Endoscopic findings of rings, furrows, exudates, edema, stricture, narrowing, and crepe paper mucosa should increase suspicion for EoE.
- ≥15 eos/hpf (~60 eos/mm^2) on esophageal biopsy
  - Eosinophilic infiltration should be isolated to the esophagus.
- Assessment of non-EoE disorders that cause or potentially contribute to esophageal eosinophilia

Unresponsive to PPI criteria was removed

Dellon et al Gastroenterology 2018

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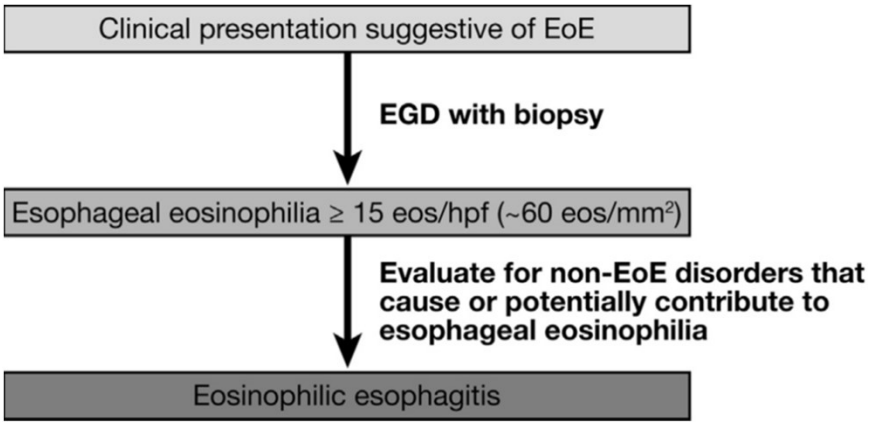
Updated EoE Diagnostic Algorithm



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The presence of esophageal eosinophilia on histologic examination without further consideration of the clinical presentation is not diagnostic of EoE

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Esophageal dysfunction

- Dysphagia (older children)
  - Food impaction ± ER visit
  - Food sticking, slow bolus transit or bolus sensation
  - Choking on food
- Reflux symptoms, abdominal pain and vomiting (younger children)
- Abnormal compensatory eating behaviour
  - Slow eater
  - Chew excessively
  - Cut food into small pieces
  - Lubricate foods
  - Avoid certain foods

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Endoscopy and Biopsy

Endoscopic signs of EoE (including esophageal rings, longitudinal furrows, exudates, edema, strictures, or narrow caliber esophagus, ideally quantified using the EoE Endoscopic Reference Score) and for alternative esophageal disorders. In all cases where EoE is a clinical possibility (even when normal mucosa is visualized), esophageal biopsy specimens should be obtained. As per prior guidelines, **multiple biopsied specimens from 2 or more esophageal levels, targeting areas of apparent inflammation, are recommended to increase the diagnostic yield**. Gastric and duodenal biopsy specimens should be obtained as clinically indicated by symptoms, endoscopic findings in the stomach or duodenum, or high index of suspicion for a mucosal process.

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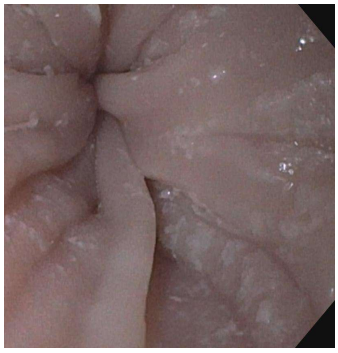
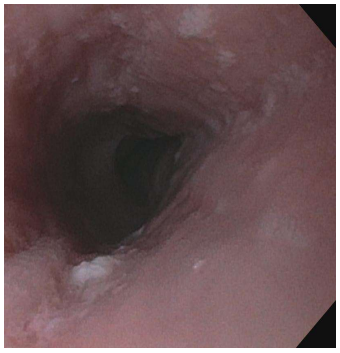
Endoscopy done on 6 weeks PPI





Marked diffuse basal cell hyperplasia is noted with basal cells extending to just beneath the surface. Many intraepithelial eosinophils are present often exceeding 150/high power field at the G-E junction, up to 200/high power field in the distal esophagus and up to 75/high power field in the proximal esophagus.

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Esophageal Eosinophilia

- Eosinophilic Esophagitis
- Gastroesophageal reflux disease
- PPI-responsive esophageal eosinophilia (now a subgroup of EoE)
- Celiac disease
- Crohn's disease
- Eosinophilic gastroenteritis
- Hyper eosinophilic syndrome
- Achalasia
- Infection
- Graft-versus-host-disease
- Vasculitis, pemphigus, connective tissue disorder

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Incidence and prevalence of EoE

- Incidence
  - Over all incidence of 3.7/100,000/Year (Range 2.1 to 12.8)
  - Adult 7.0 /100000/year
  - Children 5.1/100000/year
- Prevalence
  - Over all prevalence of 22/7/100,000 (95% CI 12.4- 36)
  - Adult 43.4/100000 (95% CI 22.5-71.2)
  - Children 29.5/100000 (95% 17.5-44.7)

Aliment Pharmacol 2016;433-15

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Incidence of EoE in Northern Alberta per 100,000/year (2015-2018) under 15 years of age

Age (years)	Edmonton	N. Alberta	Rural	Urban
0 - 4	8.7 (21)	6.4 (33)	0.9 (1)	8.0 (32)
5 - 9	7.6 (17)	9.4 (47)	6.0 (7)	10.4 (40)
10 - 14	18.1 (35)	12.1 (54)	5.5 (6)	14.2 (48)
0 - 14	11.1 (73)	9.1 (134)	4.1 (14)	10.6 (120)

JPGN Report accepted 2021

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Genetics

- First-degree male relatives of patients with EoE had 64- fold (brothers) and 43-fold (fathers) increased risk of EoE,
- Monozygotic and dizygotic twins had a 41% and 22% frequency of EoE, respectively.

Lyles et al. Curr Opin Immunol. 2019

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Risk Factors and Associated Genes

- Male
- Caucasian
- Urban areas
- Atopic background

TSLP / **TSLP-R** (major regulation of Th2 response)

Eotaxin-3 (eosinophils recruitment and activation)

TGF-β1 (tissue fibrosis)

Filaggerin (epidermal differentiation complex)

J allergy and clinl immunol 2011

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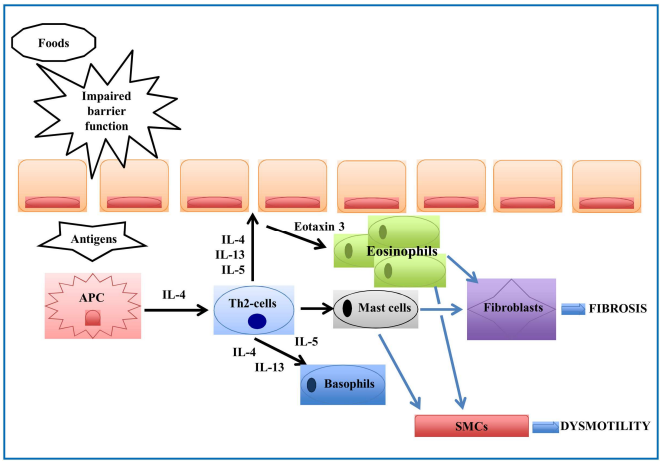
Pathogenesis



Archives de Pediatrie 2019
Am J Physiol gastrointest Liver Physiol 2018

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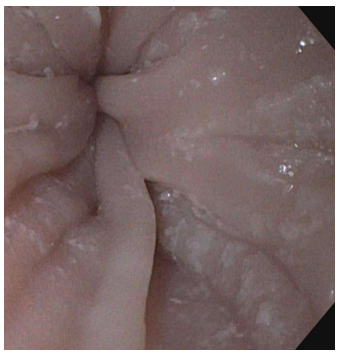
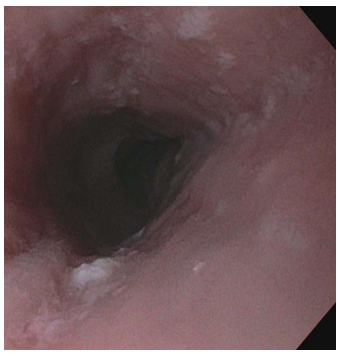
Endoscopy done on 6 weeks PPI





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Natural History of Primary Eosinophilic Esophagitis: A follow-up of 30 adult patients for up to 11.5 years

Table 3. Endoscopic and Histologic Alterations During Follow-Up

	Baseline examination	Follow-up examination	*P*
Overall intensity of endoscopic alterations (%)			
Absent	2 (6.7)	1 (3.3)	
Minimal	17 (56.7)	15 (50.0)	
Moderate	8 (26.7)	12 (40.0)	
Severe	3 (10.0)	2 (6.7)	
Mean histologic markers of inflammatory activity			
Numbers of eosinophils in the esophageal epithelium			
Proximal part (*cells/high-power field*)	78.7 (2–158)	40.3 (0–174)	0.0025
Distal part (*cells/high-power field*)	117.5 (29–402)	40.8 (0–143)	0.0654
Basal cell hyperplasia (%)	65.1 (20–80)	49.5 (20–80)	0.0009
Papillary hyperplasia (%)	79.7 (50–90)	66.4 (60–40)	0.0352

Significance level set at $P = 0.05$.

Gastroenterology 2003;125:1660–1669

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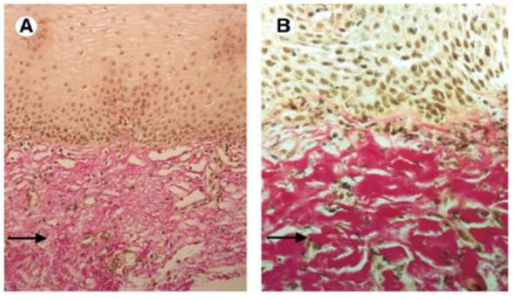

Figure 3. Development of structural changes. (*A*) Photomicrograph from a healthy control individual showing unaffected subepithelial stroma (*black arrow*). (*B*) Photomicrograph from a 46-year-old male patient with a 10-year history of confirmed primary eosinophilic esophagitis. Findings include severe proliferation of the subepithelial fibrous tissue and sclerosis of the subepithelial stroma (*black arrow*). (*A* and *B*: van Gieson staining; original magnification 40 × 10.)

Gastroenterology 2003;125:1660–1669

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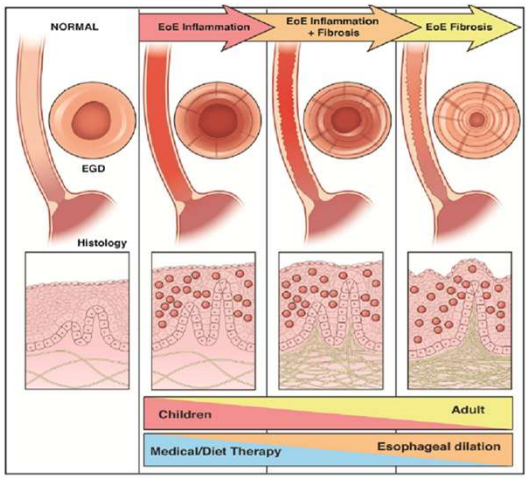
Natural history of EoE



- Risk of fibrostenotic disease
  - double every decade
  - Increase 5% for each year of symptoms
  - Worsening severity of stricture with delay diagnosis
    - >16mm delay up to 5yrs
    - 10 - 16 mm up to 11 yrs
    - < 10mm up to 15 yrs

Dellon ES and Hirano I. Gastroenterology (2017)

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Stricturing disease in pediatric cohort (2015-2018)

	Patients	Median Age at Dx *years* (IQR)	Median Duration Symptoms‡ *months* (IQR)	Symptoms at presentation (%)				
				Food impact.	Dysphagia	Nausea/ Emesis	GER	Heartburn/ Chest pain
Strictures	8	13.1 (9.6-14.0)	15 (12-84)	88	88	25	25	25
*Strictures req. dilatation	4	13.3 (11.0-14.0)	18 (12-84)	75	100	25	0	25
Subtle signs narrowing	11	9.0 (5.4-13.9)	36 (24-60)	55	64	18	9	18
No narrowing	166	9.5 (5.6-12.8)	12 (6-36)	20	55	44	21	17
Overall	185	9.7 (5.7-13.3)	12 (6-36)	25	56	41	20	18

	Median # scopes (IQR)	Scope findings at diagnosis (%)				
		Furrow	LOVP	Trachea.	Exudate	Narrowing
Strictures	3.5 (3-5)	50	63	63	38	88
*Strictures req. dilation	5 (4.5-7)	25	50	50	25	100
Subtle signs narrowing	2 (2-3)	91	82	27	55	55
No narrowing	2 (2-3)	77	54	7	55	0
Overall	2 (2-3)	78	57	11	55	8

Burnett et al JPGN report accepted 2021

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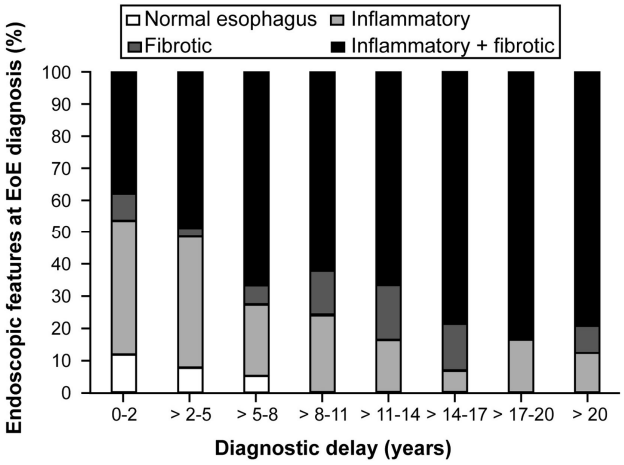
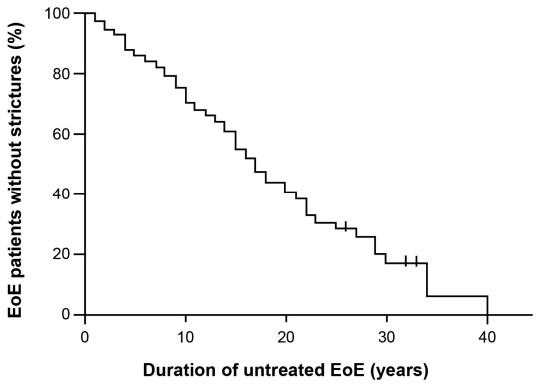
Incidence of Stricturing disease





Schoepfer et al Gastroenterology 2013

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Treatment Considerations

- Not all patients develop fibrostenotic disease: risk benefit analysis of therapy important
- Intermittent therapy may be enough in some cases
- Long term PPI therapy reduces symptoms and eosinophilia in about 50% of patients
- Duration of untreated disease is the best predictor of stricture risk, but it can take decades to develop

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Variability in EoE phenotype

- Symptoms :
  - No Symptoms or Minimal sx
  - Non specific symptoms e.g abdominal pain
  - Dysphagia symptoms - mild to severe
  - Associated with GERD
- Endoscopy / Imaging
  - Inflammatory to stricturing

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Treatment

- Dietary
- Medical
  - Proton-pump inhibitor therapy
  - Steroid – budesonide slurry, swallowed fluticasone
- Management of complications
    - Stricture dilation

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Conclusions

- Diagnostic Criteria for EoE has evolved PPI no longer needed for diagnosis – PPI-REE is considered a subgroup of EoE
- Incidence and risk of stricturing disease is uncertain but likely high
- The pathogenesis of EoE is incompletely understood but involves genetic, environmental, and host immune system factors. The esophagus of EoE patients has an impairment of epithelial cell differentiation and barrier function
- It remains uncertain whether long-term treatment change the natural history of the disease

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Acknowledgements

women & children's health research institute

Canadian Association of Gastroenterology L'Association Canadienne de Gastroentérologie

STOLLERY CHILDREN'S HOSPITAL FOUNDATION

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Case Presentations

- Dr. Mary Sherlock, MB BCh BAO, PhD, FRCPC
- McMaster University, Hamilton

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Acknowledgement

- Pathology slides were provided courtesy of Dr. Jorge Arredondo, Pediatric Pathologist, McMaster Children's Hospital

2

Case 1

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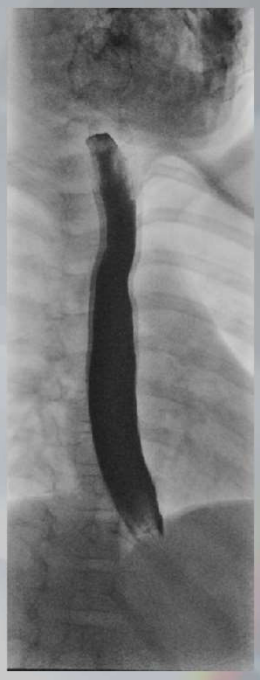
Case 1

- 12 year old boy, referred for dysphagia and 'choking' for several years
- Episodes have occurred with rice and meats
- Has never needed to come to an ER – episodes self resolve
- Past medical history: asthma – on puffers, no eczema or allergic rhinitis
- Brother has asthma
- No known food allergies
- Physical Examination: normal, well grown

Investigations:

- Upper GI barium – normal, no stricture
- Skin prick testing – positive to grass and mold
- Upper endoscopy is planned



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Question #1

- What would you do now?
- Options
  - 1. Start proton pump inhibitor (PPI) trial to rule out reflux as a cause of esophageal eosinophilia prior to doing a scope?
  - 2. Proceed directly to upper endoscopy without a trial of PPI?

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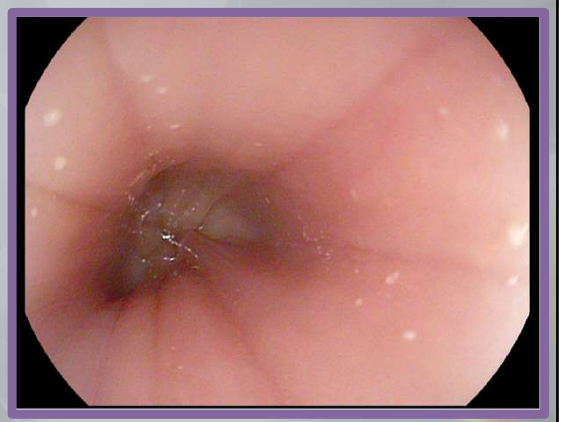
Upper endoscopy completed

Findings:

- Mild linear furrows in distal esophagus
- No rings
- No stricture
- White plaques visible

- EREFS score for distal esophagus
  - edema (1), rings (0), exudate (1)
  - furrows (1), stricture (0)



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Question #2

- How many biopsies will you take?
- Options
  - 1 – take 2 biopsies
  - 2 – take 4 biopsies
  - 3 – take 6 biopsies

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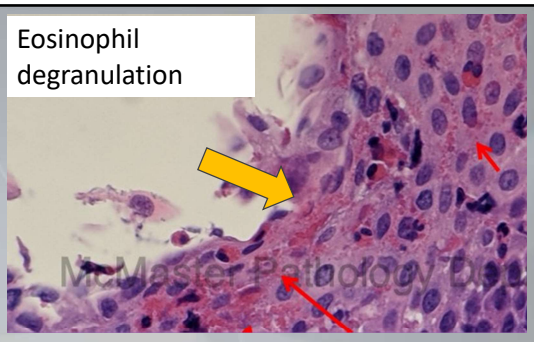
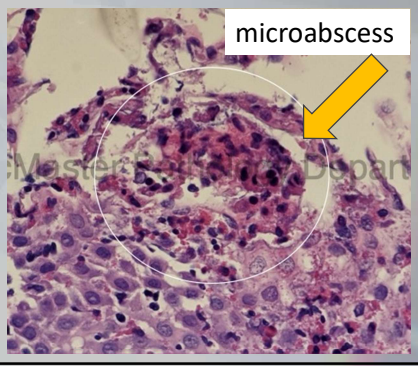
Pathology

HISTOLOGY	Distal esophagus	Mid esophagus
Eosinophil count	55	70
Other features	Eosinophilic microabscesses	





- Options discussed
  - Medical therapy
  - Elimination diet
- Family chose – milk free diet
- Important to involve registered dietician

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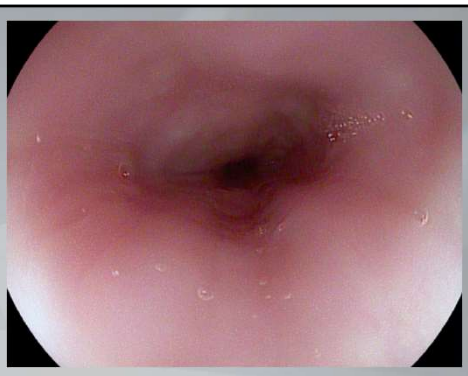
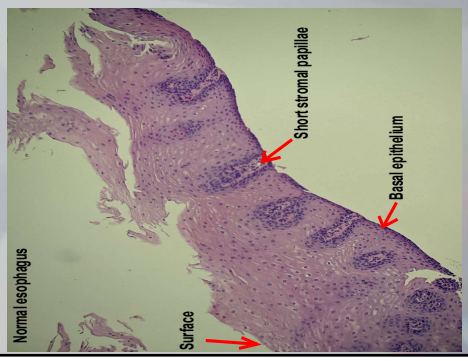
Follow-up endoscopy

- Continued milk-free diet
- Upper endoscopy – normal appearance of the esophagus
- Biopsies - no eosinophils in any level

- Ongoing plan: to continue with milk-free diet
- Ensure adequate calcium and vitamin D intake
- Close attention to growth





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Case 2

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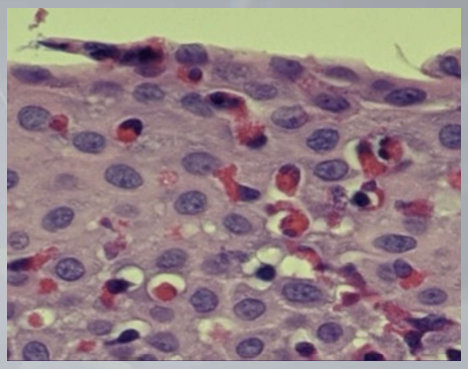
Case 2

HISTORY

- Background: frequent spitting up as a baby, history of eczema
- Dysphagia at 6 years of age (initially to solids then to liquids) – referred to GI at age 10 years
- Weight and height on the 3rd percentile
- Upper endoscopy – narrowing 'stricture' in proximal esophagus
- Other investigations: CBC, albumin CRP, fecal calprotectin and MRE – no evidence of Crohn's Disease



Scope #1			
Esophageal Location	Proximal	Mid	Distal
Eosinophil count/hpf	42	N/A	54
Other features	Eosinophilic abscesses, stricture noted (proximal esophagus)		

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Question #3

- Management options – what would you choose?
  - Option 1: Proton pump inhibitor therapy
  - Option 2: Swallowed topical steroids
  - Option 3: Dietary elimination therapy

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Question #4

- Family chose Elimination Diet – what would you choose?
  - Option 1: Allergy test directed food elimination diet
  - Option 2: 1- food (milk) elimination diet
  - Option 3: 2- food (milk and wheat) elimination diet
  - Option 4: 6 - food elimination (milk, wheat, soy, egg, nuts, shellfish) diet

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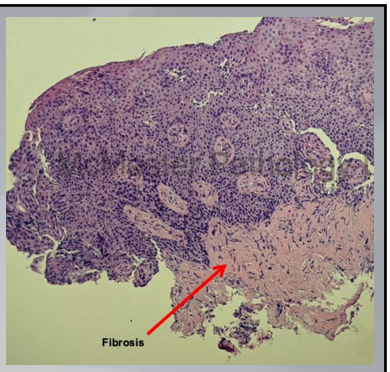
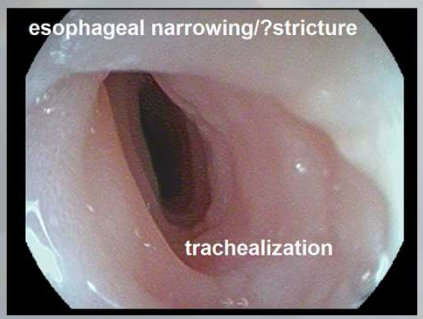
Family chose allergy test directed elimination diet

Patch testing:
reacted to beef, chicken, milk, rice





Scope # 2 (Dietary Restrictions)			
Esophageal Location	Proximal	Mid	Distal
Eosinophil count/hpf	Not reached	150	Not biopsied
Other features	Spongiosis, basal hyperplasia		

Treatment Change
Started swallowed budesonide 1.0 mg PO BID

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Follow up

- Feels well on budesonide
- Occasional dysphagia with large food pieces
- Scope reported as showing no stricture – but size 2.4 scope used (size 2.8 was not available)
- Histology: 33 eosinophils/hpf in distal esophagus biopsy, none seen in mid and proximal biopsy

- Subsequent course: finished budesonide, still had some food restrictions, intermittent use of budesonide to help with dysphagia
- Annual 8 am cortisol levels, and one ACTH stimulation test (normal)

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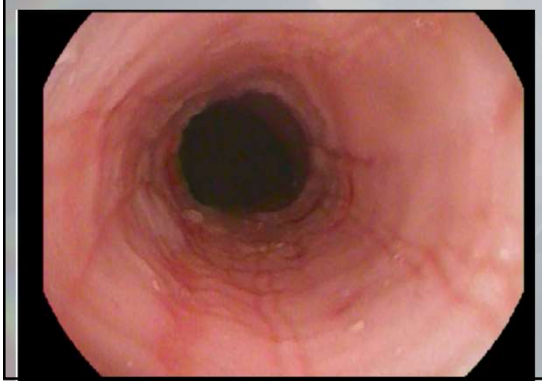
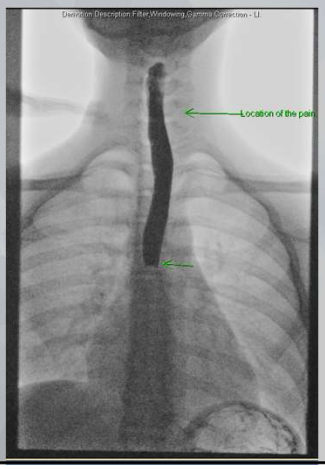
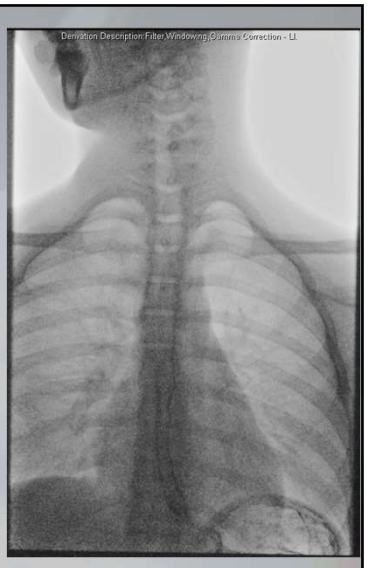
A few years later…….

- Variable food restrictions
- Used budesonide intermittently
- Noted increasing dysphagia



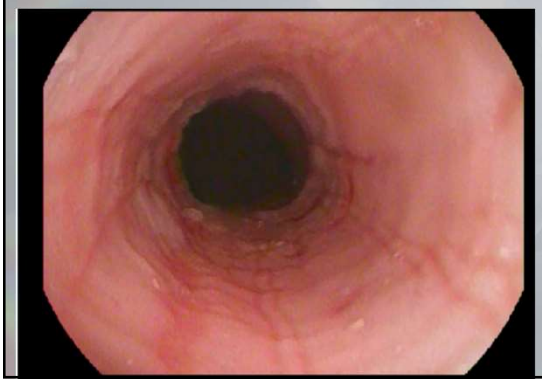


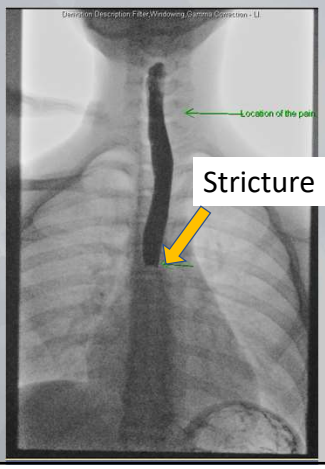


16

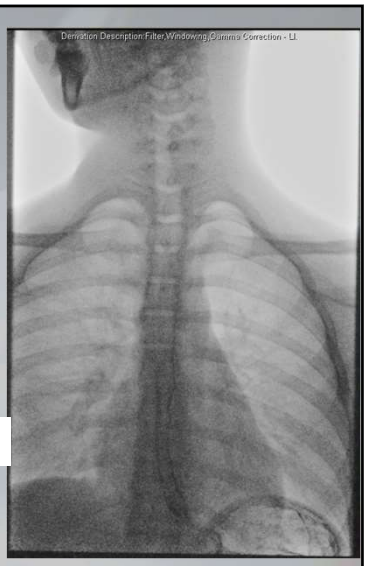
A few years later…….

- Variable food restrictions
- Used budesonide intermittently
- Noted increasing dysphagia





Stricture



Underwent dilation in interventional radiology

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Next steps

- Given the stricture and active EoE on biopsy → 8 weeks of swallowed budesonide after the stricture was dilated
- Discussed ongoing budesonide versus empiric elimination diet
- Height remains on low centile, but has normal growth velocity
- Normal ACTH stimulation test
- Family chose 6-food elimination diet

Eliminated milk, wheat, soy, eggs, nuts, fish

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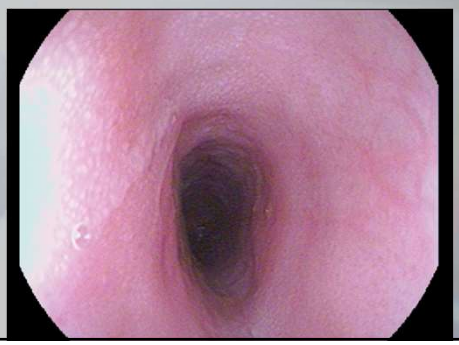
Follow up scope

- Macroscopically normal, though some resistance to scope passage in mid esophagus
- Biopsies normal
- Scope with dairy introduction – active EoE
  - Confirming milk as a true allergen
- Now trying to reintroduce wheat
- Plan to reintroduce foods in a sequential manner



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Case 3

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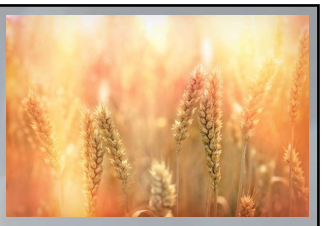
Case 3

- 2 year old child, referred for failure to thrive
- Anemia (Hgb 74), iron deficient, anti-TTG positive: level of 125 CU, lab normal < 30

21

Case 3



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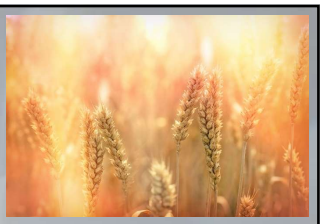
→ Celiac Disease Suspected

22

Case 3



- 2 year old child, referred for failure to thrive
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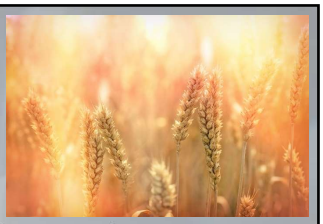
→ Celiac Disease Suspected

- Upper endoscopy: **stricture** in distal esophagus and scope did not pass through
- White plaque covering 40% of the surface area with possible underlying ulcer
- Proximal to the narrowing, there was furrowing of the esophagus and it appeared leathery, difficult to obtain biopsy → 2 esophageal biopsies obtained, no duodenal biopsies

23

Case 3



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- Proximal to the narrowing, there was furrowing of the esophagus and it appeared leathery, difficult to obtain biopsy → 2 esophageal biopsies obtained, no duodenal biopsies

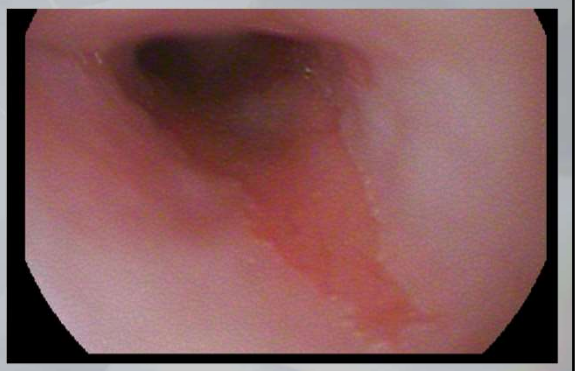
→ Suspicious for EoE

- Retrospective history – some dysphagia, esp for meats, would gag vomit up foods
- Histology – marked basal cell hyperplasia, eosinophil count 30/hpf
- Six-food elimination diet initiated along with PPI

24

Follow up endoscopy

- On 6 food elimination diet (dairy, wheat, soy, egg, nuts, shellfish)
- Mucosa looked normal - ? Small tongue at site of healed stricture
- No white plaques or furrows
- Esophageal biopsies: mild spongiosus, no increase in eosinophils.
- Duodenal biopsies were normal (remember, still gluten-free)



25

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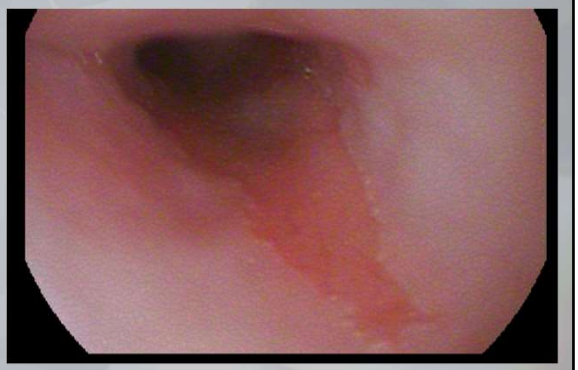
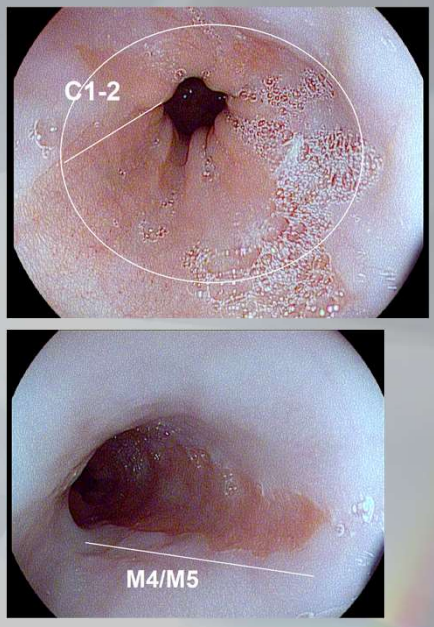


Six-food elimination diet has been a success

26

Subsequent course

- Gradual reintroduction of all foods, followed by scopes after each food reintroduction
- Continued on proton pump inhibitor
- No recurrence of esophageal eosinophilia
- Duodenal biopsies normal when gluten reintroduced
- HLA DQ2/DQ8 – absent
- Continued to see salmon-coloured tongue in the esophagus – columnar epithelium



27

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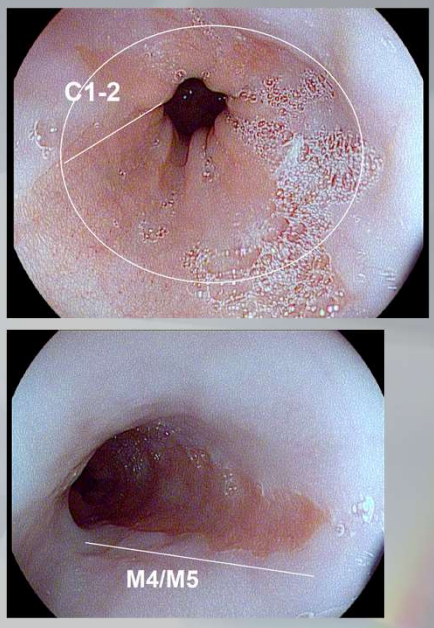

Barrett's Esophagus

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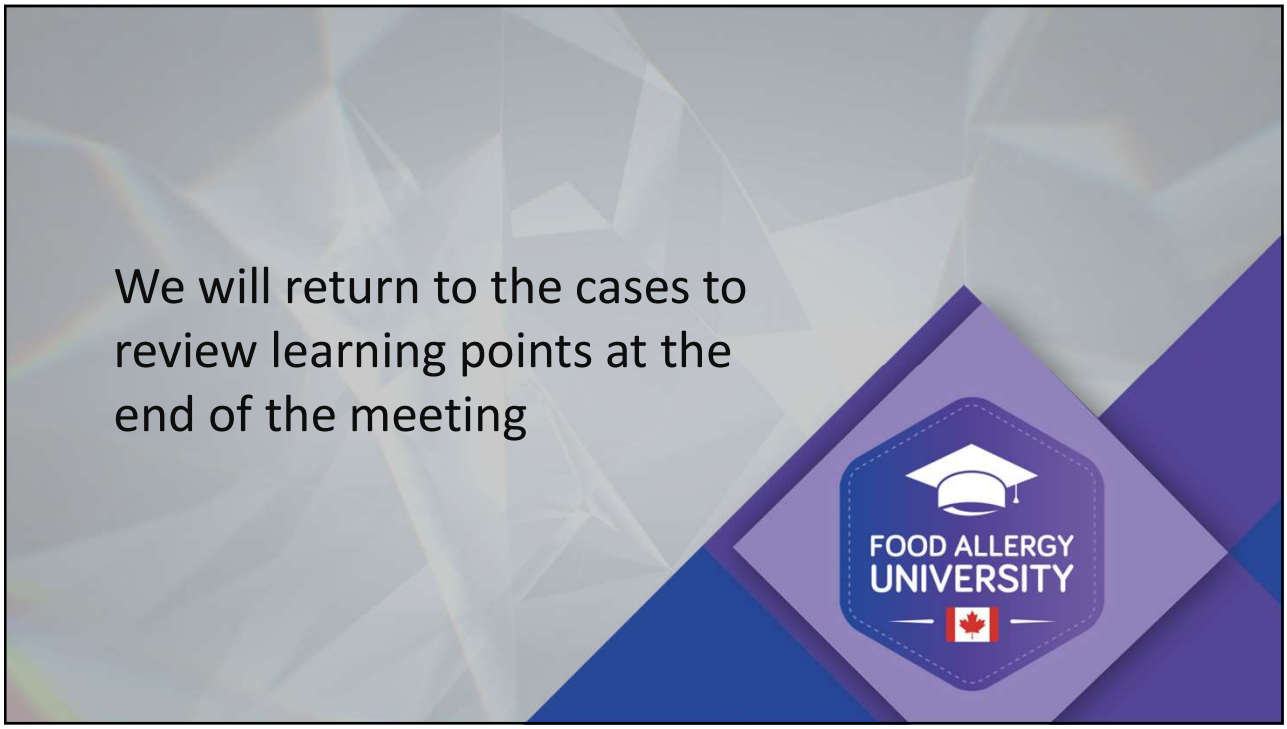
We will return to the cases to review learning points at the end of the meeting
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Nutritional Management of EoE

Implementation of elimination and/or elemental diets

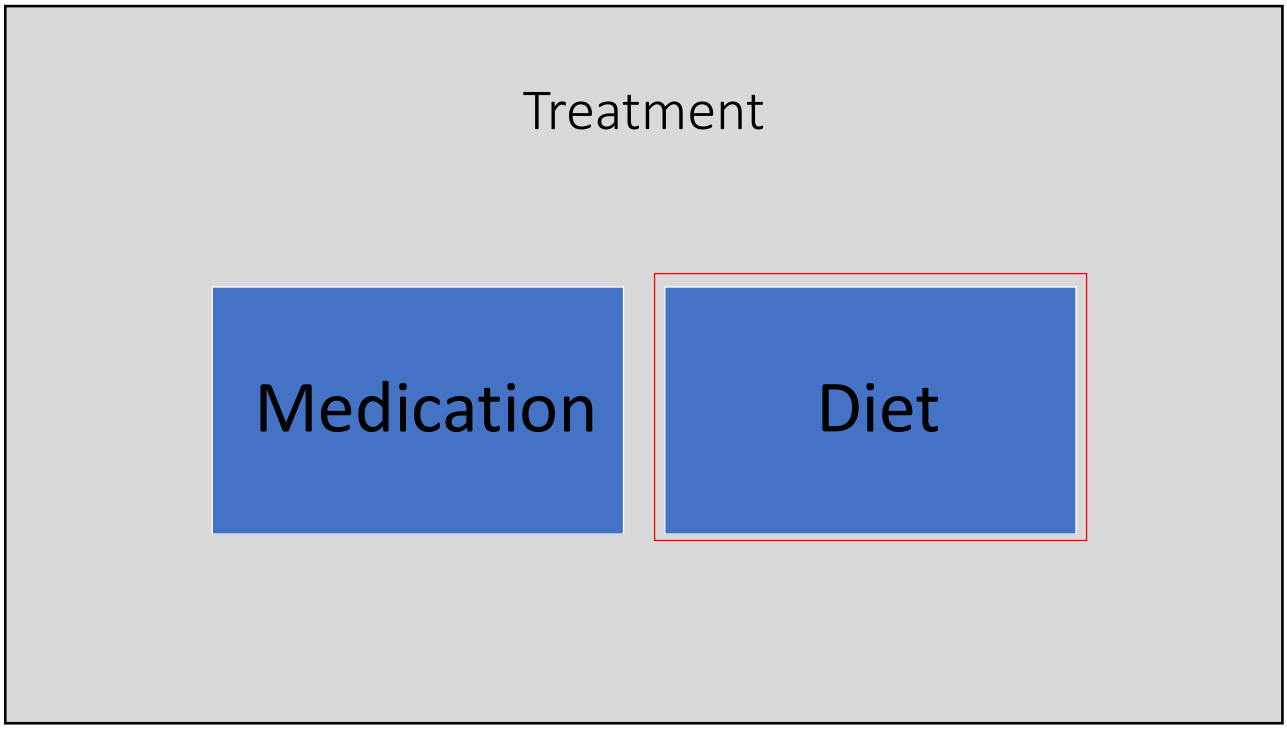
Vishal Avinashi, MD
BC Children's Hospital

1

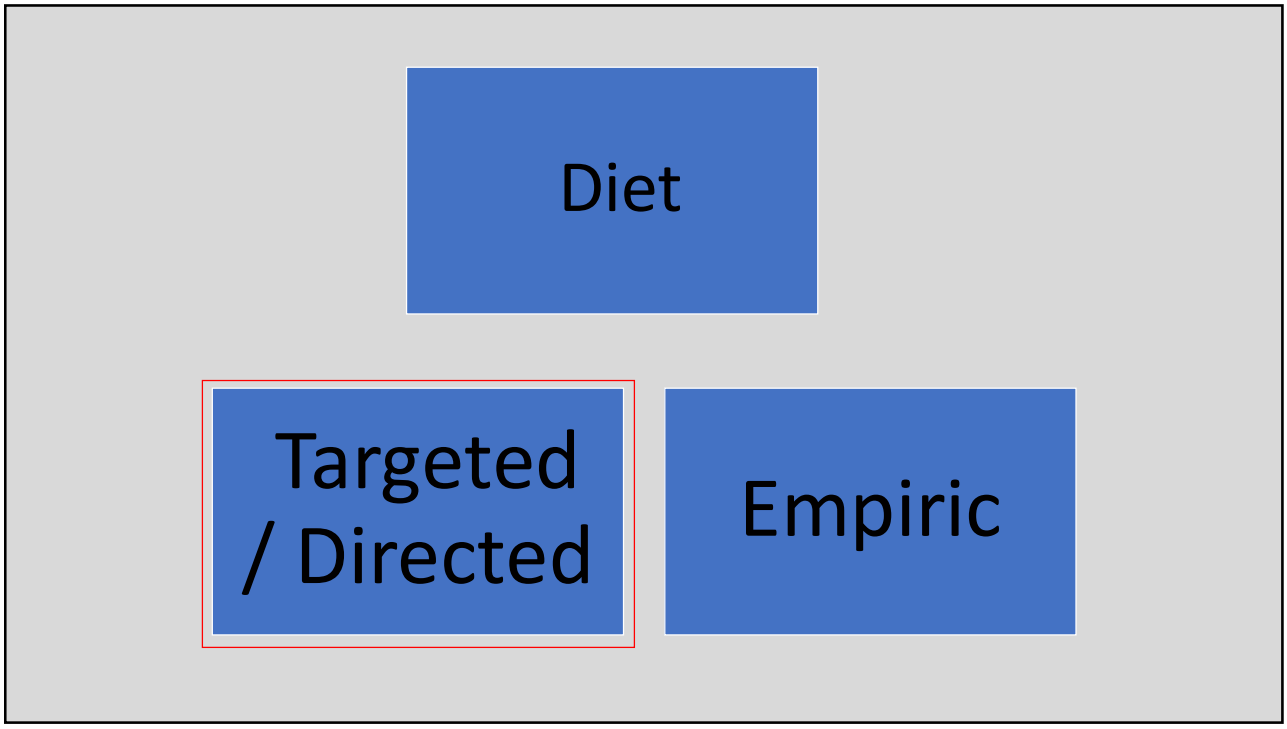
Objectives

- 1. Understand the breadth of dietary interventions for the management of EoE
- 2. Evaluate the current literature in terms of efficacy of food elimination
- 3. Highlight circumstances where you may not want to consider dietary interventions

2

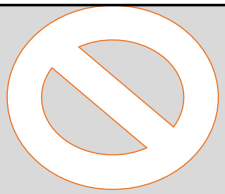

Treatment
Medication
Diet

3


Diet
Targeted / Directed
Empiric

4

Directed Elimination



- Use testing to decide what to eliminate
- SPT useful for IgE responses
- APT – patch testing
  - poor standardization
  - not very available
- Inconsistent results
- 24-65% response

Henderson, C. et al. 2012 J Allergy Clin Immunol
Liacouras, C. A et al. (2005) Clin Gastroenterol Hepatol 3(12): 1198-206.
AGA – GI / Allergy Guideline - Gastroenterology 2020;158:1776–1786

5

Management

Diet

Targeted / Directed

Empiric

6

Dietary Management in EoE

- **Elemental**
  - Formula, No other food
- **6 Food Elimination Diet (FED)**
  - No Milk, Soy, Eggs, Wheat, Nuts and Seafood
- **4 FED**
  - No Milk, Soy, Eggs, Wheat
- **2 FED**
  - No Milk, Wheat
- **1 FED**
  - No Milk

7

Dietary Management in EoE

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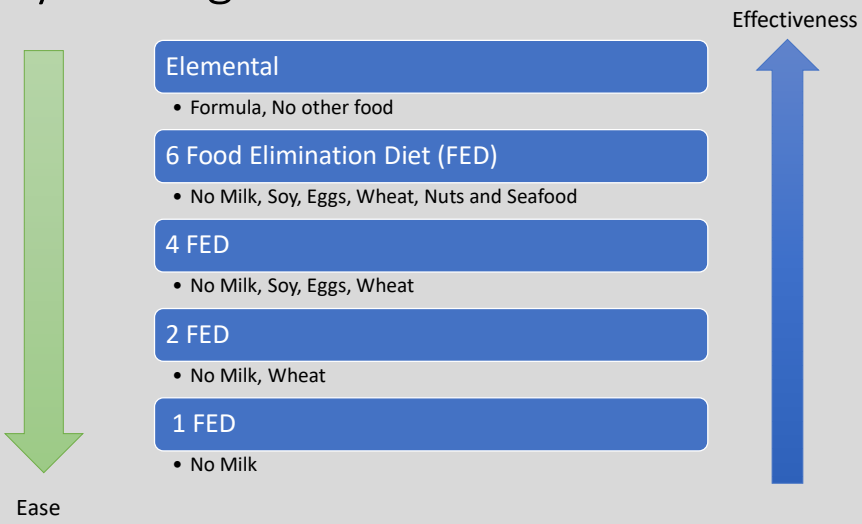
8

Dietary Management in EoE



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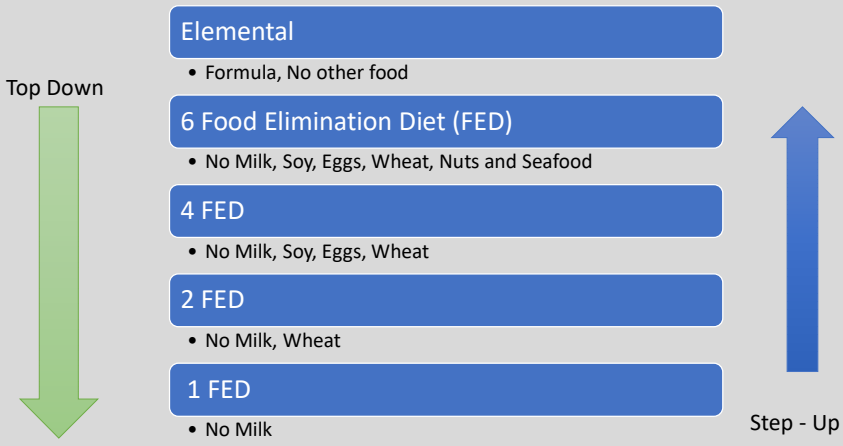
Dietary Management in EoE



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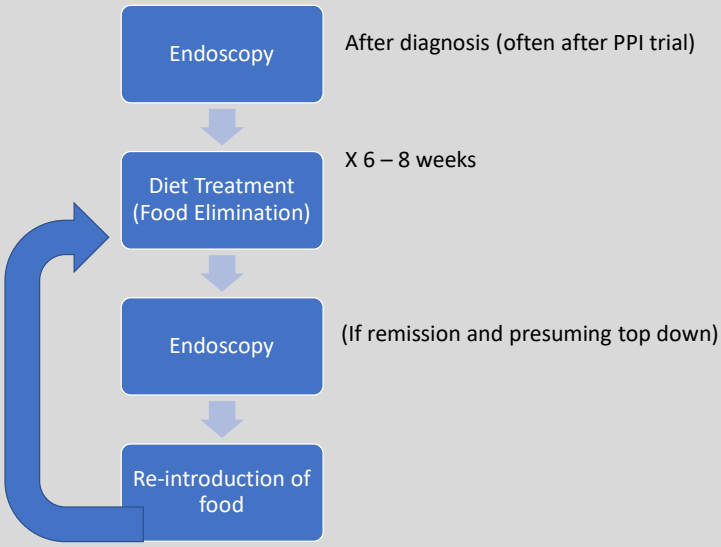
Process of dietary treatment



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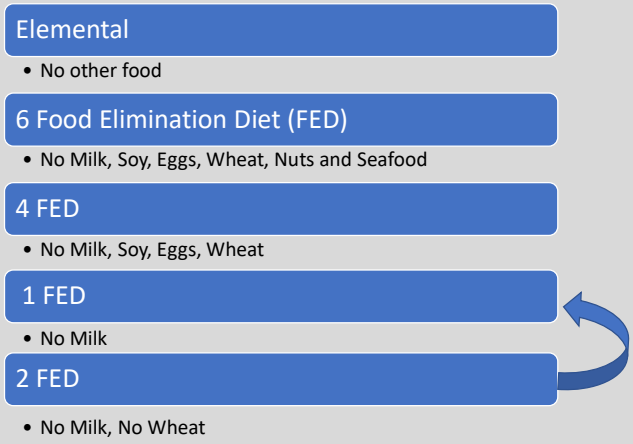
Historic Perspective Management in EoE



12

Elemental

Historic Perspective

- Kelly, 1990s identified patients not responding to typical GERD treatments, some with fundos, with persistent symptoms and high esophageal eosinophils

- The FIRST treatment was an **elemental diet** x weeks (amino acid treatment) with demonstration of improved symptoms (resolution in most) and decrease (often resolution) of esophageal eosinophils.

Kelly, K. J., A. J. Lazenby, et al. Gastroenterology. 1995 109(5): 1503-12.
Davis CM, Sampson HA. J Allergy Clin Immunol Pract. 2021 Sep;9(9):3288-3289.

13

Elemental

- Most effective dietary approach
  - > 95% response rate
- Barriers:
  - $$$
  - Palatability
    - Often need NG support
  - Hard to maintain
  - Reoccurs with food reintroduction
  - QOL

Markowitz, J. E., J (2003). Am J Gastroenterol 98(4): 777-82.

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6 Food Elimination Diet

Re-introduction of foods after 6FED

~70% response

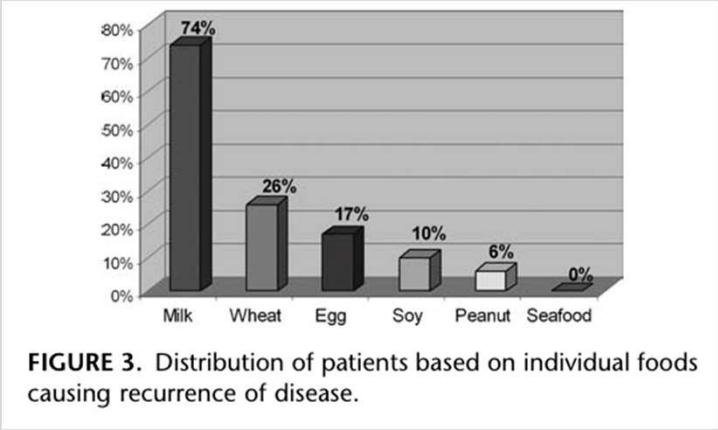

FIGURE 3. Distribution of patients based on individual foods causing recurrence of disease.

Kagalwalla AF, 2006 Sep;4(9):1097-102.
Kagalwalla et al, JPGN 2011; Aug 53:145-149

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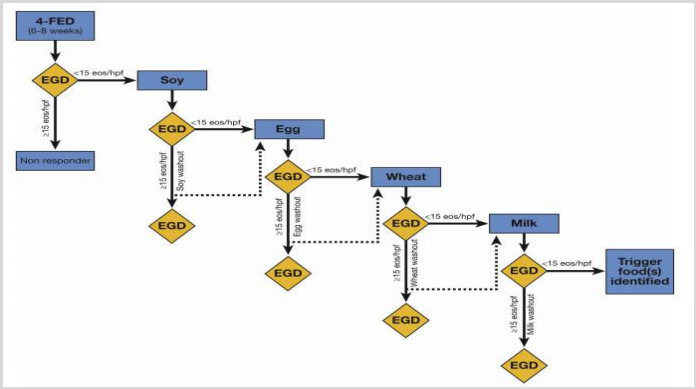
4 Food Elimination Diet

- Easier than six foods
- Fewer scopes
- 64% histological remission



Kagalwalla AF, et al Efficacy of a 4-Food Elimination Diet for Children With Eosinophilic Esophagitis. Clin Gastroenterol Hepatol. 2017 Nov;15(11):1698-1707.e7

16

1 FED = Milk Free Diet / Dairy Free Diet

n= 31

Strict

- No milk or trace of dairy products
- 67% response

Liberalized

- Avoid milk, cheese, yogurt and other major sources of dairy
- Allows baked products containing milk
- 29% response

Teoh T, Mill C, et al (2018) Journal of the Canadian Association of Gastroenterology.

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2 FED

- Newer Approach
- Start with milk and wheat elimination
- Suggestion to step up if no response to diet
  - Aka 2 - 4 - 6
- Trial re-introduction if in remission
- Has been shown to decrease number of endoscopies and time through trials (~ 30%)

Molina-Infante J (2018). J Allergy Clin Immunol.

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Diet Name	What's Eliminated?	Response rate
Elemental	All Intact Protein	96-97%
6FED	Milk, Soy, Eggs, Wheat, Seafood, Nuts/peanuts	70%
4FED	Milk, Soy, Eggs, Wheat,	64%
1 FED	Milk Strict vs. Liberalized	25-60%
2-4-6 FED	2- Milk and Wheat 4- Egg and Legumes 6- Nuts and Seafood	43% (2FED)

Citation
Gonsalves, N., G. Y (2012). Gastroenterology 142(7): 1451-9 e1
Kagalwalla AF, et al. (2017) Clin Gastroenterol Hepatol. 2017;15:1698-1707.e7.
Kagalwalla et al, (2011) JPGN; Aug 53:145-149
Kagalwalla, A. F., T. A. (2006). "Clin Gastroenterol Hepatol 4(9): 1097-102.
Kelly, K. J., A. J. Lazenby, et al. (1995). Gastroenterology 109(5): 1503-12.
Liacouras, C. A., J. M. Spergel, et al. (2005). Clin Gastroenterol Hepatol 3(12): 1198-206.
Markowitz, J. E., J (2003). Am J Gastroenterol 98(4): 777-82.
Molina-Infante J (2018). J Allergy Clin Immunol.
Molina-Infante, J., Lucendo, A. J. (2020) Current Opinion in Gastroenterology 36(4):359-363
Teoh T, et al. (2018) Journal of the Canadian Association of Gastroenterology.

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Various dietary management strategies for EoE – pooled response rates

Dietary Management Strategy	Children %	Adult %
Elemental diets	90	94
Six-food elimination diet	73	71
Four-food elimination Diet	60	46
Two-food elimination diet	43*	
Milk elimination diet (1 food only)	66	100
Allergy test-directed diet	48	32

Arias A, González-Cervera J, Tenias JM, Lucendo AJ. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. Gastroenterology. 2014 Jun;146(7):1639-48. *Chang JW, Haller E, Dellon ES. Dietary Management of Eosinophilic Esophagitis: Man Versus Food or Food Versus Man? Gastroenterol Clin North Am. 2021 Mar;50(1):59-75.

20

Unknowns

- How do we evaluate adherence?
- Definition of Response?
  - Is there a role for symptomatic improvement? Is remission defined the same?
- How strict one must be with the eliminated food(s)?
  - Is baked ok?
  - Are trace amounts ok? Soy Lecithin?
  - Beyond QOL, is strict elimination increasing risk of IgE?
  - Is it wheat or gluten elimination?
  - Why do some places eliminate legumes (lentils) with soy.
  - How about Peanut, shouldn't that be with legumes or with nuts?
  - Why do some places eliminate – beyond – meats, corn, other….

21

When would you consider against dietary interventions

- It is not PATIENT centred
  - Including awareness of repeat endoscopic evaluation
  - Not sustainable – i.e. treatment is worse than the underlying condition
- Poor nutritional status
- Poor relationship with food / aversion / ARFID
- Multiple IgE food allergies
- Resources / Education
  - $ - diary and wheat free alternatives are more costly
  - Parental - Social
  - Lack of RD to support families
- Patient has a stricture

22

Real life

- It's how you sell it – about 45% of our patients have tried dietary therapy
  - Females slightly more

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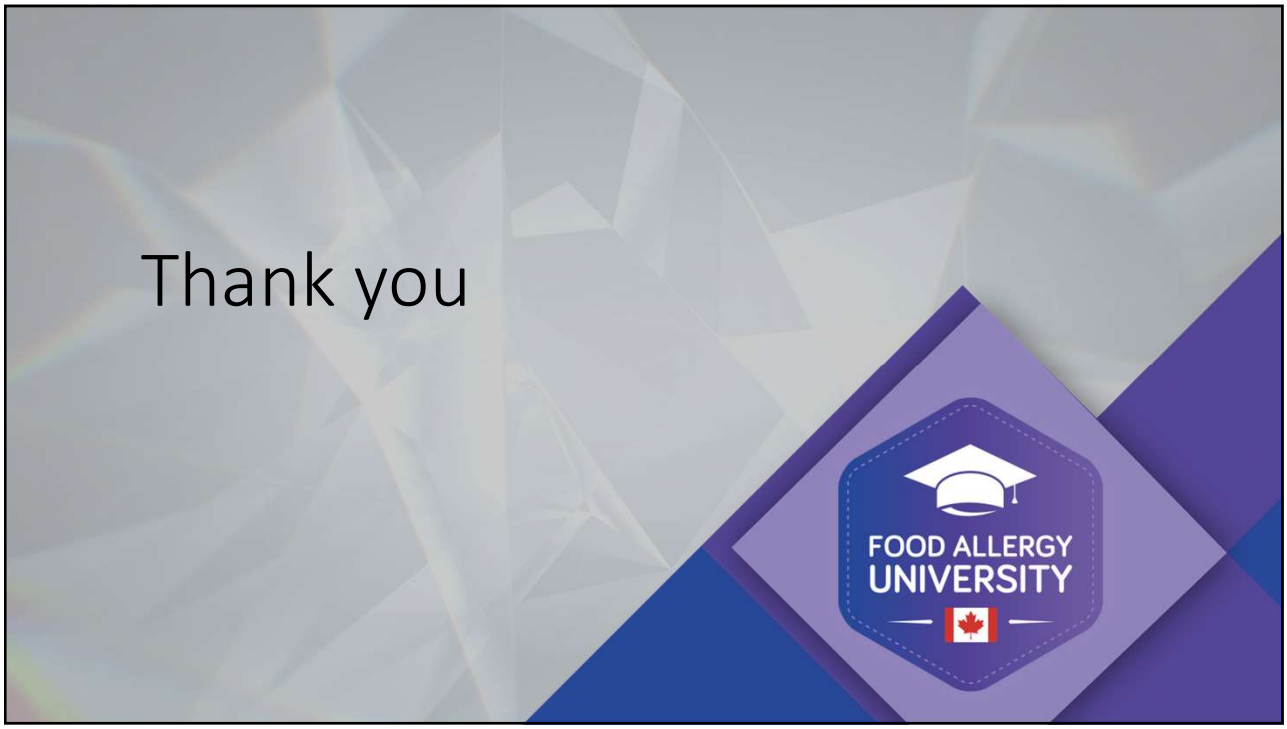
Objectives

- 1. Understand the breadth of dietary interventions for the management of EoE
- 2. Evaluate the current literature in terms of efficacy of food elimination
- 3. Highlight circumstances where you may not want to consider dietary interventions

24



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What does elimination diet look like for families? Empowering your patients on an elimination diet

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Inez Martincevic MSc, RD
The Hospital for Sick Children
January 12, 2022

1

Learning Objectives

1. Review evidence for the efficacy of an elimination diet in managing EoE
2. Highlight the nutritional considerations of an elimination diet in EoE
3. Discuss practical considerations in implementing an elimination diet for EoE

2

EoE: Diet Management

EoE is a chronic immune condition mediated by allergic sensitization to food antigens

- Concept of food allergens as "trigger" for EoE introduced in 1995
- Management: amino acid–based formula for at least 6 weeks

Subsequently many studies have reported the effectiveness of dietary management for EoE in children and adults

- Dietary goal is to identify food triggers that will induce and maintain remission
- Limited evidence for the use of elimination diet in managing EGIDs

Kelly KJ, et al., 1995; Lucendo AJ, et al., 2017; Molina-Infante J and Lucendo AJ, 2018; Cotton CC, et al.., 2019

3

Dietary Management: Approaches

Dietary Approaches in Managing EoE	
Diet	**Foods Eliminated**
• Elemental	• Eliminate food antigens • Amino acid formula

• Food allergy guided elimination diet
  • Skin prick testing
  • Atopy patch testing
	• Eliminate food that elicits +ve test response

• Empiric elimination diet
  • Six-food elimination diet (SFED)
  • Four-food elimination diet (FFED)
  • Two-food elimination diet (TFED)
  • Dairy/CMP free
	• Eliminate specific foods:
	  • Dairy, wheat, egg, soy/legumes*, tree nuts, fish & seafood
	  • Dairy, wheat, egg, legumes*
	  • Dairy, wheat

*Legumes includes beans, soy, lentils, peas and *peanut*
(In Spain, lentils, chickpeas and/or peas may be consumed)

Lucendo AJ, et al., 2017; Molina-Infante J and Lucendo AJ, 2018

4

Dietary Management: Efficacy

Diet	Outcomes

• Elemental
• Allergy-guided
• Empiric elimination (*step-up* vs step-down)
	• 90% histological remission rate among children and adults
	• Utility of allergy tests in the identification of food triggers
	  • Poor in adults (~30% remission rate)
	  • Variable in children (~50% clinical ± histological remission rate)
	• Variable remission rates (~40-80%)

Molina-Infante J and Lucendo AJ, 2018; Arias A, et al., 2014; Warners MJ, et al., 2017; Warners MJ, et al., 2017; Peterson KA and Boynton KK, 2014 Spergel JM, et al., 2002; Spergel JM, et al., 2002; Molina-Infante J, et al., 2012; Wolf WA, et al., 2014; Wright BL, et al., 2016; Molina-Infante J, Arias A, et al., 2018

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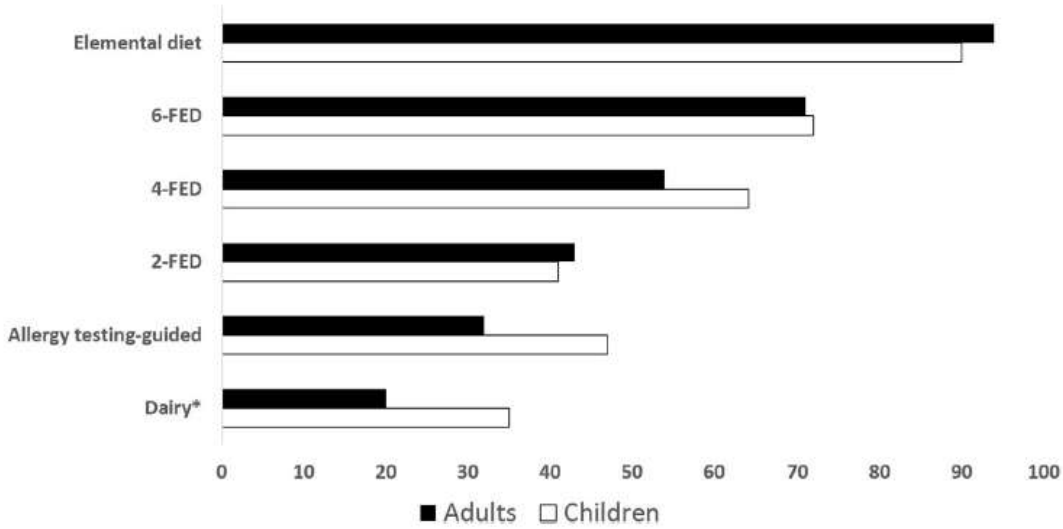

FIG 1. Histologic remission rates broken down by age group and shown by different modalities of dietary therapy (elemental diet, empiric elimination diet, and allergy testing–guided elimination diet) for EoE. *Indirect data from prospective studies on 4-FEDs and 2-FEDs. Efficacy of milk elimination diets in children ranges from 33% to 56%.

Molina-Infante J and Lucendo AJ, 2018

6

Dietary Management: Benefits and Challenges

Benefits	Challenges
Elemental Diet	
• Efficacious • Quick response time	• Palatability (administration route) • Cost • Adherence • Long term use in children may impact oral-motor and developmental skills
Empirical Diet	
• Moderate efficacy • Less foods to reintroduce vs elemental (endoscopies) • No allergy testing • May be cost effective long term (vs topical steroids)	• No standardized approach • Psychosocial impact • Long term data lacking e.g. risk of developing IgE allergy, change to gut microbiota

Molina-Infante J and Lucendo AJ, 2018; De Vlieger L, et al., 2021; Chehade M and Brown S, 2020

7

Dietary Management: Considerations

Considerations
Age of patient
Nutritional status • Presence of malnutrition • Feeding issues (e.g. dysphagia) • Food avoidance issues (e.g. anxiety, fear) • Foods already restricted (e.g. confirmed allergy)
Psychosocial • Assessing patient/family willingness, motivation • Social support system • Financial support • Readiness to undergo multiple endoscopies (based on individual clinical practice)

Chehade M and Brown S, 2020

8

EoE: Nutritional Status

Assessing Nutritional Status
Disease • *Severity and symptoms* • *Comorbidities e.g. IgE food allergy, ASD, etc.*
Anthropometrics • Height, weight and BMI
Intake
Biochemical • Nutritional deficiencies

TABLE 1 Common Symptoms of EoE in children and adults

Children	Adults
Feeding difficulties n	Dysphagia
Food aversion	Food impaction
Decreased appetite	Decreased appetite
Heartburn	Heartburn
Chest pain	Uncommon
Abdominal pain	Uncommon
Gagging	Uncommon
Nausea	Nausea
Regurgitation	Regurgitation
Sialorrhea	Sialorrhea
Vomiting	Vomiting
Slow growth/failure to thrisev/weight loss	Uncommon
Cough	Uncommon
Dysphagia (older children)	Common
Food impaction (adolescence)	Common

Cianferoni A, et al., 2019

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EoE: Under- and Over-Nutrition

Table 3. Studies reporting underweight and failure to thrive in children and adult patients with EGIDs.

Author, Year	Country	Study Design	Sample Size	Population	Outcomes
Hoofien et al., 2019 [39]	Europe	Multicentric retrospective study	410 EoE patients	Children	The most frequent indications for endoscopy were dysphagia (38%), gastroesophageal reflux (31.2%), food impaction (24.4%), and FTT (10.5%).
Chehade et al., 2018 [40]	U.S.A.	Multicentric study	705 EoE patients	Children and adults	FTT was present in 21.3% of enrolled subjects and was significantly common in children. Common pediatric comorbidities were neurological/developmental disorders, gastric tube placement, prematurity, atopic dermatitis, and food allergy.
Alhmoud et al., 2016 [41]	U.S.A.	Retrospective study	13 EoGE patients	Children and adults	FTT and weight loss were observed only in children. Two children (15%) had severe mucosal involvement leading to malabsorption, FTT, and weight loss.
Paquet et al., 2016 [42]	Canada	Retrospective study	62 EoE patients	Children	Sixty-two children were enrolled. Of these, 15 (24%) met at least one criterion for FTT.
Colson et al., 2014 [43]	France	Retrospective study	59 EoE patients	Children	Most children had negative WFH z scores, and 10% had nutritional indices compatible with moderate malnutrition. Nutrition therapy (elemental and six food elimination diets) did not impair nutritional status.
Spergel et al., 2009 [44]	U.S.A.	Retrospective study	620 EoE patients	Children	FTT/feeding issues and GERD-like symptoms were the most common presentations in the youngest children. (118 patients).

EoE, eosinophilic esophagitis; EoGE, eosinophilic gastroenteritis; FTT, failure to thrive; GERD, gastroesophageal reflux disease; WFL, weight-for-length.

- Further studies needed to substantiate clinical reports regarding the relationship between EGID's and overweight/obesity

Votto M, et al., 2021

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EoE: Intake

Table 6. Useful questions to ask patients with EoE (Adapted from Muir et al., 2019) [59].

Does the patient take longer than others to eat?
Does the patient have to be reminded to chew a lot?
Does the patient need to cut food, especially steak, into small pieces?
Does the patient always need to drink during the meals?
Does the patient eat steak or crusty bread?

- Symptoms
  - Adherence to prescribed intervention
- Feeding behaviour(s)
- Food restriction(s)
- Psychosocial

Cianferoni A, et al., 2019; Votto M, et al., 2021; Groetch M, et al., 2013; Skypala I, et al., 2021

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Dietary Management: Foods to Eliminate

Strict elimination requires:

- Avoidance of all sources of potential antigen e.g. CMP
  - Some ingredients may be allowed e.g. soy lecithin
- Knowledge and understanding of product label reading
  - E.g. “may contain” statements

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Milk	Wheat	Egg	Soy	Peanuts and Tree Nuts	Fish and Shellfish
Milk and dairy products Including: Casein; lactalbumin; lactoferrin; lactoglobulin; lactose; milk protein hydrolysate; milk solids; milk sugar; whey	Foods containing wheat and wheat flour such as bread, pasta, crackers, cookies, cereals, and cereal bars Including: Bulgar; couscous; cracker meal; enriched wheat flour; farro; hydrolyzed wheat protein; kamut/wheatgrass; matzoh; semolina; spelt; wheat bran; wheat ger; wheat gluten; wheat malt; whole wheat berries	Egg whites and egg yolks from birds such as chicken, duck, turkey, goose, and quail Including: albumin; ovalbumin; meringue; livetin; lysozyme; ovoglobulin, globulin; ovo vitellin, vitellin; ovomucin;	Soybeans and soy products Including: Edamame; tofu, bean curd; tempeh; miso; natto; soy, shoyu, tamari sauce; soy-based cheese, flour, ice cream, milk, nuts, sprouts, yogurt; soy protein isolate, texture vegetable protein; hydrolyzed vegetable protein **Legumes may also be trigger foods**	Whole peanuts and tree nuts as well as processed foods containing peanuts and tree nuts Including: Artificial, beer, mixed, ground monkey nuts; cold pressed, expeller, or extruded peanut or tree nut oils; arachis oil; all tree nuts, nut butters; natural nut extract; nut meal, paste, meat, pieces	All fish and shellfish
Milk may also be present in: Baked goods e.g. bread, rolls, etc.; cereals; crackers; artificial butter flavor; lactic acid starter culture and other bacterial cultures; non-dairy products (such as non-dairy creamer); luncheon meat, hotdogs and sausage	Wheat may also be present in: Starch (modified, vegetable); soy sauce; surimi; ready-made foods e.g. gravy and soups **Foods labelled gluten-free are also wheat free**	Egg may also be present in: Bakes goods e.g. bread, rolls, etc.; marshmallows; pasta/noodles; surimi	Soy may also be present in: Asian cuisine; vegetable gum, starch, or broth; meatless or veggie burgers; margarine	Nuts may also be present in: Pesto; baked goods; candy; Asian, African or Mexican cuisine; enchilada, mole sauce	

Skypala I, et al., 2021

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Foods to Eliminate: Considerations

Concerns

- Adherence
- Risk of Developing Allergy

Strictness

- Traces of antigen e.g. CMP in margarine
- Baked goods e.g. cookies, muffins

Baked

- Heat/temperature of at least 350 F
- Baking for at least 30 min.
- For dairy allergy: mix ~1:1 dairy to grain flour

Leung J, et al., 2013; Brown TM and Leung J, 2019; Teoh T, et al., 2019

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EoE: Biochemical

- Compromised dietary intake affects nutrient stores
- Limited data reporting nutrient deficiencies pre- and post-intervention for EoE
  - Except vitamin D status; etiology unclear e.g. diet, geographical, etc.

Fissinger A et al., 2021; Groetch M, et al., 2013

Nutrient	Common Food Sources of Nutrient
Protein	Meat & poultry, seafood, legumes, milk and dairy products, soy products, egg, nuts, seeds
Vitamin D	Fortified cow milk or other fortified beverages, fish (salmon, sardines, herring), fortified yogurt or alternative yogurt, irradiated mushrooms
Zinc	Red meat, poultry, legumes, nuts, whole grains, fortified breakfast cereals, wheat germ, pumpkin and sesame seeds, dark chocolate, oyster and crab, milk and dairy products
Calcium	Enriched beverages and products, milk and dairy products, greens (beet, collard, mustard, turnip, spinach), rhubarb, beans, almonds, salmon, shrimp, tofu
Iron	Red meat, poultry, fish (salmon, tuna), fortified cereal bars, oatmeal, fortified cereals, cream of wheat, wheat germ, prunes, raisins, tofu, enriched bread, nuts, legumes, seeds, turnip greens, winter squash, spinach, enriched pasta
Fat	Meat, poultry, fatty fish, full-fat milk and dairy products, vegetable oils, margarines, processed foods, baked goods, fried foods.

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Meeting Nutritional Needs

Potential Nutrients of Concern and Food Alternatives for Dietary Management in EoE
Protein • Poultry, meat (including game), whole grains, nutritional yeast, spirulina
Fat • Oils (vegetable-based, seeds) & spreads, avocado
Iron • Poultry, meat (organ), enriched whole grains, vegetables
Vitamin D – supplement in Canada
Calcium – supplement to meet DRI
Zinc • Poultry, meat, lentils

TABLE 7 Comparison of enriched dairy-free beverages to cow's milk

	Calories	Protein	Fat	Calcium
Cow's milk (whole)	150	8	8	300
Soy milk	100-130	6	3-4	300-350
Rice milk	120-130	1	2.5	300
Coconut milk	45-90	1	5	100-450
Hemp/ sunflower/ flax milk	100	4	6	300
Oat milk	130	4	2.5	100
Potato milk	70-110	0	0	300
Nut (almond/ cashew/ hazelnut) milk	60-90	1	2.5	200-450
Pea milk	60-150	8	4.5	450

Cianferoni A, et al., 2019

- Amino acid or dairy free formula ± nutrient supplements (e.g. amino acid-based protein source/cereal, iron, vitamin D, etc.) may be needed in addition to diet to meet nutritional needs

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TABLE 4 Nutrients in major food allergens and appropriate substitutes on 6-food elimination diet

Food	Nutrients	Substitutions
Milk	Protein, calcium, phosphorus, vitamin D, riboflavin, pantothenic acid, vitamin B12.	Meats, legumes, whole grains, nuts, fortified foods and enriched beverages (dairy, soy, tree nut-free), fortified orange juice
Wheat	Iron, niacin, riboflavin, thiamin, folate, fibre	Fortified foods, fruits,vegetables, other fortified grains (barley, oat, corn, rice, rye). Alternative grains such as buckwheat, quinoa, millet, teff, amaranth
Egg	Protein, choline, vitamin A, riboflavin, pantothenic acid, biotin, selenium.	Meats, legumes, whole grains (gluten-free) or enriched gluten-free grains
Soy	Protein, thiamin, riboflavin, B6 folate, calcium, phosphorus, magnesium, iron, zinc.	Meats, other legumes, enriched beverages (as above)
Peanuts/tree nuts	Protein, selenium, zinc, manganese, magnesium, niacin, phosphorus, vitamin E, B6, alpha linolenic acid, and linoleic acid	Meats, seeds, seed butters, legumes, vegetable oils
Fish/shellfish	Protein, iodine, zinc, phosphorus, selenium, niacin Fatty fish: vitamin A, vitamin D, omega-3 fatty acids	Meats, legumes, seeds, vegetable oils (canola/flax), enriched beverages as above

Cianferoni A, et al., 2019

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Healthy Eating

Recommendations by Health Canada
• Choose whole, fresh foods more often   • Limit highly processed /packaged foods
• Eat plenty of vegetables and fruits   • About half of your meals and snack
• Choose whole grains more often
• Choose more plant-based sources of protein more often
• Choose water as your drink
• Understand and use food labels

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Practical Considerations in Implementing Dietary Management in EoE

Patient ± caregiver:
- Understand the food eliminations in detail for the type of diet offered
- Label reading
- Costs
- Accessibility
- Food preparation and cooking
- Meal planning (risk of meal monotony)

Psychosocial:
- Reduced quality of life (e.g. increased stress)
- Medical burden (e.g. frequency of appointments, procedures)
- Tension between caregivers and children directly related to food eliminations (e.g. eating out, participating in events like birthdays, etc.)

Lack of:
- Dietetic and/or nutrition support
- Social support groups
- Disease awareness (especially at schools)

Klinnert MD, et al., 2014; Wolf WA, et al., 2016; Mukkada V, et al., 2018; Sheedy K, et al., 2021

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Summary

Dietary management can be efficacious treatment for EoE

Diet therapy can increase risk of malnutrition among patients with EoE

- Multidisciplinary team recommended e.g. RD

Diet therapy requires consideration with respect to:

- Food(s) to eliminate
- Meeting nutritional needs ± nutrient supplementation
- Psychosocial aspects of care

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Clinical Pearls On When and How to Start Reintroducing Foods

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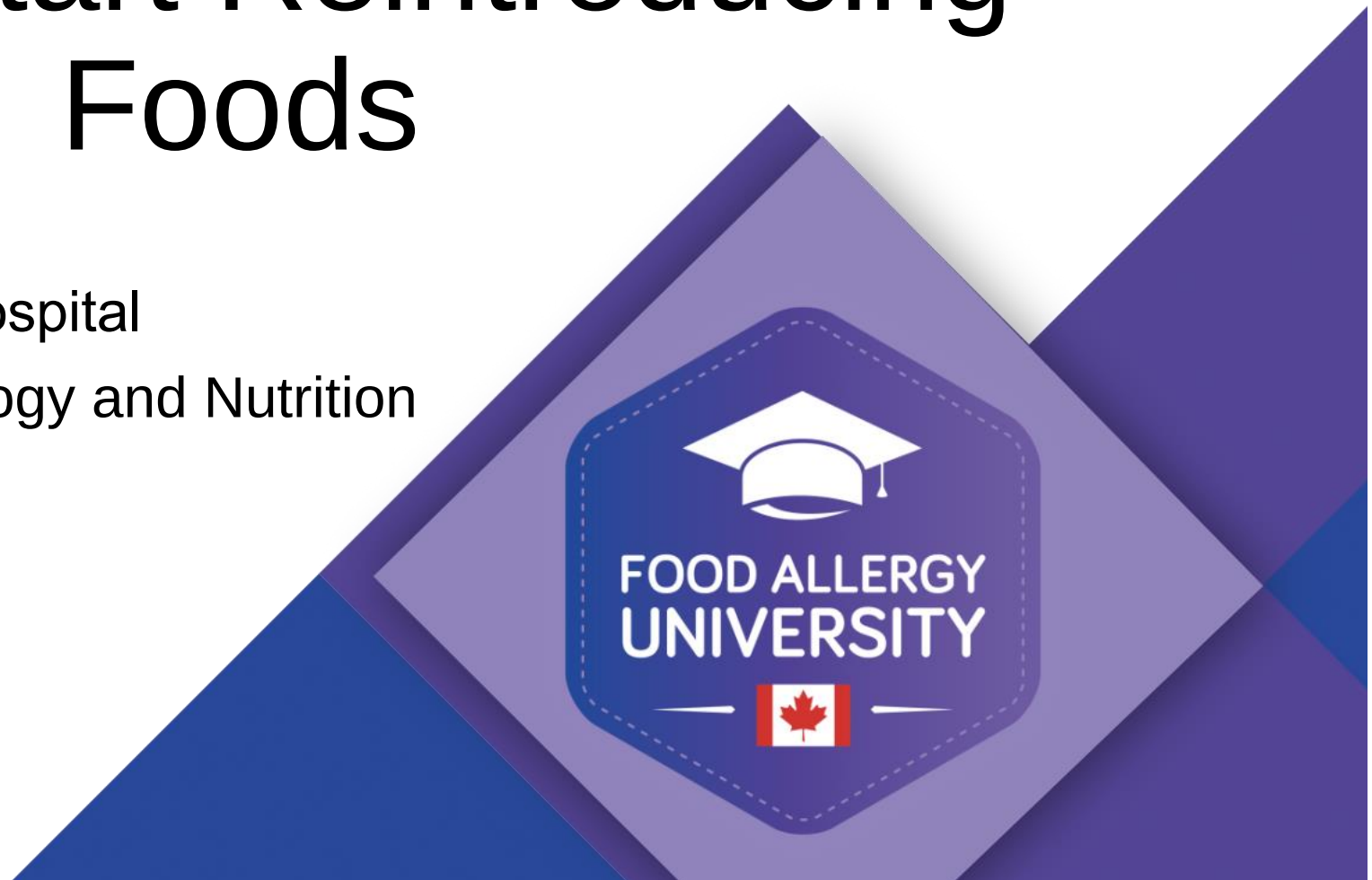
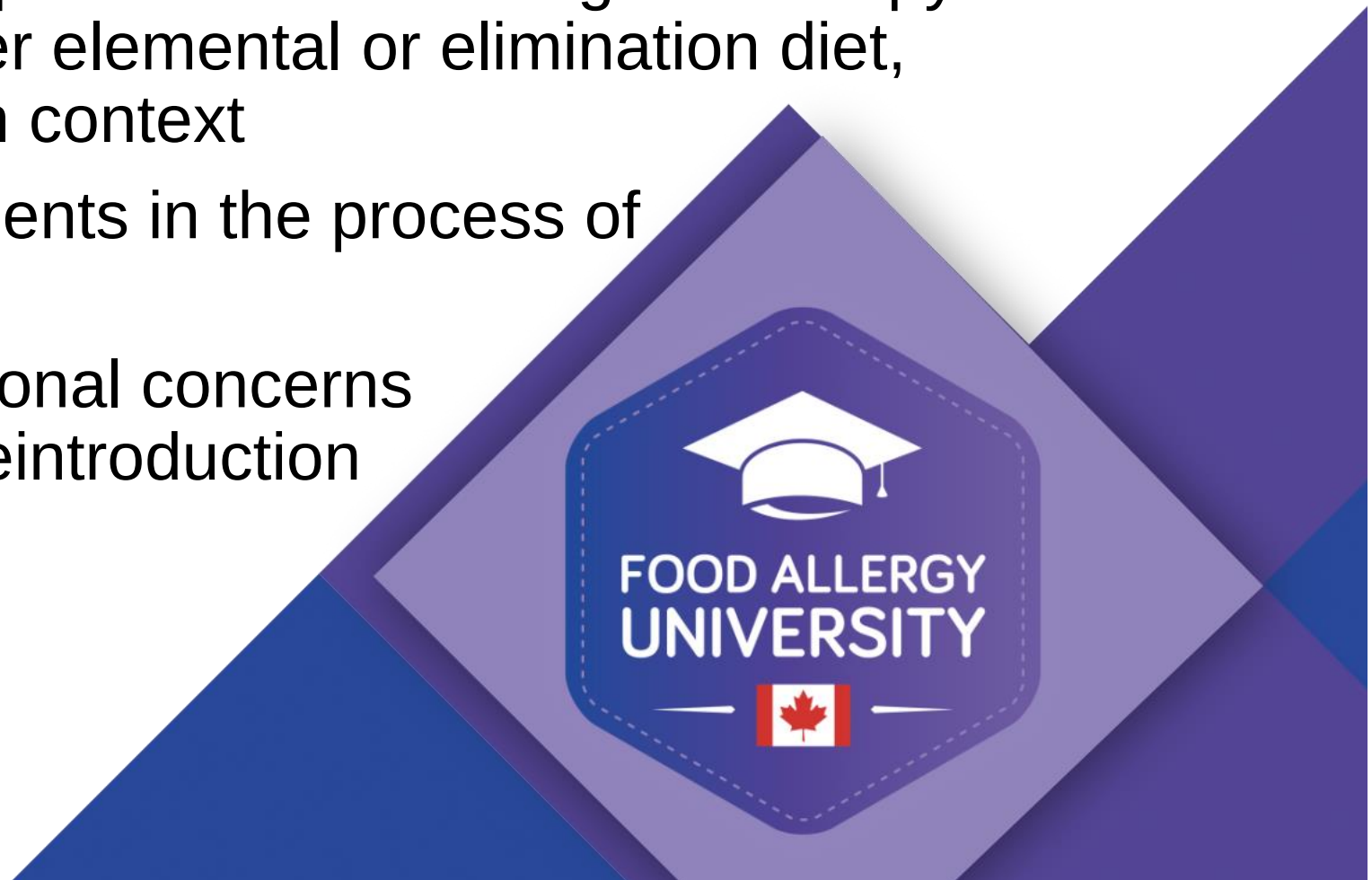


Objectives

- Discussion around the practicalities of using endoscopy in reintroducing foods after elemental or elimination diet, specifically in Canadian context
- The role of families/patients in the process of food reintroduction
- Highlight specific nutritional concerns during the process of reintroduction



Food Reintroduction

- Factors in choosing diet management:
  - Family/patient's preferences
  - Severity of disease
  - Response to previous treatments
  - Family dynamics
  - Quality of life
  - Nutritional Status
  - Feeding dynamics (? Oral aversion, fear associated with food, etc.)
- All these remain significant factors in reintroducing foods

The Dietitians Go To

“Tutorial: Nutrition Therapy in Eosinophilic Esophagitis” May 2020

- No instructions on how to reintroduce foods, length of time before re-evaluation or method of re-evaluation
- No instructions for order to reintroduce foods

Recommendations for Reintroduction in Elimination Diet – “Protocol”

- Occurs after 6-12 weeks of elimination diet and an endoscopy to confirm disease remission (ASPEN guidelines 2020)
- IF successful in achieving symptomatic and histologic remission, can begin to add back single food groups in a sequential order
- Offer foods in age appropriate serving and 5-7 days/week
  - If symptoms develop stop introduction and do a wash out period (6 – weeks)
- Recommended endoscopic evaluation after each separate allergen
  - Absence of symptoms does not mean EoE remains inactive

Kliewer et al, 2018

Recommendations for Reintroduction after Elemental Diet

- After 8-12 weeks remission confirmed by endoscopy (ASPEN 2020)
- Single ingredient foods are added.
- Number of foods added between endoscopic re-evaluation and length of time of trial is not standardized
- One protocol – new “single ingredient” food every 2 weeks with endoscopic evaluation every 12 weeks
- Advance food in order of increasing allergenicity (fruits and vegetables, then wheat free grains, then meats/legumes)

An example of the process

The Detailed Process:

EoE Suspected

⬇

EoE diagnosed by endoscopy and pathology

⬇

Failed trial of PPI (Proton Pump Inhibitor)

⬇

Elimination of 6 most common food allergens

⬇

EGD (Esophageogastroduodenoscopy) after 6 weeks

⬇

Introduce 2 least likely offending food groups

⬇

EGD at week 12

⬇

Introduce 2 addition offending food groups

⬇

EGD at week 18

⬇

Introduce milk products

⬇

EGD at week 24

⬇

Introduce wheat products

⬇

EGD at week 30

UW Health 2015 Patient Handout

Food Reintroduction Progression

Group A:

Vegetables: Carrots, squash, sweet potatoes, white potatoes, broccoli, lettuce, string beans.

Fruit: Apples, pears, peaches, plums, apricots, grapes (noncitrus, nontropical)

Group B:

Fruit: Citrus and Tropical fruits – oranges, grapefruit, lemons, limes, bananas, kiwis, pineapples, mangoes, papayas, guavas, avocado

Melons – honeydew, cantaloupe, watermelon

Berries – strawberries, cherries, blueberries, raspberries

Group C:

Grains: Rice, oat, barley, rye

Meat: lamb, chicken, turkey, pork

Fish/Shellfish

Tree nuts: almond, walnut, hazelnut, brazil nut, pecan

Group D:

Corn, peas, peanut, wheat, beef, soy, egg, milk

Adapted from Gastroenterol Clin N Am 32(2003) 949-966

“Safe” Foods

- Sugar
- Dextrose
- Corn syrup
- High fructose corn syrup
- Corn syrup solids
- Sucrose
- Maltodextrin
- Artificial flavours
- Artificial sugars
- Soy lecithin
- Soy oil or any refined oil
- Citric acid
- Malic acid
- Salt
- Sodium nitrate
- Artificial colour

J Allergy Clin Immunol Pract 2017

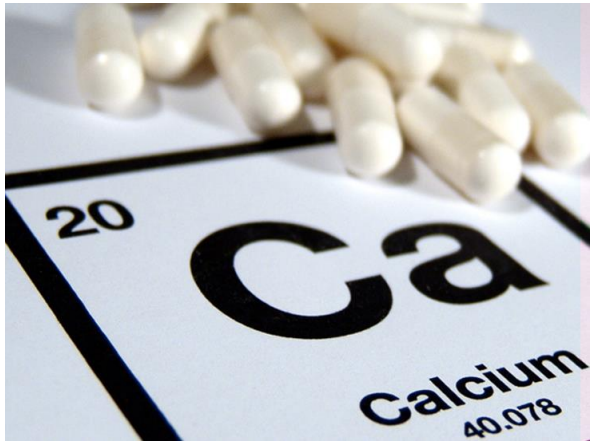
Complicating Factor: Adherence

- Varies by age, but 33% of children reported exposure to at least one food allergen in a 2 week period
- Factors impacting adherence include perceived effectiveness of the diet, social situations, diet related anxiety, palatability of foods

Hommel 2012, Wang 2018

Nutritional Concerns

- Macronutrients:
  - Fats – eliminating milk, egg, fish shown to have negative impact on Omega 3 levels (Aldamiz-Echevarria 2008)
  - Protein – depends on foods eliminated, acceptance of meat protein
  - Fibre – encourage pseudo grains (e.g. quinoa, millet, buckwheat, amaranth)
- Micronutrients:
  - Calcium/Vitamin D
  - Possibly zinc, copper, selenium, B vitamins
  - Theoretically vitamin B12 with long term PPI use



Nutritional Concerns: Feeding Dynamics

- Delayed oral motor skills – children under age 3
- Disrupted “Division of Responsibilities” in feeding
- Specific behaviours include:
  - Food refusal
  - low volume/variety
  - poor acceptance of new foods
  - spitting food out
  - Grazing
  - lack of mealtime structure
  - prompting to eat
  - inconsistent patterns of eating

Clinical Scenarios: What do you do now?

A family wants to do diet therapy to manage the EoE but does not want to put their child through multiple endoscopies. What do you do?

a) Recommend not using dietary elimination

b) Proceed with dietary eliminations but use symptoms to guide reintroduction

You have a parent that is very motivated to try dietary elimination, but the patient is not interested in adhering to diet restrictions. What do you do?

a) Recommend medical management instead

b) Go ahead with dietary eliminations as it has less potential side effects then medication

c) Explore with the patient what their reasons are for not wanting to do dietary eliminations

Proton-Pump-Inhibitors as a Treatment Option for EoE

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Jan. 12, 2022

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Learning Objectives

- Understand the proposed mechanism of PPI therapy in EoE
- Understand the classification of CYP2C19 metabolism in relation to PPI therapy
- Optimize the utility of PPI as therapy for EoE by performing pharmacogenetic testing in patients

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Mechanism of Action of PPIs in EoE

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Background

- Trial of PPI responsiveness to rule-out GERD is **outdated**
- "PPI-responsive EoE"
- Much of how PPIs work in EoE is unknown
- Efficacy of PPI in EoE is about 30-70%
  - Depends on initial dose, frequency of dose

Dellon ES. Gastroenterology 2018
Molina-Infante. Clin Gastroenterol Hep. 2011.
Gutierrez-Junquera. JPGN 2018;67: 210–216)

4

PPI Efficacy – Systematic Review

- 33 studies
- 619 patients with symptomatic EoE
  - 188 pediatric patients
- PPI induced:
  - **Clinical** response in **60.8%**
  - **Histologic** remission in **50.5%**
- Lansoprazole and rabeprazole showed highest efficacy
  - limited number of studies, small sample size, heterogeneity among studies

Lucendo. Clinical Gastroenterol and Hepatol. 2016.

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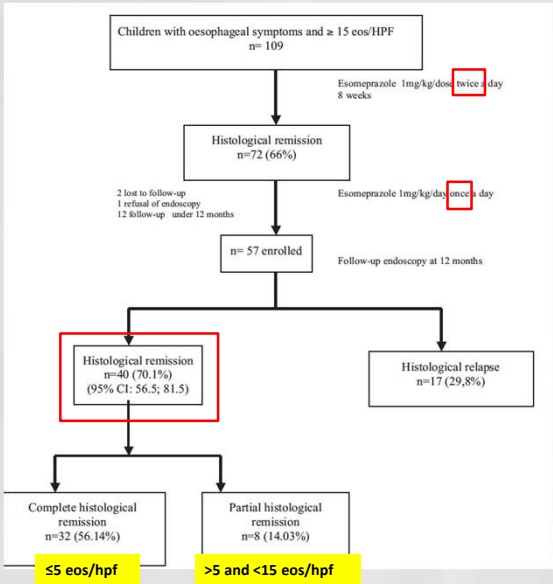
PPI Efficacy in Children with EoE



- 57 **children**, **1mo-15yo** in **remission** after an **8wk** trial of **esomeprazole** 1mg/kg/d **BID**
- Then lowered to 1mg/kg/d for 1 year
- **Scoped** at 12mo
- **70%** in histological and clinical remission

Gutierrez-Junquera. JPGN 2018;67: 210–216)

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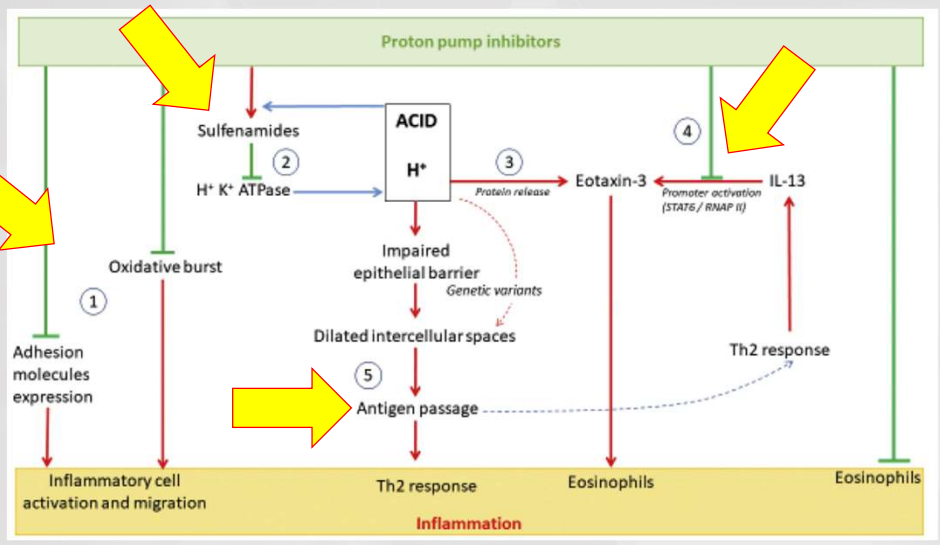
Anti-Inflammatory Effects of PPIs in EoE



Dellon ES. Gastroenterology 2018

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CYP2C19 Metabolism

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What is CYP2C19?

- Member of cytochrome P450
- Variable expression in childhood
- Enzyme involved in the metabolism of 1st-generation PPIs
- Expression differs based on ethnicity

El Rouby. Expert Opinion on Drug Metabolism and Toxicology. 201.8
CYP2C19. Wikipedia. Dec. 28 2021. https://en.wikipedia.org/wiki/CYP2C19

9

CYP2C19 Allelic Variants

Allelic Variant
Normal (wildtype)
Decreased Function (loss of function mutation)
Increased Function (gain of function mutation)
No Function

JPGN Volume 69, Number 5, November 2019
Scott SA, et al. Clin Pharmacol Ther. 2013;94(3):317-23. www.pharmgkb.org

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CYP2C19 Allelic Variants

Allelic Variant	Numeric Designation
Normal (wildtype)	*1
Decreased Function (loss of function mutation)	*2, 3, 4, 5, 6, 7, 8
Increased Function (gain of function mutation)	*17
No Function	*9

JPGN Volume 69, Number 5, November 2019
Scott SA, et al. Clin Pharmacol Ther. 2013;94(3):317-23. www.pharmgkb.org

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CYP2C19 Phenotypic Variants

Phenotype	Definition
Poor Metabolizer	• 2 copies of a decreased function allele
Intermediate Metabolizer	• 1 copy of a normal function allele and 1 copy of a reduced function allele • 1 copy of a decreased function allele and 1 copy of an increased function allele
Normal Metabolizer	• 2 copies of a normal function allele
Rapid Metabolizer	• 1 copy of a normal allele and 1 copy of an increased function allele
Ultrarapid Metabolizer	• 2 copies of an increased function allele

JPGN Volume 69, Number 5, November 2019
Scott SA, et al. Clin Pharmacol Ther. 2013;94(3):317-23.
www.pharmgkb.org
Lima et al. Clin Pharmacol Ther. 2020.

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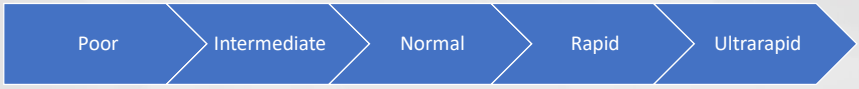
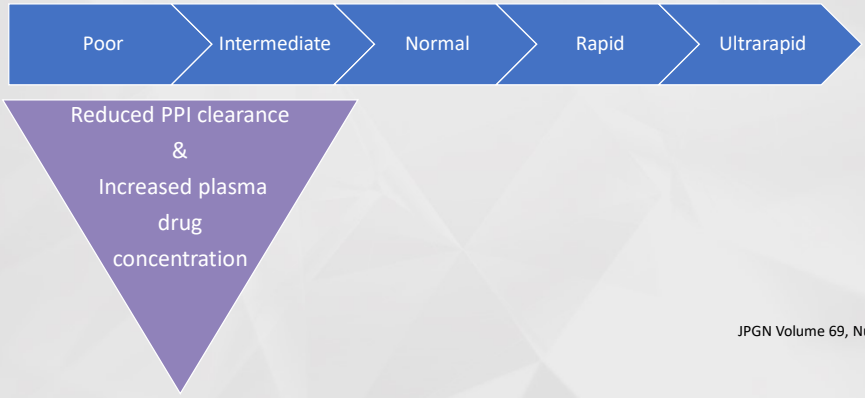
CYP2C19 gene



JPGN Volume 69, Number 5, November 2019

13

CYP2C19 gene



JPGN Volume 69, Number 5, November 2019

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CYP2C19 gene

Associated with PPI non-responsiveness in children with EoE

Poor → Intermediate → Normal → Rapid → Ultrarapid

Increased PPI clearance & Decreased plasma drug concentration

JPGN Volume 69, Number 5, November 2019

15

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Associated with PPI non-responsiveness in children with EoE

Poor → Intermediate → Normal → Rapid → Ultrarapid

Increased PPI clearance & Decreased plasma drug concentration

JPGN Volume 69, Number 5, November 2019
Mougey. Clinical Gastroenterol and Hepatol. 2020.

16

CYP2C19 gene

Associated with PPI non-responsiveness in children with EoE

JPGN Volume 69, Number 5, November 2019
Mougey. Clinical Gastroenterol and Hepatol. 2020.
Cicali. Clin Translational Sci. 2019.

17

CYP2C19 gene

Associated with PPI non-responsiveness in children with EoE

JPGN Volume 69, Number 5, November 2019
Mougey. Clinical Gastroenterol and Hepatol. 2020.
Cicali. Clin Translational Sci. 2019.
Tang. Contemporary Clinical Trials. 2019.

18

CYP2C19 Genotype Testing Use in Disease

Disease	Affect
Reflux esophagitis	• RM is a risk factor to PPI non-responsiveness
GERD	• association between CYP2C19 increased function allele (*17) and decreased acid suppression suggesting inadequate dosing in CYP2C19*17 carriers • genotype affects recurrence rates
H. pylori	• LOF alleles are associated with increased eradication rates in patients taking 1st-generation PPI, no class effect with 2nd-generation PPI • Eradication rate in RM and URM is lower than in PM
Esophageal atresia	• genotyping of CYP2C19 **failed** to predict PPI-refractory non-allergic esophagitis in children with and without EA

Ichikawa. J Gastroenterol Hepatol. 2016., Saito. World J Gastroenterol. 2015., Hui-Lin. Plos one. 2013., Furuta. Clin Pharmacol Ther. 521-528. 2007., Franciosi. J Clin Pharmacol. 2018., Yasuda. Neurogastroenterol and Motility. 2020., Lima. Clin Pharmacol Ther. 1417-1423. 2021.

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H. pyl	n
	• Eradication rate in RM and URM is lower than in PM
Esophageal atresia	• genotyping of CYP2C19 **failed** to predict PPI-refractory non-allergic esophagitis in children with and without EA

- Many of these studies have been conducted in Asian populations (higher allelic frequency of LOF mutations and low frequency of GOF mutations)
- Paucity of data on how to dose RM and URM

Ichikawa. J Gastroenterol Hepatol. 2016., Saito. World J Gastroenterol. 2015., Hui-Lin. Plos one. 2013., Furuta. Clin Pharmacol Ther. 521-528. 2007., Franciosi. J Clin Pharmacol. 2018., Yasuda. Neurogastroenterol and Motility. 2020., Lima. Clin Pharmacol Ther. 1417-1423. 2021.

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Optimizing PPI utility using Pharmacogenetics

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What is Pharmacogenetics (PGx)?

- The study of how genetic variants affect a person's drug metabolism and response to drugs
- **End goal of using PGx:** develop medications and DOSES that are effective and safe, and tailored to a person's genetic makeup

  → avoid treatment failures and prevent adverse effects
- Common example: evaluation of TMPT activity before starting IBD patient on azathioprine

Why is it important?

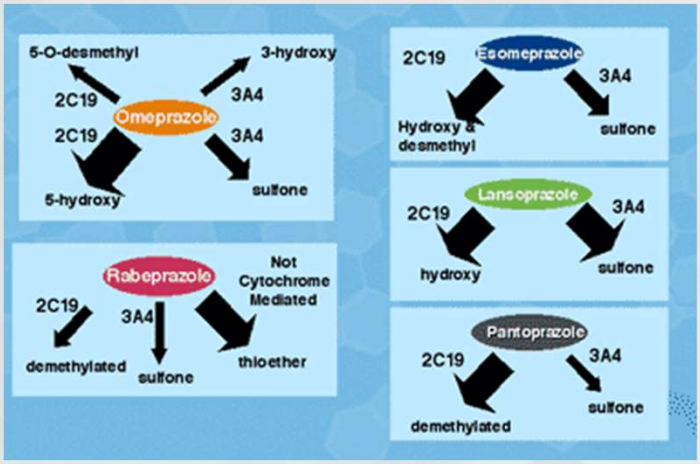
- Knowing which variants are present can help predict whether a medication will be effective and guide prescription dosage aiding in prevention of adverse drug reactions

Bernal. Pediatrics 2019.
Lima et al. J Pediatr 2013

22

CYP2C19 testing in patient - choice of PPI

- PPIs are metabolized primarily by CYP2C19 and CYP3A4



Martis, S et al. "Multi-ethnic distribution of clinically relevant CYP2C genotypes and haplotypes." *The pharmacogenomics journal* vol. 13,4 (2013): 369-77.

23

Types of PPIs

1st-generation

- Omeprazole
- Lansoprazole
- Pantoprazole

Dependent on CYP2C19 pathway

2nd-generation

- Esomeprazole
- Rabeprazole

Less dependent on CYP2C19 and therefore ***less influenced by genetic variability in the gene***

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EoE - PPI PGx study in our center

- Single centre, non-interventional descriptive pilot/feasibility study investigating the pharmacogenetics of CYP2C19 patients with EoE on PPI therapy
- In collaboration with the Clinical Pharmacogenetics Team at SickKids (Dr. Cohn, Dr. Verstegen, Dr. Ito)

- **Primary Aim:** to describe the PPI metabolizer status in children and adolescents with EoE on PPI therapy and estimate the clinical utility of PGx testing in the management of disease
- **Secondary Aim:** to determine the % of patients who will experience a change in their EoE therapy based on CYP2C19 results

  Change in therapy = change in PPI dose or swapping to steroids or DET

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PPI PGx study in our center – outcomes

Primary Outcomes

- CYP2C19 metabolizer status on PGx testing
- Changes in PPI drug therapy following PGx testing

Secondary Outcomes

- Improvements in remission rates following PGx testing and results and changes in PPI therapy

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PPI PGx study – Patient population

- A subset of EoE patients (n=50) referred for pharmacogenetics testing who are also included in **EoE-AHEAD registry**

INCLUSION:
Patients with newly diagnosed EoE who will start PPI therapy in "standard" high dose (2 mg/kg/day, max 30 mg BID lansoprazole)
Patients where retrial of PPI is considered on clinical grounds:
- patient not in remission on current therapy and never tried on PPI
- never dosed correctly according to current clinical guidelines (< 2 mg/kg/day, max 30 mg BID pantoprazole).

EXCLUSION:
Patients in remission on current PPI treatment
Patients in remission on current combination treatment including PPI
Patients who failed high dose PPI treatment

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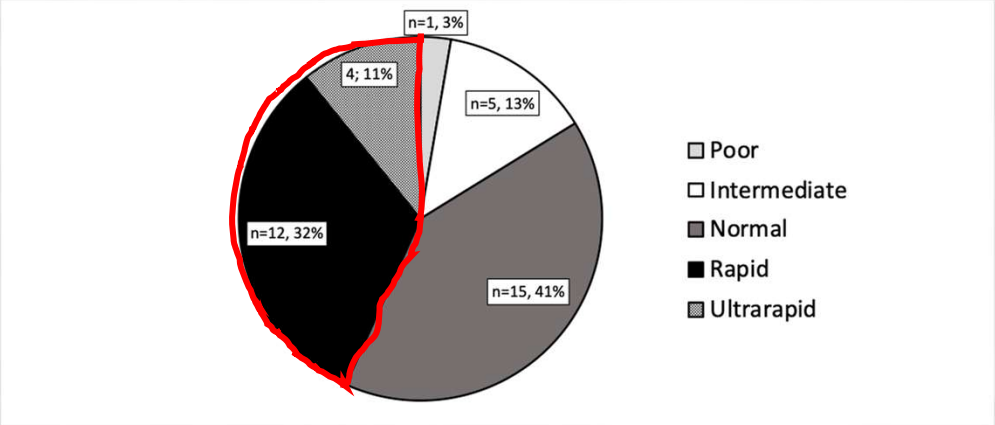
PPI PGx study– preliminary results

CYP2C19 Metabolizer status in first 37 patients included:



Bortolin K et al., 2022

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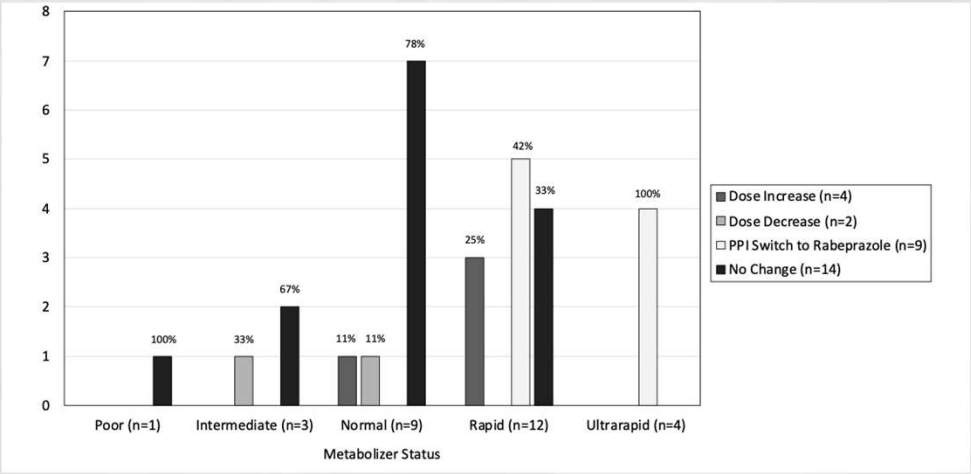
PPI PGx study– preliminary results

CYP2C19-guided changes in medical therapy (n=29)



Bortolin K et al., 2022

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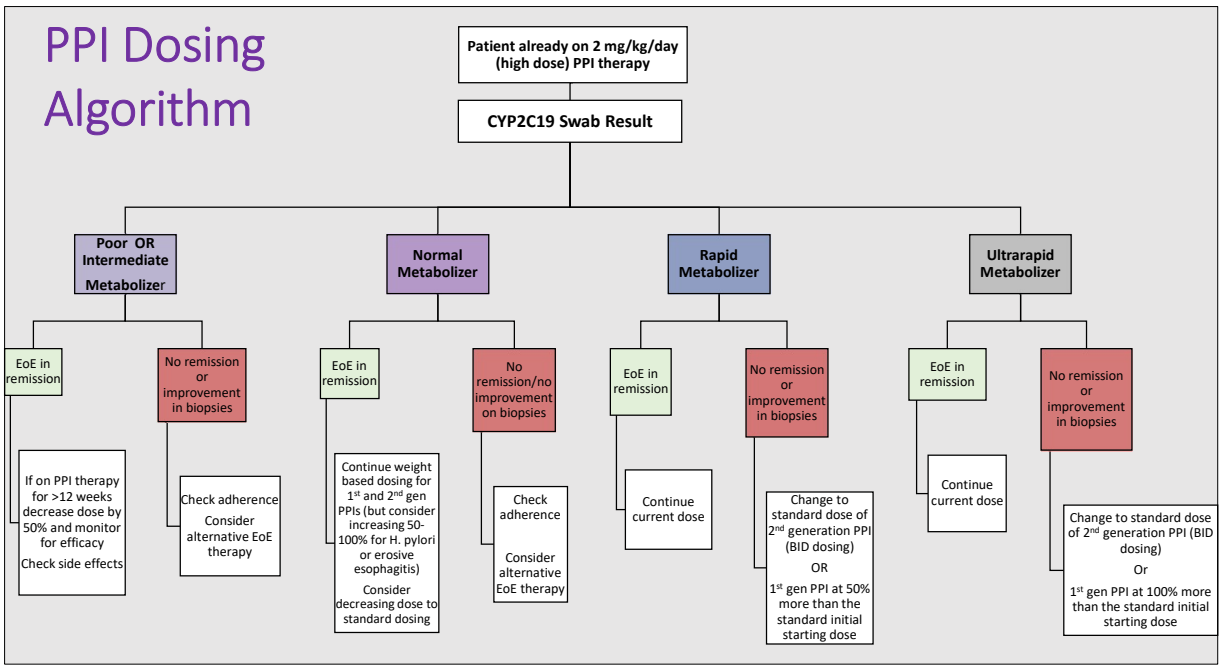
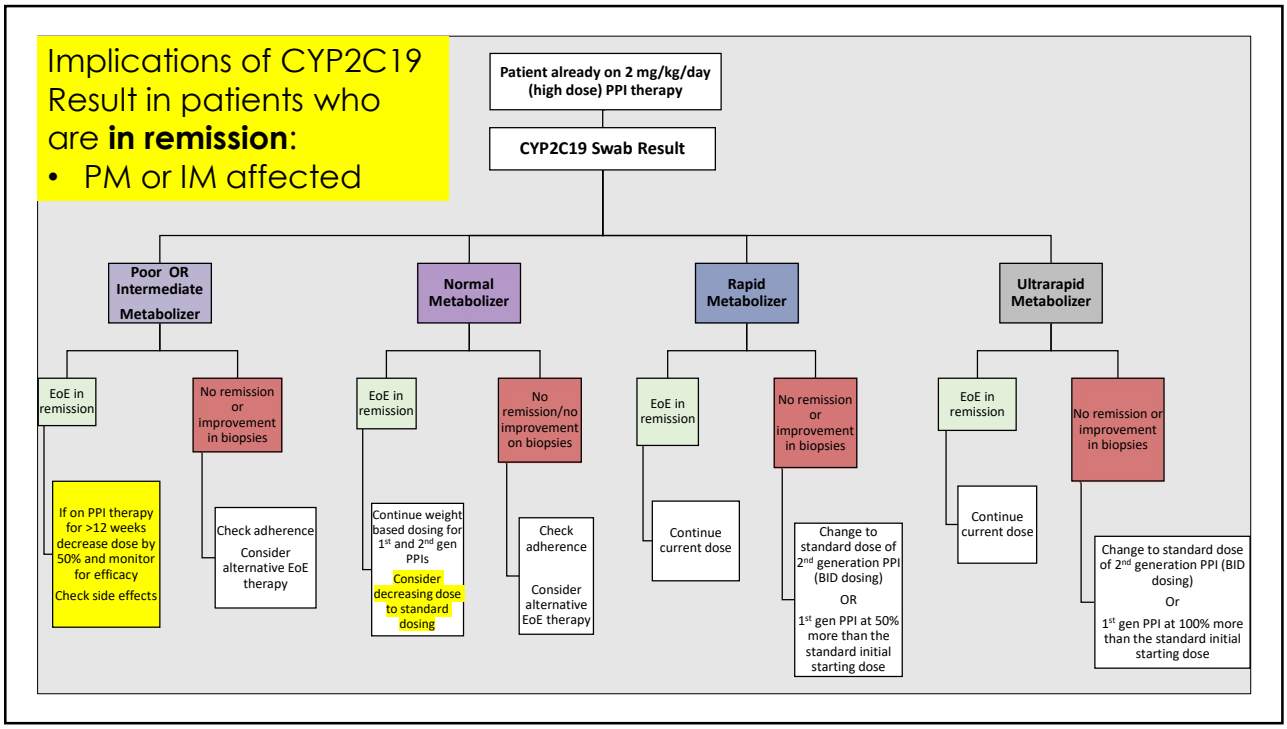
PPI Dosing Algorithm



30


Implications of CYP2C19 Result in patients who are **in remission**:
• PM or IM affected
Patient already on 2 mg/kg/day (high dose) PPI therapy
CYP2C19 Swab Result
Poor OR Intermediate Metabolizer
Normal Metabolizer
Rapid Metabolizer
Ultrarapid Metabolizer
EoE in remission
If on PPI therapy for >12 weeks decrease dose by 50% and monitor for efficacy
Check side effects
No remission or improvement in biopsies
Check adherence
Consider alternative EoE therapy
EoE in remission
Continue weight based dosing for 1st and 2nd gen PPIs
Consider decreasing dose to standard dosing
No remission/no improvement on biopsies
Check adherence
Consider alternative EoE therapy
EoE in remission
Continue current dose
No remission or improvement in biopsies
Change to standard dose of 2nd generation PPI (BID dosing)
OR
1st gen PPI at 50% more than the standard initial starting dose
EoE in remission
Continue current dose
No remission or improvement in biopsies
Change to standard dose of 2nd generation PPI (BID dosing)
Or
1st gen PPI at 100% more than the standard initial starting dose

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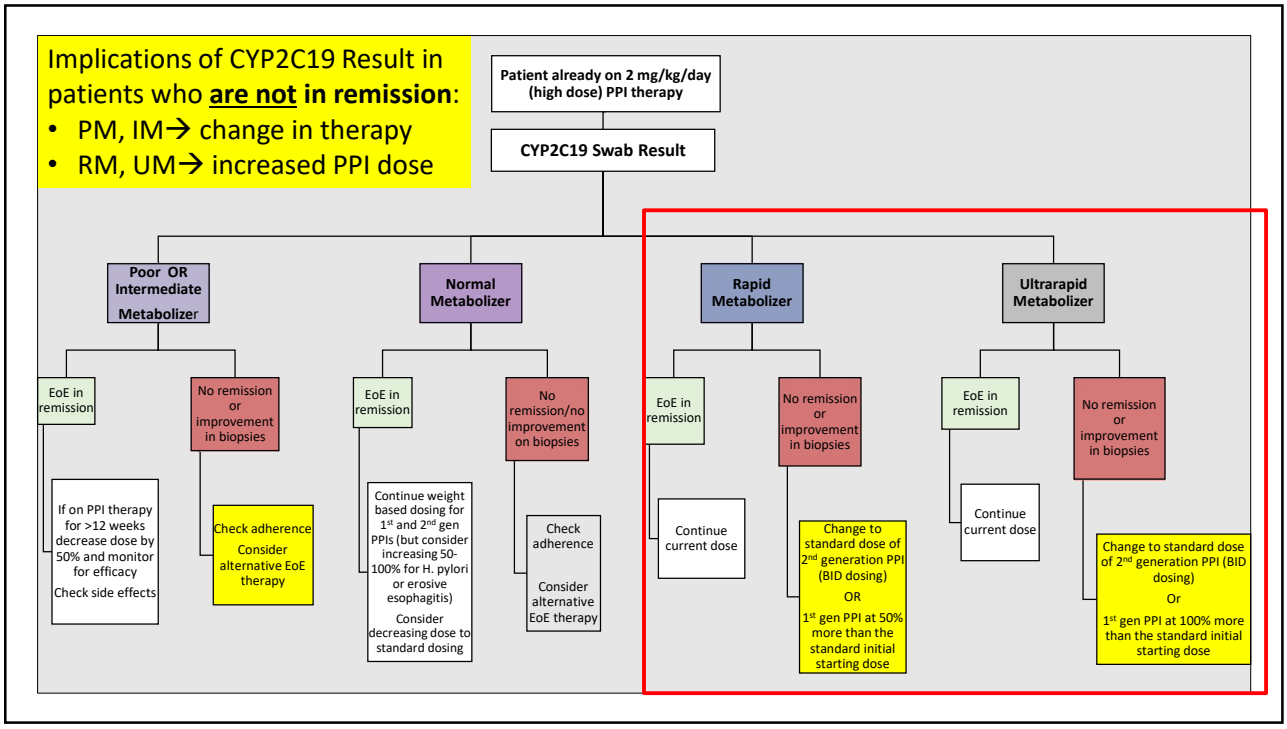
Implications of CYP2C19 Result in patients who **are not in remission**:
• PM, IM→ change in therapy
• RM, UM→ increased PPI dose
Patient already on 2 mg/kg/day (high dose) PPI therapy
CYP2C19 Swab Result
Poor OR Intermediate Metabolizer
Normal Metabolizer
Rapid Metabolizer
Ultrarapid Metabolizer
EoE in remission
If on PPI therapy for >12 weeks decrease dose by 50% and monitor for efficacy
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Continue weight based dosing for 1st and 2nd gen PPIs (but consider increasing 50-100% for H. pylori or erosive esophagitis)
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EoE in remission
Continue current dose
No remission or improvement in biopsies
Change to standard dose of 2nd generation PPI (BID dosing)
Or
1st gen PPI at 100% more than the standard initial starting dose

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Patient example 1

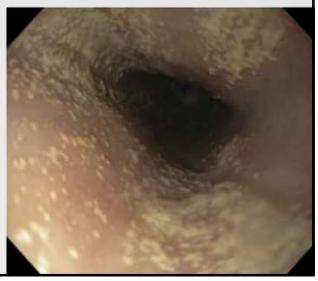
Boy, 15 years old, 51 kg

- Diagnosed with **EoE** age 13 y (vomiting and abdo pain)
- Also known with **kiwi** and **shellfish** allergy + **environmental** allergies
- Previous therapy: **budesonide** slurry (remission), **lansoprazole** OD and **dairy free diet**

- Scope in March 2021 while on dairy free diet and after increase in PPI to 30 mg BID:
  - Macroscopically: EREFS score: E0R0E2F1S0; significant exudate, worst in mid part
  - Histology: severe EoE, up to 50 eos/HPF in distal, 32/HPF in mid and 23/HPF in proximal biopsies

  => worsened

- Evaluation: had not been adherent to PPI



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Patient example 1

Referred for PGX testing in meantime: rapid metabolizer

Focus Drugs:

Lansoprazole	!	Increased CYP2C19 enzyme activity may lead to decreased levels of active drug and may affect clinical response. Consider increasing dose by 50-100% for the treatment of H. pylori infection and erosive esophagitis. Daily dose may be given in divided doses. Monitor for efficacy.

Drug Summary:

Therapeutic Category	✓ Use as directed	! Use with caution	✗ Consider alternatives
Anticoagulant	Warfarin	Clopidogrel	
Cardiovascular	Atorvastatin		
	Flecainide		
	Metoprolol		
	Propafenone		
	Simvastatin		
Dentistry	Cevimeline		
Endocrinology	Hormonal contraceptives for systemic use		
Gastroenterology	Dronabinol	Dexlansoprazole	
	Metoclopramide	Lansoprazole	
	Ondansetron	Omeprazole	
	Tropisetron	Pantoprazole	
Genetic disorder	Eliglustat		

=> Switched to **rabeprazole** 20 mg BID

=> Awaiting follow-up endoscopy

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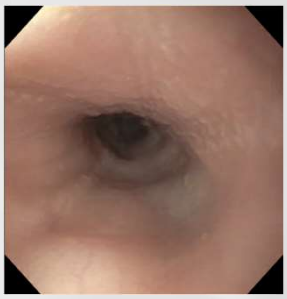
Patient example 2

Boy, 5 years old

- Diagnosed with **EoE** age 2y (persistent vomiting – thought to have GERD, not able to wean of PPI)
- Known with multiple **food allergies** with **restricted diet** (dairy, soy, wheat, peanut, eggs)
- Scope in February 2020 while on exclusion diet showed high numbers of Eos in biopsies (distal: 95, mid: 100, proximal: 34 eosinophils per HPF) but clinically well



=> increased PPI dose to 1 mg/kg BID (lansoprazole)

35

Patient example 2

- **Reassessment Scope, March 2021:**
  - Macroscopically: EREFS score: E0R0E0F0S0
  - Histology: no significant intraepithelial inflammation in distal ar biopsies and a single eosinophil in the proximal biopsy. The pro biopsy also shows mild spongiosis

Referred for PGX testing in meantime: Intermediate metabolizer

=> Will first try to ease diet restrictions in collaboration with Allergist

=> Later step could be to decrease dose of PPI if he remains in remission

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Take Home Points

- **PPIs** are valuable medications in the treatment of EoE and have multiple mechanisms of action
- **CYP2C19** is the main enzyme that metabolizes 1st generation PPIs, contributing to the variability in patient response
- Significant variation in **CYP2C19 metabolizer status** is shown in our EoE patients and knowledge of status has consequences for medical management

Pharmacogenetic testing as standard care done prior to starting PPIs in EoE patients could lead to **increased efficacy of PPI treatment** or **avoidance of PPI** in those with a low likelihood of clinical benefit, leading to better disease management with earlier remission or avoidance of long-term adverse events

Further correlation with endoscopy and histology findings of patients after PGx-guided therapy changes will follow

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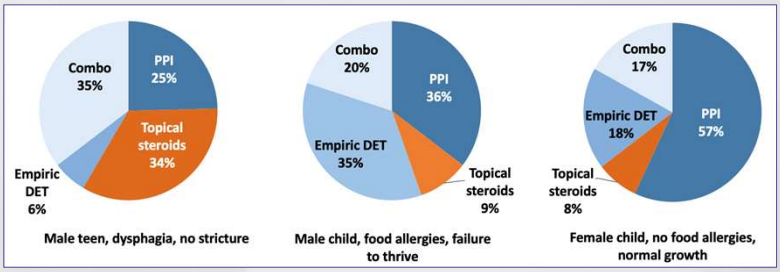
Discussion

- Are you using CYP2C19 testing for PPIs in EoE? In any patient using a PPI?
- What are your experiences with using esomeprazole or rabeprazole?
- What issues are you having with these 2nd generation PPIs (funding, availability of formulations suitable for young children)?
- What scenarios would you start a PPI treatment?



Bortolin KA, et al. (2021). Wide variation in clinical management of paediatric eosinophilic esophagitis: a Canadian experience. 2021.

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Thank you for your attention!
We are happy to answer any questions you may have
FOOD ALLERGY UNIVERSITY
kristen.bortolin@sickkids.ca
jessie.hulst@sickkids.ca

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Topical Steroids as treatment option for Eosinophilic Esophagitis

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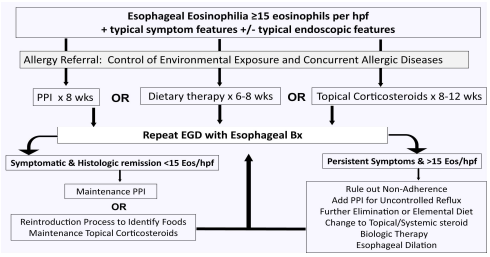
Pediatric Gastroenterologist
Assistant Professor of Pediatrics
University of Ottawa

1

Treatment algorithm for patients with confirmed eosinophilic esophagitis (EoE)



Gonsalves NP et al *J Allergy Clin Immunol* 2020;145(1): 1-7

2

Topical Steroid Treatment

- EoE is a chronic progressive disease
- Most have relapse when therapy is stopped
- Swallowed topical steroids (STS) mainly successfully evaluated for short-term treatment of EoE
- Limited data for long-term treatment
- Three year follow-up study in 51 adults treated with STS showed*:
  - Relapse in 91% of patients in average of 9 months' time once STS (fluticasone) d/c
  - 69% of patients required repeated STS treatment at least once

*Helou EF et al *Am J Gastroenterol* 2008;103:2194

3

Topical steroid treatment strategies

Pediatrics
- 6-12 weeks (include taper*)
- Budesonide (OVS)
  - Under 20 kg: 0.5 mg daily*
  - Children (<10 years): 1 mg daily
  - Adolescents: 2 mg daily
- Fluticasone (MDI puffed & then swallowed)
  - 88-440 µg BID to QID (maximal adult dose)

Adults
- 6-12 weeks
- Budesonide (OVS)
  - 2 mg daily (range 2-6 mg/day)
- Fluticasone
  - 440-880 µg BID
- BOT**
  - 1 mg BID for 6 weeks' time
  - Maintenance: 0.5 mg BID

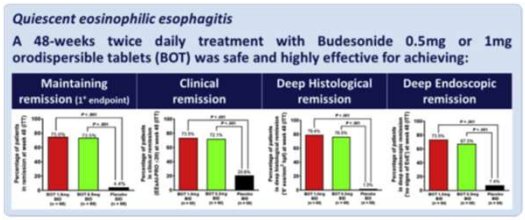
(length of time as per MD)

Dellon ES et al *Am J Gastroenterol* 2013;108:679-692
Liacouras CA et al *J Allergy Clin Immunol* 2011;128:3-20.e6
Schlag C *Gastroenterology* 2019;156:S-715**

Dr. J. Barkey 2022

4

BOT Maintenance EOS-2 Trial



Gastroenterology

Straumann A et al *Gastroenterology* 2021;159:1672

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5

Side-effects of topical steroids

- Generally well-tolerated with good safety profile
- Most common side-effect: Candida esophagitis (8.7% of patients)*
  - Usually asymptomatic
  - If suspected, then need GI endoscopy confirmation
  - Anti-fungal treatment with fluconazole/nystatin for 7-14 days**
- Long-term use of high dose STS (asthma patients)
  - Impaired growth in children, decreased BMD, skin thinning, bruising, cataracts
- Adrenal axis suppression***
  - Morning cortisol levels
  - ACTH stimulation testing

*Chuang MY et al *Clin Transl Gastroenterol* 2015;6:e82
**Lucendo AJ *United European Gastroenterol J* 2017;5:335-358
***Harel S *JPGN* 2015;61:190-193
Ahmet A et al *Allergy Asthma Clin Immunol* 2016 Oct 10;12:49

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6

EoE in Adults and Transition to Adult Care

New Frontiers in Eosinophilic Esophagitis Management

UNIVERSITY OF CALGARY

Dr. Milli Gupta
Clinical Assistant Professor
University of Calgary

January 12, 2022

1

Disclosures

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Commercial or Non-Profit Interest	Relationship
Abbvie	Advisory Board, Research Support
AVIR pharma	Speaker
MedTronic	Advisory Board
Sanofi	Medical Advisor

2

Learning Objectives:

1. Demonstrate the role of dilation in the schema of therapy (3Ds – drugs, dilation and diet), and an algorithmic approach to EOE care
2. Understand what is Healthcare Transition (HCT) and demonstrate its impact on moving patients from pediatric to adult care
3. Review HCT data in EoE, highlight the gaps and propose some solutions

3

EoE Care in Adults – 3 Ds

- Drugs and Diet - Excellent talks already delivered
- Dilation : Treatment for strictures, which are deemed to be end stage complication of untreated, inflammation-driven EoE.
- Unclear why some patients more likely to develop these than others (phenotypic variability).
- Predictors of fibrostenotic disease variant are still being elucidated
- Dilations help with symptoms, but do not alter disease progression

4

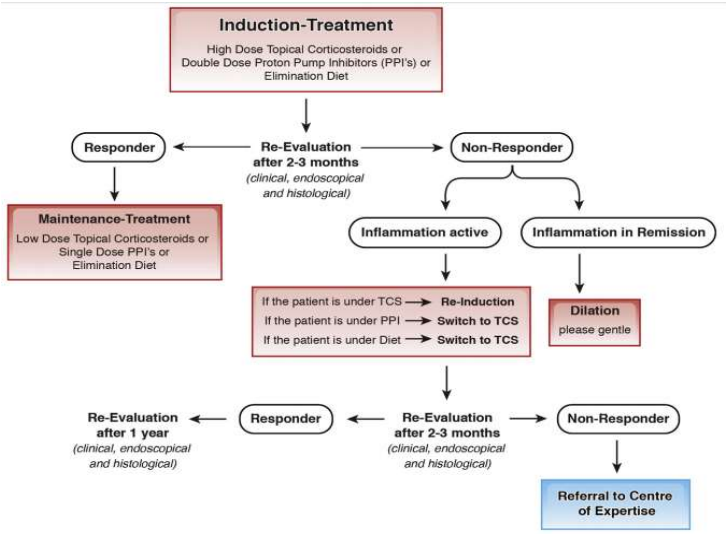
Meta Analysis Data on Dilations in EoE

- 2017 meta analysis reviewed 27 studies
- Quality of the studies were low to moderate
  - Most studies were retrospective, with only one prospective trial
- 845 patients (including 87 peds) and 1820 dilations
  - Perforation 0.38% (95% CI:0.18%-0.85%, I^2 : 0%, 27 studies)
  - Hemorrhage 0.05% (95% CI: 0%-0.3%, I^2 : 0%, 18 studies) and
  - Hospitalization 0.67% (95% CI: 0.3%-1.1%, I^2 : 44%, 24 studies)
- Mean number of dilation: 3 (range: 1-35)
- Clinical improvement: 95% of patients
- Type of dilator did not impact results (Bougie vs. balloon)
- "When" and "how" to optimally perform dilation remains uncertain.

Moawad, Molina-Infante, Lucendo et al., APT 2017

5

EoE Adult Care - Algorithm



Straumann and Katzka, Gastro 2018

6

Table 2. Candidates for Long-term Maintenance of Pharmacologic Therapy

1. Small caliber esophagus
2. Symptomatic or objective progression of stricture formation
3. Rapid return of symptoms off therapy
4. Recurrent food impactions
5. Co-morbid conditions increasing risk of endoscopy and dilation
6. Prior spontaneous or dilation induced perforation
7. Travel to areas where food impaction causes greater risk

- Adjunct drug or dietary-based therapy reduces the need of dilation and future stricture formation.

Straumann and Katzka, Gastro 2018

7

What is HealthCare Transition (HCT)

- "purposeful planned movement of adolescents and young adults with chronic physical and medical condition from child centered to adult oriented health care systems… with the optimal goal of providing health care that is uninterrupted, coordinated, developmentally appropriate, psychologically sound and comprehensive."[1]
- Survey of adult GI docs, residents in IM and Peds demonstrate lack of knowledge and confidence in transition care[2].
  - ~80% adult GI docs noted inadequacies in the preparation of IBD pts transferred from pediatrics GI
  - ~80% pediatric GI docs considered a structure transition to be important, comparted to 47% of adult GI docs

1. Blum R et al., J Adolesc Health 1993; 14:570-6
2. Hait et al., J Peds Gastro Nutr 2009; 48:61-5
3. Sebastian et al., J Crohns Colitis. 2012 Sep; 6(8):830-44

8

Why is HCT important

- Poor transfer to adult care has been associated with reduced adherence to medical treatment[1], increased disease severity[2], and undue stress for patients, families, and healthcare providers[3]
- A systematic review on youth with T1DM showed that structured transition led to reduced episodes of severe hypoglycemia and Diabetic Keto-Acidosis, as well as improvied HbA1c post-transfer
- Various consensus statements have declared importance of transition, but variable models of implementation[4]

1. Pai & Ostendorf, 2011. Children's Health Care, 40(1), 16–33.
2. Annunziato et al., 2007. Peds Transplant. 2007 Sept 11(6): 608-14
3. Goodhand et al., IBD 2010 Jun; 16(6) 947-52
4. Pyatak et al., J Adolesc Health. 2017 Feb; 60(2):212-218.

9

Transfer versus transition

- Unlike a transfer, which is a single event, transition is a gradual process, allowing young adult to acquire behavioral skills and knowledge to assume full responsibility for their health care needs and management of their disease
- NASPGHAN published recommendations on transition in IBD care, and its currently standard of care within GI
  - However it is 20y old so limitations are acknowledged

Baldassano et al., JPGN 2002 Mar; *34(3):245-8.*

10

NASPGHAN consensus document

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- Four major recommendations for successful transition:

(i) Seeing adolescent patients without their parents to build a relationship that promotes independence and self-reliance;

(ii) Discussing with the patient and family the benefits of transition to an internal medicine gastroenterology practice;

(iii) Developing a relationship with an adult gastroenterologist who is knowledgeable in caring for young adults with a history of childhood-onset IBD;

(iv) Providing all of the necessary medical records and summaries so that the family will realize that all providers are working together to deliver excellent care

Baldassano et al., JPGN 2002 Mar; *34(3):245-8.*

11

Healthcare Provider Transitioning Checklist

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AGE	PATIENT	HEALTH CARE TEAM
12-14	**EARLY ADOLESCENCE** *New knowledge and responsibilities* ☐ I can describe my GI condition ☐ I can name my medications, the amount and times I take them ☐ I can describe the common side effects of my medications ☐ I know my doctors' and nurses' names and roles ☐ I can use and read a thermometer ☐ I can answer at least 1 question during my health care visit ☐ I can manage my regular medical tasks at school ☐ I can call my doctor's office to make or change an appointment ☐ I can describe how my GI condition affects me on a daily basis	☐ Discuss the idea of visiting the office without parents or guardians in the future ☐ Encourage independence by performing part of the exam with the parents or guardians out of the examining room ☐ Begin to provide information about drugs, alcohol, sexuality and fitness ☐ Establish specific self-management goals during office visit
14-17	**MID ADOLESCENCE** *Building knowledge and practicing independence* ☐ I know the names and purposes of the tests that are done ☐ I know what can trigger a flare of my disease ☐ I know my medical history ☐ I know if I need to transition to an adult gastroenterologist ☐ I reorder my medications and call my doctor for refills ☐ I answer many questions during a health care visit ☐ I spend most of my time alone with the doctor during visit ☐ I understand the risk of medical nonadherence ☐ I understand the impact of drugs and alcohol on my condition ☐ I understand the impact of my GI condition on my sexuality	☐ Always focus on the patient instead of the parents or guardians when providing any explanations and ☐ Allow the patient to select when the parent or guardian is in the room for the exam ☐ Inform the patient of what the parent or guardian must legally be informed about with regards to the patient condition ☐ Discuss the importance of preparing the patient for independent status with the parents or guardian and address any anxiety they may have ☐ Continue to set specific goals which should include: • Filling prescriptions and scheduling appointments • Keeping a list of medications and medical team contact information in wallet and backpack
17+	**LATE ADOLESCENCE** *Taking charge* ☐ I can describe what medications I should not take because they might interact with the medications I am taking for my health condition ☐ I am alone with the doctor or choose who is with me during a health care visit ☐ I can tell someone what new legal rights and responsibilities I gained when I turned 18 ☐ I manage all my medical tasks outside the home (school, work) ☐ I know how to get more information about IBD ☐ I can book my own appointments, refill prescriptions and contact medical team ☐ I can tell someone how long I can be covered under my parents' health insurance plan and what I need to do to maintain coverage for the next 2 years ☐ I carry insurance information (card) with me in my wallet/purse/backpack.	**DISCUSS IN MORE DEPTH:** ☐ The impact of drugs, alcohol and non adherence on their disease ☐ The impact of their disease on sexuality, fertility ☐ Future plans for school/work and impact on health care including insurance coverage. ☐ How eventual transfer of care to an adult gastroenterologist will coordinate with future school or employment plans ☐ Remind patient and family that at age 18 the patient has the right to make his or her own health choices ☐ Develop specific plans for self-management outside the home (work/school) ☐ Provide the patient with a medical summary for work, school or transition ☐ Discuss plans for insurance coverage ☐ If transitioning to an adult subspecialist, provide a list of potential providers and encourage/facilitate an initial visit.

Digestive Health for Life | CDHNF Children's Digestive Health & Nutrition Foundation | NASPGHAN North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

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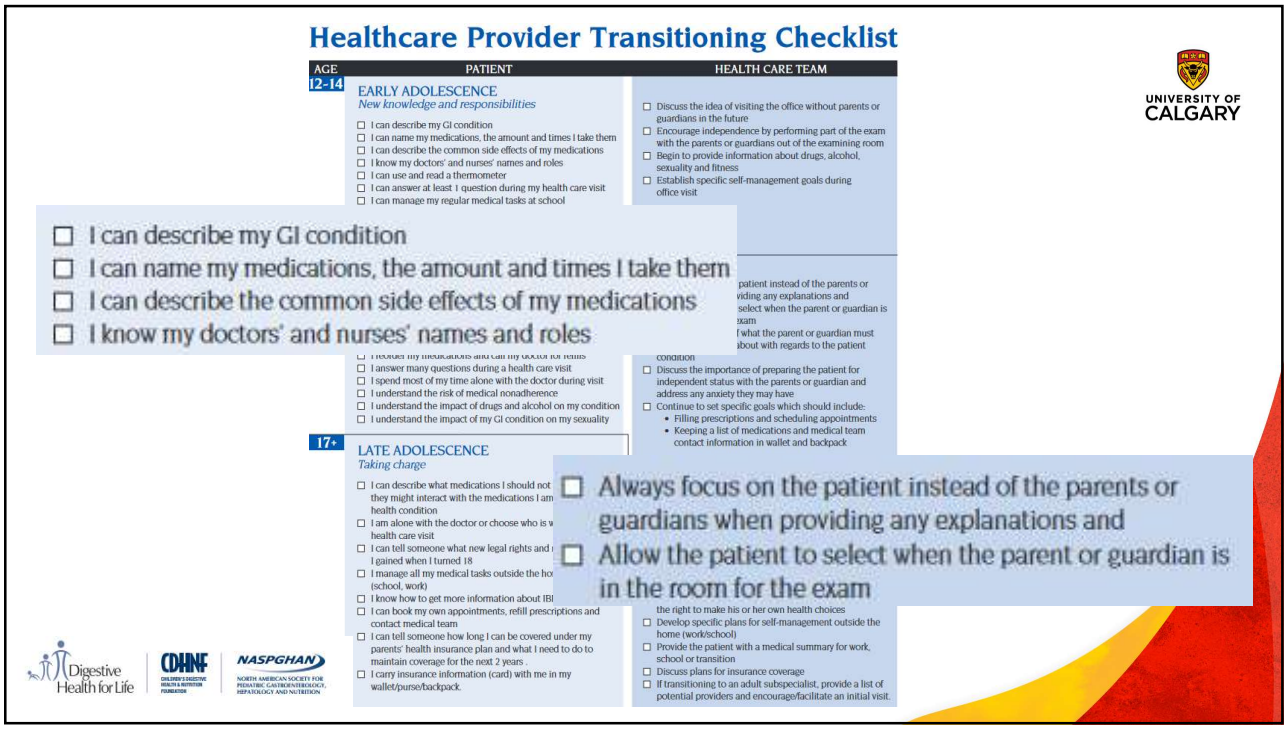

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Transitions are hard

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- Readiness of the young adult, and family dynamics, influence transition
- Patients are often transitioning in other areas of their lives (graduation, college/university employment, financial independence, moving away from home, less oversight by caregiver, etc.)
- Disease specific factors are an additional layer to the process
  - Phenotype
  - Treatment strategies (biologics, drug level testing, mucosal healing endpoint, etc.)
  - Shift in focus from growth, puberty and psychological development to disease specific care

Afzali and Wahbeh. WJG 2017; May 28; 23(20): 3624-31

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Transition in healthcare delivery

- Healthcare system specific transition
  - Propofol vs. conscious sedation for endoscopies*
    - Trans nasal endoscopy (TSE) would not be suitable for this patient group
  - Fee For Service vs. Academic Alternate Funded Physicians have different constraints on their time and availability to allow for repeat/expanded conversations on differences in delivery of care
  - Multidisciplinary model and support staff availability in community practices vs. academic centers are variable
- Preparation of the patient and the team accepting patient's care is key!

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Canadian context for HCT

- 2019 JCAG publication from survey of IBD transition of care
  - Focus was current transition policies/practices, and the participant's ideal transition program
- 9 centers participated - 5 were transfer centers and 4 were transition clinics
  - 3 of 4 transition clinic were run jointly by peds and adult GI, and new patients were seen together once, often along with a multidisciplinary team, before they transferred to adult care
  - 1 of 4 transition clinic had peds and adult GI see patients on separate days, over a variable period of time

Jawaid et al., JCAG 2019 Aug 3;3(6):266-273

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Canadian context for HCT

- The strongest predictor of success was health care provider interest in transition and complete information transfer.
  - Information package from Peds is key
- Adult practitioners did not have a standardized method to assess transition readiness
  - It was presumed to be a Peds initiative
- Areas for improvement were resource focused: financial, logistics and personnel (NC/NP nominated).
- All centers agreed a consensus statement is needed

Jawaid et al., JCAG 2019 Aug 3;3(6):266-273

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EOE and Healthcare Transition knowledge

- 2017 study conducted survey of patients 13-25 years old and parents of patients with EOE/EGE who were diagnosed 13- 25 years
- 75 patients and 245 parents completed $STARQ_x$ to assess readiness to transition from peds to adult care (no parent-child pairs participated)
  - Recruited from APED and CURED websites (highly motivated group)
  - 20% male patients and 70% parents of boys with EOE/EGE
  - 80% in both groups were on active dietary therapy for EOE management

Eluri et al., JPGN 2017; 65(1):53-7

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STARQ$_x$

- Validated tool measuring self reported HCT readiness and self management for adolescents/young adults with chronic health conditions
- HCT readiness in 6 domains are assessed by 18 questions on a 5-point Likert scale
  - Medication management
  - Provider communication
  - Engagement during appointments
  - Disease knowledge
  - Adult health responsibilities
  - Resource utilization

Eluri et al., JPGN 2017; 65(1):53-72

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Results

- 78% of patients and 76% of parents had no HCT knowledge.
- Factors associated with lack of HCT knowledge for patient group –
  - Older age (24 vs. 19 years, p=0.03)
  - Older age at diagnosis (17 vs. 12 years, p<0.01)
  - Already seeing an adult GI doc (63% vs. 38%, p<0.05)
- Factors associated with lack of HCT knowledge for parent group-
  - Active steroid use (48% vs. 31%, p=0.03) (Age of child did not affect scores)
- Interest in transition was 18 years in both groups (similar to IBD and other chronic conditions)[2]

1. Eluri et al., JPGN 2017; 65(1):53-72
2. Sebastian et al., J Crohns Colitis. 2012 Sep; 6(8):830-44

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HealthCare Transition Readiness

- Data evaluated based on age groups and developmental milestones
- There was no significant difference between HCT readiness within each domain other than 'adult health responsibilities' and 'engagement during appointments'
  - Patient group: 22-25 age group did worse than 13-15 age group, in adult health responsibilities (2.8 vs. 4.7, p=0.01)
  - Parent group: Increasing age was reported to be related with increase in engagement (7.5 vs. 5.0, p=0.01)
- Mean Scores overall were considerably lower than other chronic disease conditions (43-59[1] vs. 30-35 in EOE/EGE)

Ferris et al., J Peds Nursing 2015; 30:691-9

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Healthcare Transition in EoE – Patient reported

- 2019 survey of patients (n=67) in adult GI care asked to identify areas of challenges in transition to adult care.
  - 82% comfortable in medical knowledge, but 48% concerned about managing disease effectively in the future
    - Physician referral base, 49% women responders, honorarium offered and many respondents passed few years from transition may skew the data
  - Insurance information, food planning and budgeting for meds were the biggest concerns identified
  - Academic centers were better at supporting patients, compared to community centers
    - Access to Allergists, Immunologists, Social Worker, Registered Dietician, Nurse Practitioner and repeat education likely affect results

Robinson, Furuta. J Ped Nutr: 73(6); Dec 2021. 722-6

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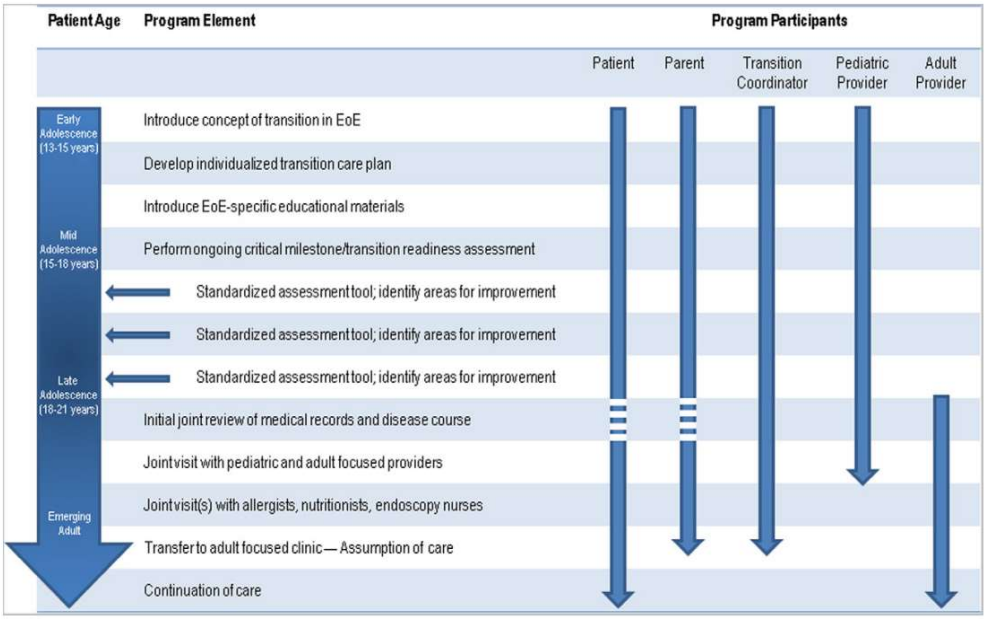

Fig. 1 Proposed model for disease-specific HCT program in EoE. This is a dynamic model with a progression of age-specific activities involving the patient, parent, transition coordinator, and pediatric and adult providers.

Dellon et al., DES 2013 (26). 7-13

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Planning for HealthCare Transition

- Escher[1] identified three goals in the transition
  1. To get the **patient** ready for transfer, having attained specific skill and knowledge
  2. To get the **parents** ready for transfer
  3. To get the **adult gastroenterologist** ready, and well informed at the time of transfer
  4. EOE considerations-
     a. Patient meeting with members of the interdisciplinary team -joint visits with allergists, dieticians, MD/NP
     b. Touring the endoscopy unit and clinic areas
     c. Transition from comprehensive model to disease specific model.

1. Escher JC. Dig Dis 2009; 27(3): 382-6

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Tips to Incorporate HCT Without an Overhaul

- Introduce concepts of transition with the patient and family early, to provide adequate adjustment time.
  - Initiative from Pediatricians, NASPGHAN a great resource
- Empower adolescent patients to visit peds gastroenterologist without caregivers to build self-reliance. (Age 12-14 years)
- Review disease specific and patient specific factors, compliance and advocacy skills
  - Structured format can have a positive effect on the psychological, clinical and medical outcome for the patient[1]
- Multidisciplinary team approach in peds may not always be available in the adult side, and awareness important[2]

1. Afzali and Wahbeh. WJG 2017; May 28; 23(20): 3624-31
2. Dellon et al., DES 2013 (26). 7-13

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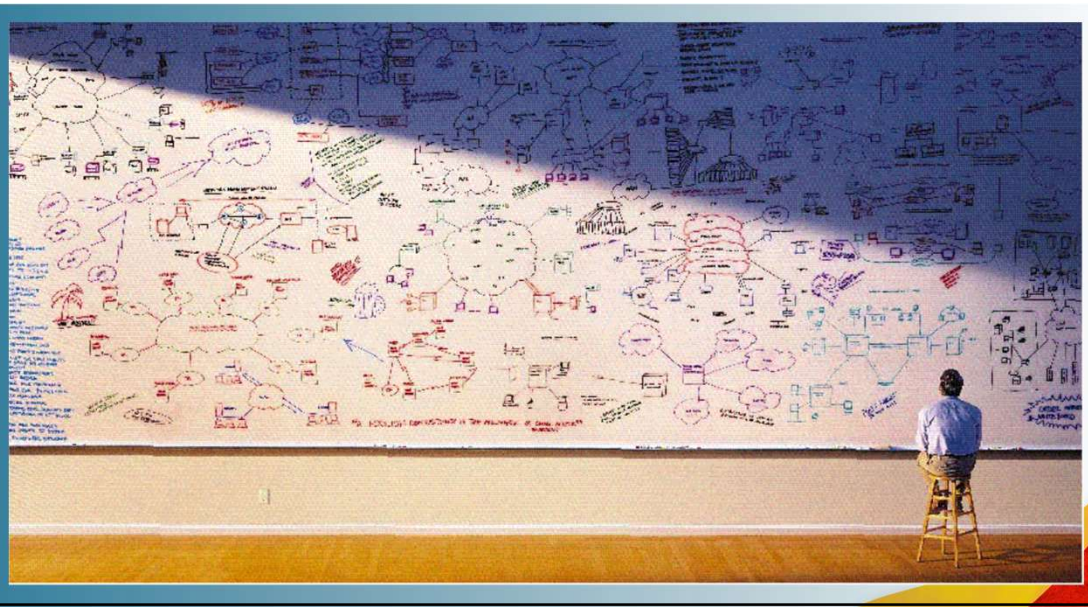
Q&A



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