Eosinophilic Esophagitis 2020

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Disclosures

Off-label use of medications:
No FDA-approved EoE Rx

Medical adviser: MC Science
Speakers bureau: Salix, Takeda

Teaching Points

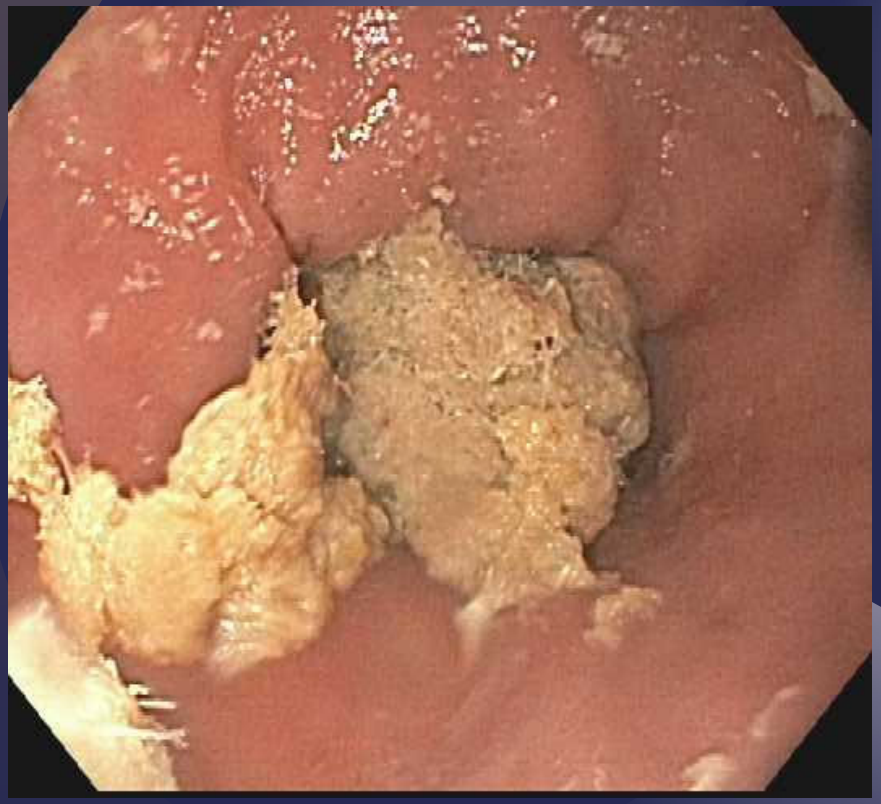
- What is the history of this disease and how does this reflect on general society?
- How is EoE recognized by history, risk factors, biopsy and endoscopy?
- How can EoE be treated?
- What role does the PCP/Integrative physician play?

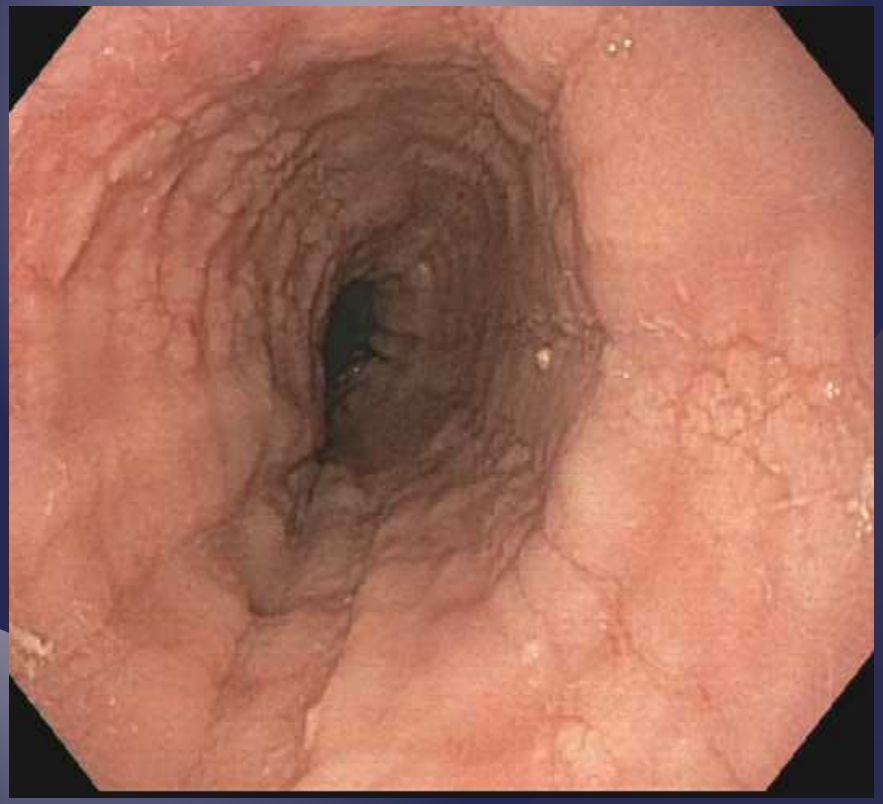
Classic Case: 20 y.o. WM

- 1 yr dysphagia – intermittent, solids, dry food, sticks in mid to upper chest
- Spastic chest pain eating apples & carrots
- PMH: seasonal allergies; asthma as child
- FHx: F - dysphagia; S - asthma

Classic Case at 10:30 PM:

"Hey Dr. W. we got a food bolus"





"Doc, I thought it would pass like it did 6 other times"

The Eosinophil

Hx: Paul Ehrlich 1879

Structure:

Bilobed nuclei

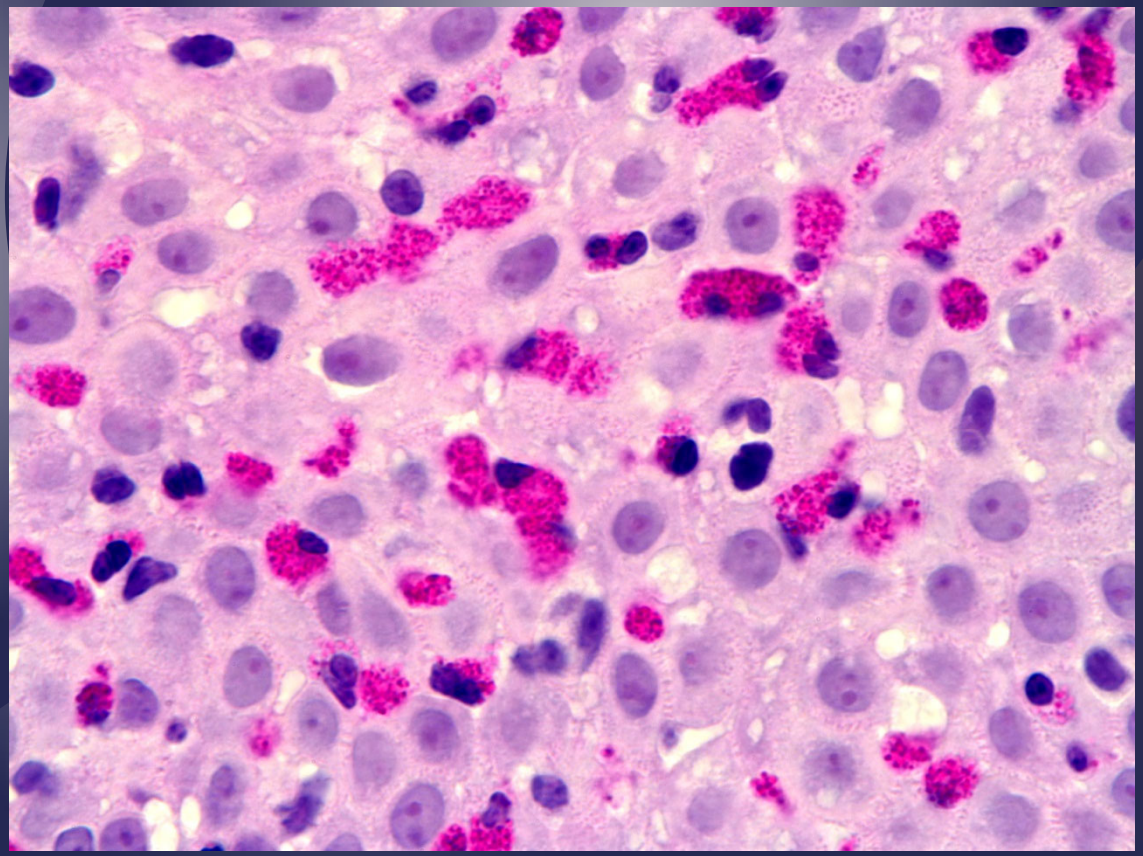
Cytoplasm filled w >200 large granules

Enzymes & proteins w different functions

(known & unknown)

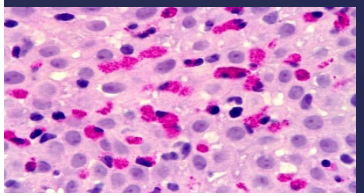
What Makes Eos Evil?

- Genes
- Allergies
- Mast cells
- Acid reflux



What Makes Eos Evil? Genes

- EoE assoc. with variants at chromosome 5q22 encompassing *TSLP* and *WDR36* (rs3806932). *TSLP* overexpressed in esoph Bx in EoE vs. controls.
- Esophageal FK506-binding protein-5 *(FKBP51)* mRNA levels increased in steroid responders. This gene activates IL-6.
- Upregulated miR-21 & miR-223 and down-regulated miR-375 strongly correlated w esoph eos levels.

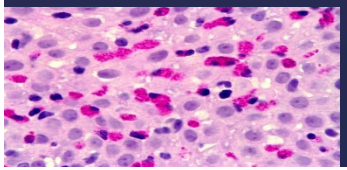


Rothenberg 2010, Caldwell, 2010,Lu 2012,

What Makes Eos Evil? Allergies

- Mouse models show IL-5 (IP) and IL-13 (IT) induced EoE … importance of allergens that caused disease by IL's
- Peds Bx study measuring mRNA expression of interferon, IL (4,5,13), eotaxin (1,2,3) & RANTES.

  Data suggests IL-5 selective TH2 response, with a possible TH1 component.



Mishra 2002, Mishra 2003, Gupta 2006

EoE and Food Allergies
Why More Common Now?

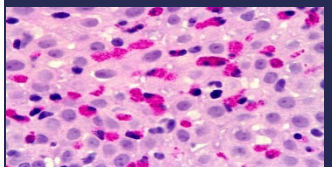
- Freq. antibiotics → altered immunity & gut flora
- Increased dietary exposure in infancy & youth
- Acute GI infections trigger chronic systemic diseases via SIBO, inflam., autoimmunity, etc.
  - 75 million cases/yr
  - “Slow vs fast food”
- Increased intestinal permeability introduces larger antigens resulting in increased eos & MCs
- Increase in ileal lymphoid follicles and interaction w food antigens & bacteria

What Makes Eos Evil? MCs

N=25 children w EoE vs. 22 GERD vs. 22 controls.
Eos & MC counted (tryptase stain).
MC activation status by IgE stain and EM

EoE vs. GERD eos counts (55 ±28 vs. 6.9 ±10, p<.0001)
& MC counts (26.3 ±12.7 vs. 7.8 ±8.9, p<.0001)
24/25 EoE pts contained IgE-bearing cells compared to
9/22 GERD Bx (p< 0.001)

EM confirmed intraepithelial MCs and changes in cytoplasmic granules indicative of MC and eosinophil activation. Evidence for MC-mediated hypersensitivity

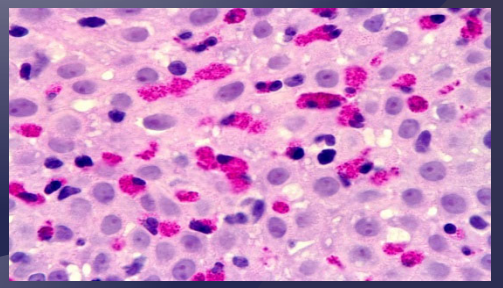


Kirsch et al. J Ped Gastroenterol Nutrit 2007

What Makes Eos Evil? MCs

N = 93 children with EoE
Bx stained for tryptase and eval for degran. MCs

Study of “Histologic Inactive EoE with Sx” defined as “<15 hpf with continued dysphagia”, Persistent Endoscopic EoE (vs. Controls)

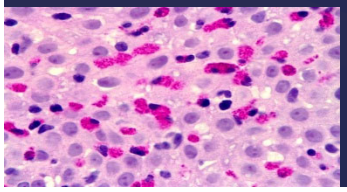


HI-EoE w Sx: 17 MC (vs. 8)
Persistent Endo EoE: 20 (vs. 13)
Degranulated MCs 8 (vs. 5)
MC/hpf – predicted furrows and rings
Low MC/hpf predicted clin. remiss.

Bolton. Am J Gastroenterol 2020.

What Makes Eos Evil? Acid

- N = 60 EoE vs 60 GERD vs 60 Controls
- Impedance-pH monitor – evaluation of:
  - Post-reflux swallow induced peristatic wave
  - Mean impedance
  - 24 hr pH
- PPI response diagnosed by improved Bx
- Results: EoE vs controls – more reflux and less post-reflux waves
- Low impedance predicted poor PPI response



Frazzoni et al. Am J Gastroenterol. 2019.

History of EoE

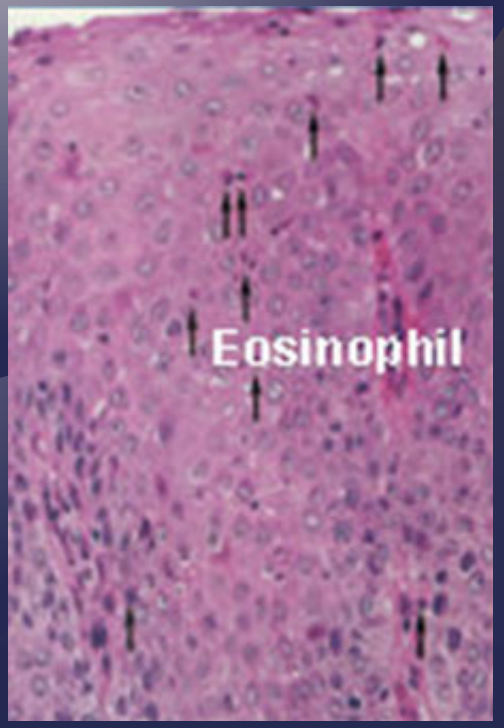
- 1978 – “Eosinophilic esophagitis in a pt w achalasia”
- 1982 – “Intraepithelial eosinophils assoc w acid reflux”
- 1993 – “Esophageal eosinophilia w dysphagia, a new entity”
- 2003 – “Natural Hx of 30 adult pts w EoE”

Landres et al, Winter et al, Attwood et al, Straumann et al

1990

2020

My first case and
longest follow up

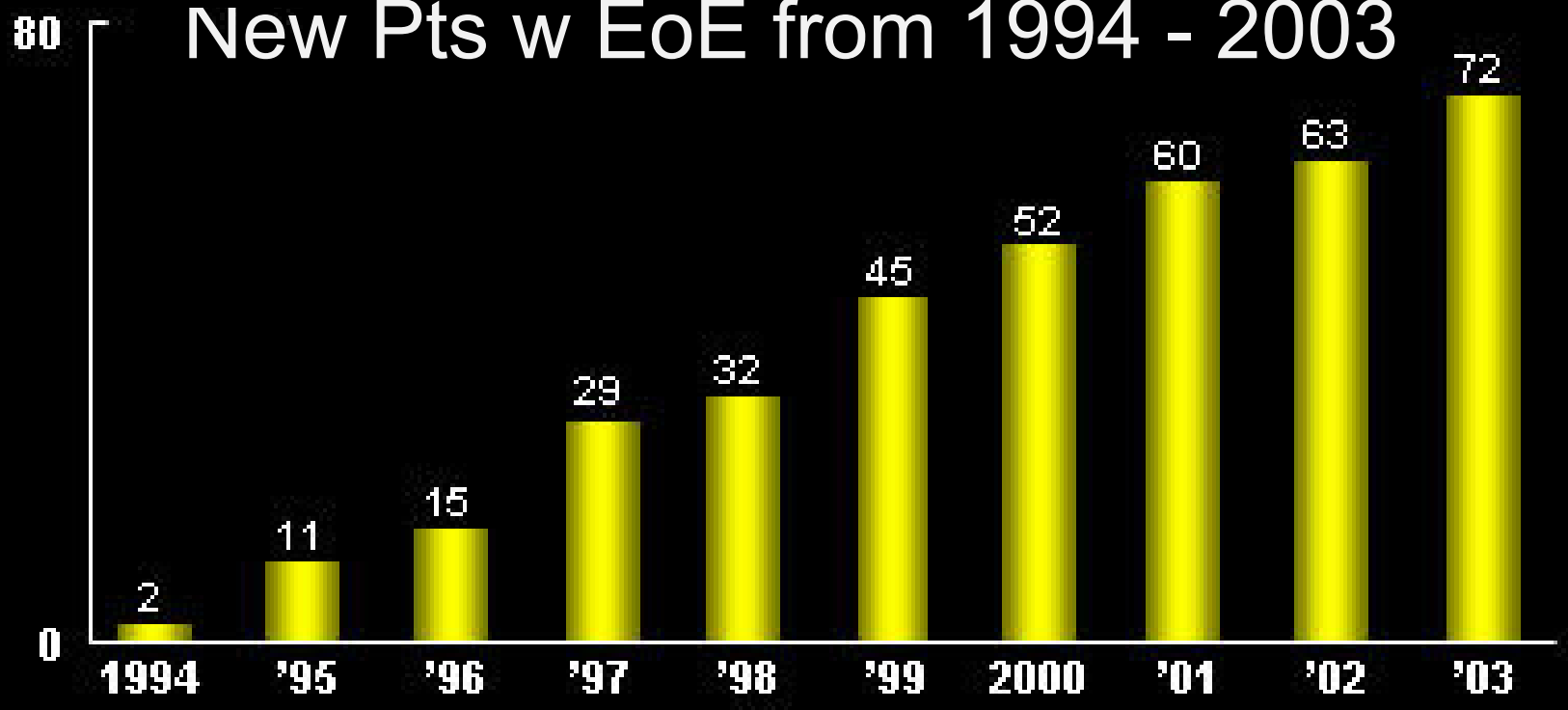


Prevalence and Character of Dysphagia in USA

- Survey 31,129 adults
- 16% experienced dysphagia (one in six)
- 92% w/i last week, 16% severe
- 51% sought medical care
- Groups likely to seek care included:
  - Elderly, males, insured, severe Sx
- Co-morbid diagnoses reported
  - GERD 30%
  - EoE 8%
  - Stricture 5%

Atkins et al. Clin Gastroenterol Hep. 2020.

Prevalence of EOE



- 2014 Prevalence: 57/100K (men 115/100K)

Straumann et al. J All Clin Immunol 2005
Dillon et al. Clin Gastro Hepatol 2014

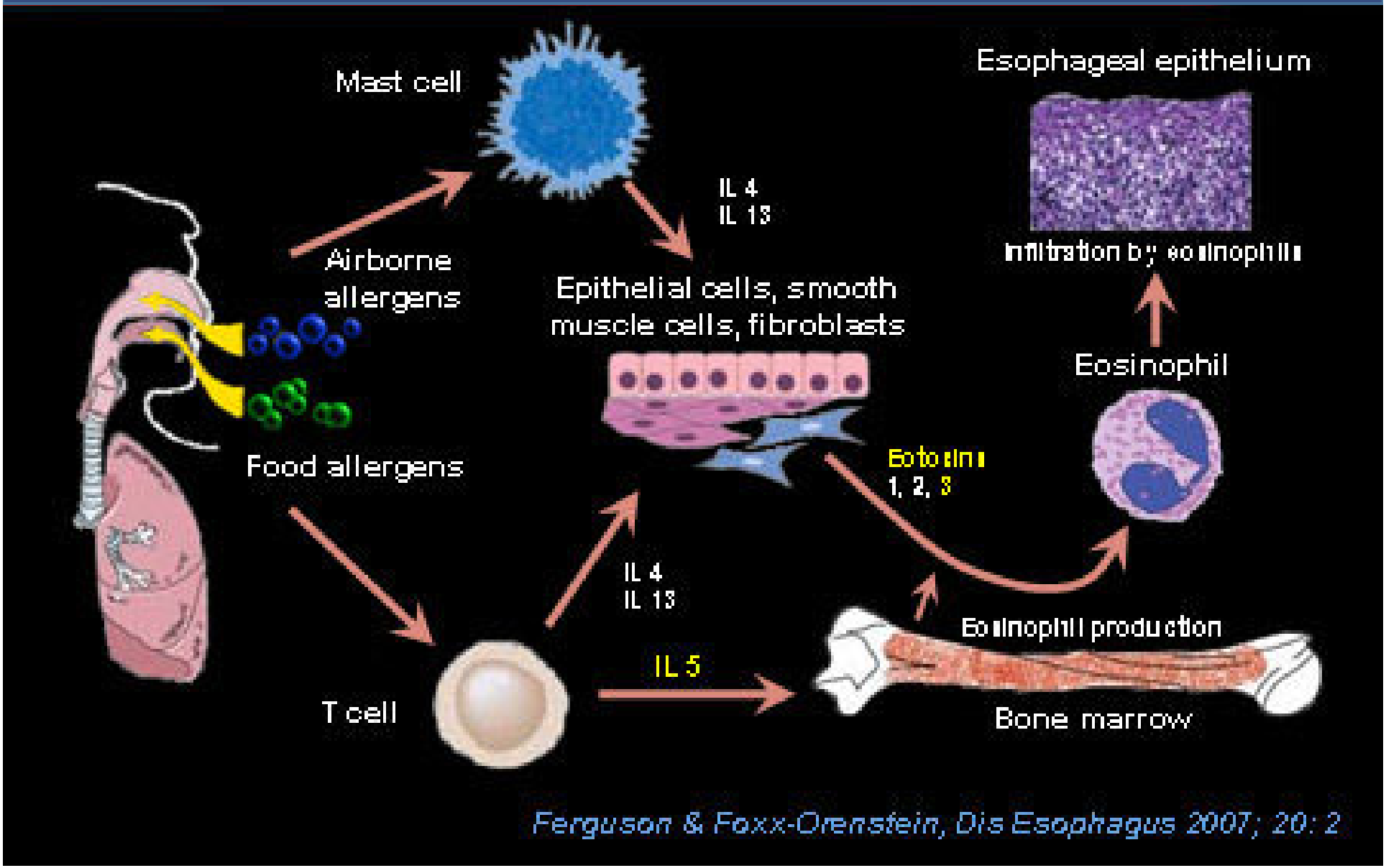
Clinical Presentation & Biopsies

- Males 75%; ages 36-42 in adults
- Allergies very common, Asthma 50%,
- Food allergies 10-30%
- Positive family history of EoE in 10%
- Peripheral eosinophilia 5 – 50%
- Increased IgE in 40-73%
- >15 Eos/hpf; yield – highest in upper and distal esophagus but can see wide variations
- Positive gastric biopsy in 10%

EoE Sx: Adults vs Children

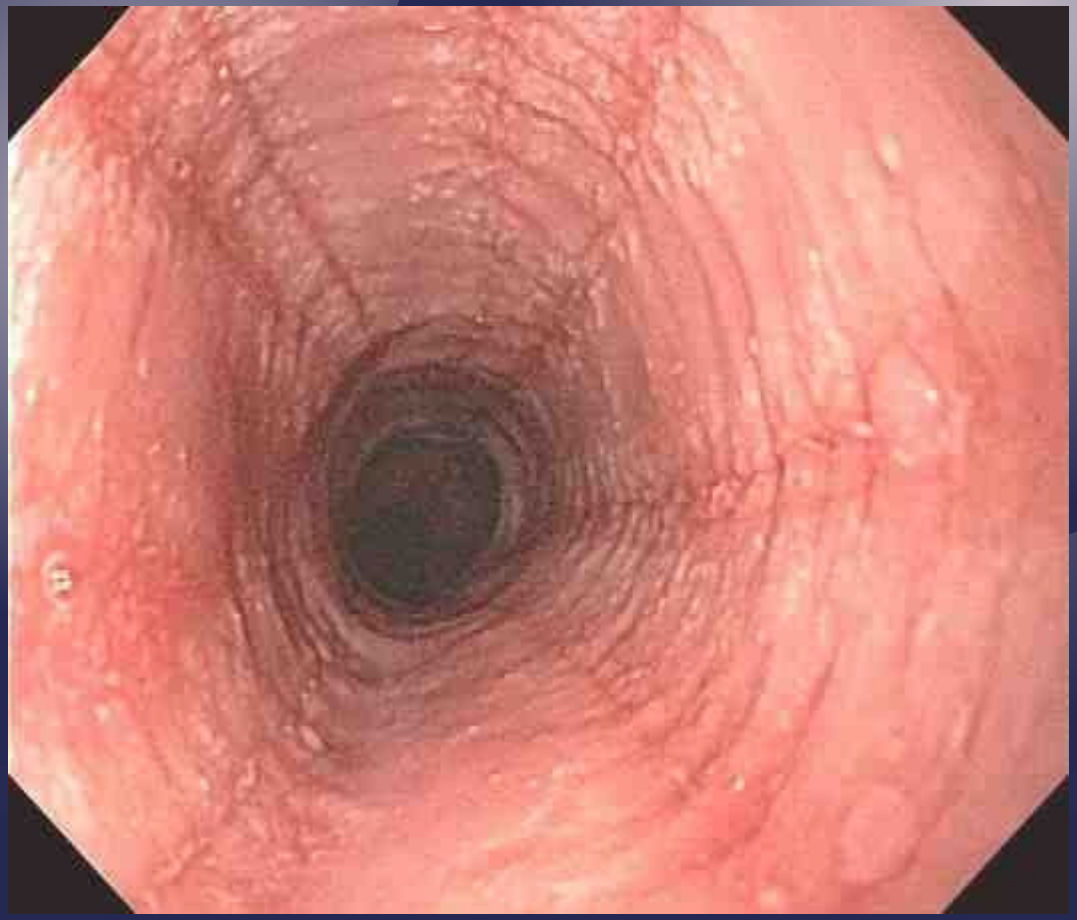
- Trouble swallowing – Adults and Children
- Food impaction – Adults
- Heartburn – Adults
- Nausea – Children
- Abdominal pain – Children

Pathophysiology of EoE



EREFS Score

Edema, Rings, Exudates, Furrows, & Strictures



Natural History: Stenosis

- Retrospective Netherland study from 1996 – 2015 – N = 721
- Inflammatory to Fibrostenotic Path
- With each yr of symptoms w/o Dx, stricture risk increased by 9%

Natural History: Seasonal?

- 18 studies with 17K pts
- No relationship for food bolus or diagnosis of EoE
- (sad finding for GI docs)

Luchendo. Meta-Analysis. Allergy 2015

Therapies – the 3 D's

Dilatation

Drugs

Diet

Dilatation

- Start small
- Go slow
- Steroids first?
- Balloon vs. Bougie

- Characteristic tear pattern
- 1% perforation risk

Dilations as Monotherapy (?)

- 30 adults (73% men), mean follow-up 7.2 yrs
- No treatment other than prn esophageal dilatation
- Dysphagia
  - increased: 7
  - stable: 11
  - improved: 11
- Only 11 patients required dilation
  - 7 single dilation and 4 repeated dilation
- Symptoms most severe in those with blood eosinophilia or pronounced endoscopic changes
- No malignant potential reported to date

Straumann et al, Gastroenterology 2003; 125: 1660

Therapies – the 3 D's

Dilatation

Drugs

- Topical steroids
  - Fluticasone
  - Budesonide
- PPI – "PPI-REE"
- Other drugs
- Biologicals

Diet

Steroids

High- vs Low-Dose Swallowed Topical Steroids for Maintenance Rx

Multicenter retrospective study

N= 82 pts with EoE in histological remission on varying doses of swallowed corticosteroid therapy (SCT)

Followed for a median of 2.2 yrs, data from 217 endoscopy visits.

Relapse occurred in 67% of patients.

Steroids

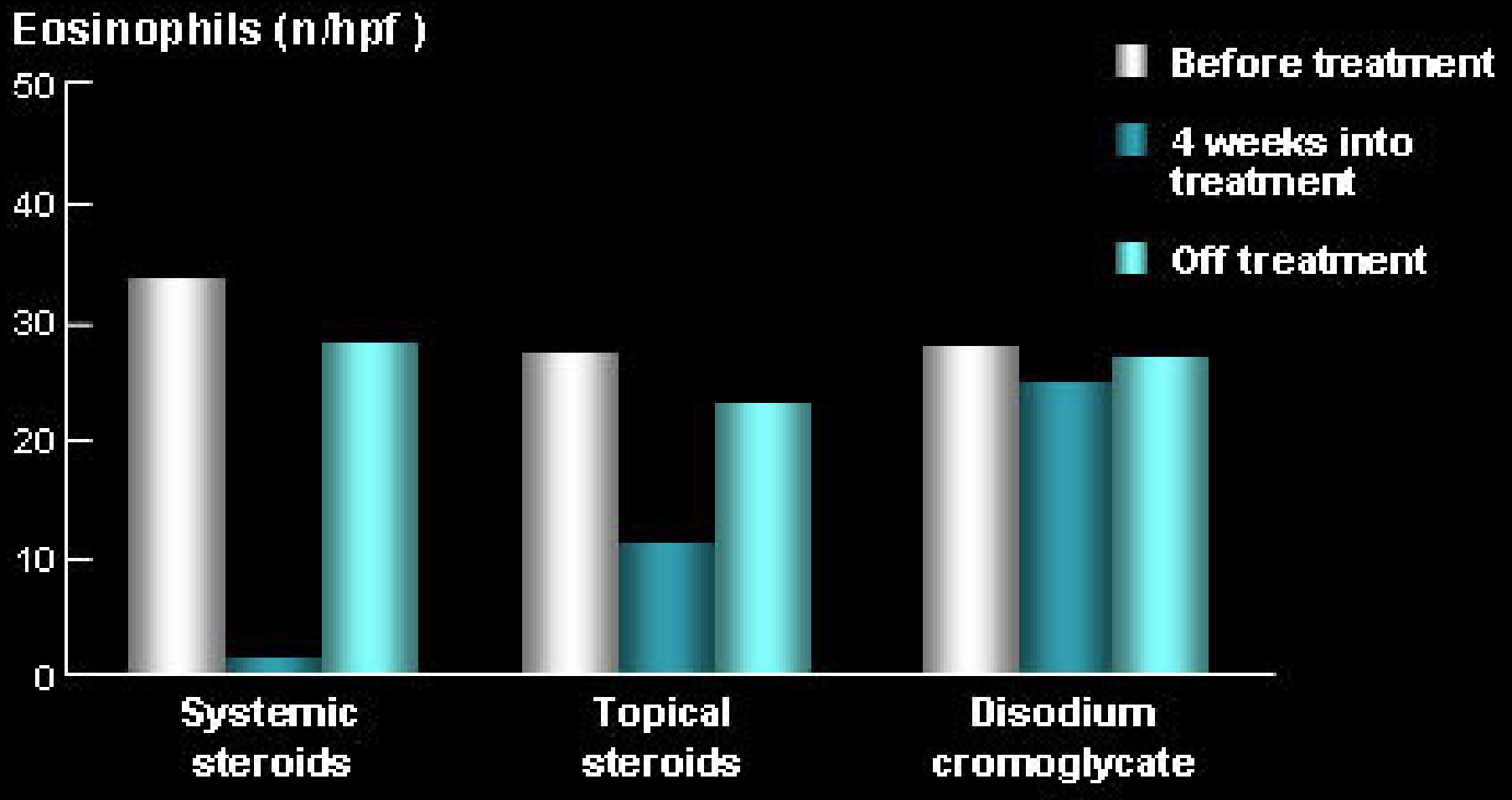
Rates comparable w low-dose (<0.5 mg/day; n=58) and high-dose (>0.5 mg/day; n=24) SCT (72% vs 54%, respectively).

Histological relapse occurred earlier with low-dose SCT (1.0 vs 1.8 years; P = .030).

Regardless of SCT, histological relapse occurs frequently in EoE, with relapse developing later in those on higher doses without an increase in side effects.

Overall advantages of high-dose SCT appear small.

Relapse after Steroid Monotherapy



Liacouras et al, Clin Gastroenterol Hepatol 2005; 3: 1198

Recurrence of EoE after Cessation of Medicines

N=58 EoE w histo response entered into F/U phase; Bx at relapse or after 1 yr

- 33/58 (57%) developed Sx before 1 yr
- Median time 244 d but 130 d in those that relapsed before 1 yr
- 78% histological relapse
- Control of inflm reduced dilatations by 65%

Dis Esoph 2017;30:1-7.

Inhaler Tricks

- Fluticasone 4 puffs (220 µg/puff)
- Twice daily, after breakfast and dinner
- Duration: 6 weeks
- Ensure delivery to esophagus (rather than lung) by removing the spacer
- Inspire deeply, depress the inhaler, and swallow the aerosol
- Rinse mouth with water and avoid food and drink for 2–3 hours

Role of PPI's in EoE

he EDP differentiated patients with EoE from control subjects with 100% accuracy among the 4 clinical sites.

Bioinformatics analysis revealed largely overlapping transcriptomes between pts with PPI-REE and those with EoE, including genes for eosinophil chemotaxis *(*eotaxin 3, *CCL26)*, barrier molecules *(*desmoglein 1, *DSG1)*, tissue remodeling *(*periostin, *POSTN)*, and mast cells *(*carboxypeptidase A, *CPA3)*..

Wen. J Clin All Immunol..2015

Role of PPI's in EoE

PPI monotherapy alone almost completely reversed the allergic inflammatory transcriptome of pts with PPI-REE.

Wen et al identified a set of candidate genes to differentiate pts with EoE from those with PPI-REE before Rx

Wen. J Clin All Immunol..2015

Other Drugs in EoE

Azathioprine – potential help for refractory EoE disease

Cromolyn - No

Monteleukast – No

Infliximab - No

Future Steroids in EoE

TAK-721 – budesonide oral suspension

APT-1011 – fluticasone disintegrating tablet

Biological Drugs in EoE

In future:

- Dupilumab weekly SC injection – phase 3: 69% reduction in EoE. Indications steroid refractory, multiple allergy co-morbidities
- Antolimab – IV, Siglec-8 monoclonal antibody
- Etrasimod oral, highly selective, sphingosin 1-phoshate receptor modulator

Integrative approach to EoE

Therapies – the 3 D's Plus***

Dilatation

Drugs

Diet

- Six food and variations
- Allergy directed
- 2-4-6 FOOD
- (milk and gluten are worst)

Immuno-Rx – desens., MC Rx, LDN…

Food Allergy and Intolerance

- Increasing prevalence of food allergies:
  - 8% of kids age 1 - 3
  - 4% of adults
- Most common food allergens: peanuts, tree nuts, fish, shellfish, soy & dairy
- Immune mediated include IgE & non-IgE antibodies
- Non-immune-mediated reactions are most common reactions (“food intolerance”)

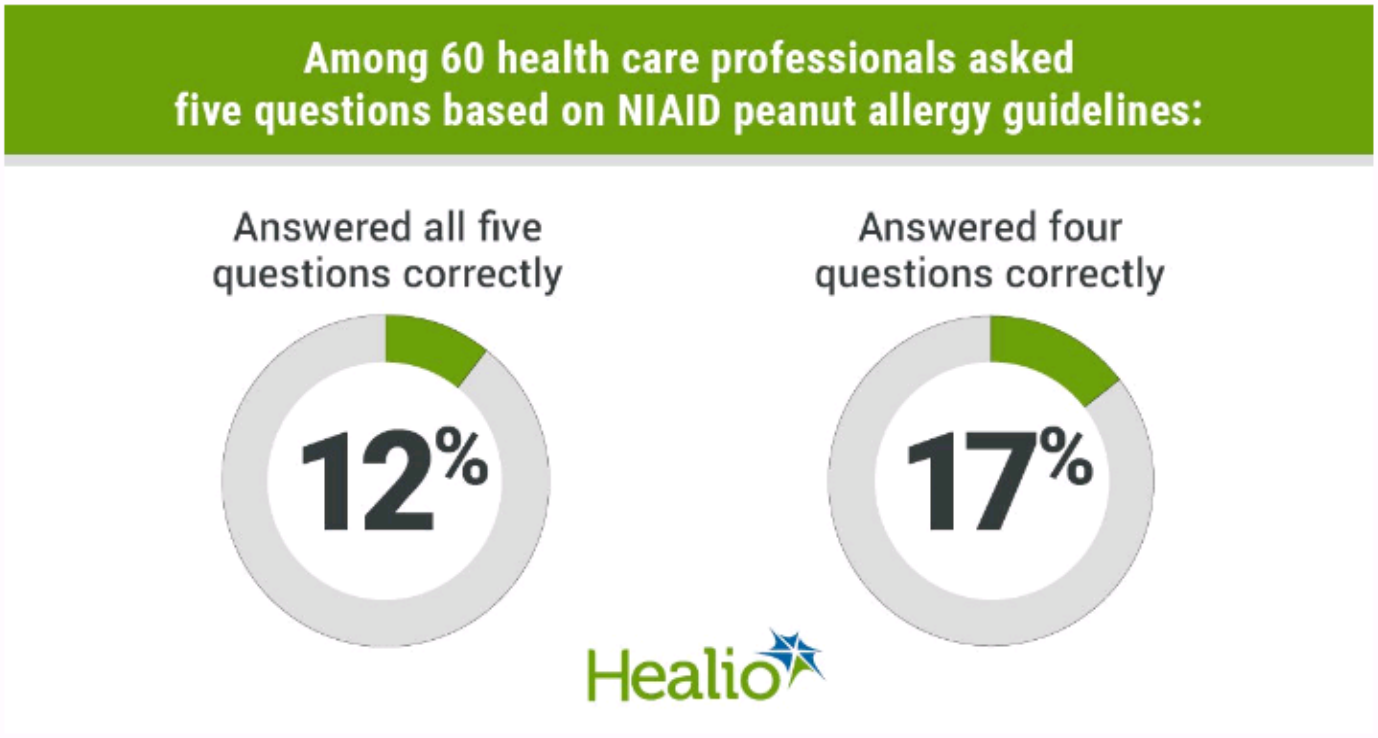
Latest Guidelines to Reduce Peanut Allergy

National Institute of Allergy and Infectious Diseases guidelines:

Introduce peanuts to infants who are approximately 6 mo old and have mild to moderate eczema.

Infants as early as 4 mo of age with severe eczema and/or egg allergy be “strongly considered” for peanut sensitivity testing.

How Well Do We the Recommendations?



Reference: Mehta P, et al. A*nn Allergy Asthma Immunol*. 2020;doi:10.1016/j.anai.2020.06.037.

6 Food Elimination Diet in Adults

No dairy, eggs, wheat, soy, peanut/tree nuts, fish/shellfish for 6 wks

Histologic response in 10/21 responders

Reed. Aliment Pharm. 2017.

Step-up Empiric Elimination Diet: 2-4-6

Background

<u>Overall Efficacy</u>
Elemental - 90.8%
SFED - 72.1%
Food Elimination - 45.5%

TFGED = 2 food group elimination diet

Methods:

Prospective study conducted in 14 centers.
Pts underwent a 6-wk 2-food-group elimination diet (TFGED: milk and gluten-containing cereals).
Remission defined by Sx improvement and <15 Eos per HPF

Non-responders were gradually offered a 4-food-group elimination diet (FFGED; TFGED plus egg and legumes) and a 6-food-group elimination diet (SFGED; FFGED plus nuts and fish/seafood)

In responders eliminated food groups were reintroduced individually, followed by endoscopy.

Results:

130 pts (25 pediatric patients), 97 completed study phases

TFGED achieved EoE remission in 56 (43%) pts, age independent. Triggers in TFGED responders were milk (52%), gluten-containing grains (16%), and both (28%).

EoE induced only by milk was present in 18% and 33% of adults and children, respectively.

Remission rates with FFGEDs and SFGEDs were 60% and 79%, with increasing food triggers, especially after an SFGED. Overall, 55 (91.6%) of 60 of the TFGED/FFGED responders had 1 or 2 food triggers.

Compared with the initial SFGED, a step-up strategy reduced endoscopic procedures and diagnostic process time by 20%.

Step-up Empiric Elimination Diet: 2-4-6

Conclusions:

A TFGED diet achieves EoE remission in 43% of children and adults.

A step-up approach results in early identification of a majority of responders to an empiric diet with few food triggers, avoiding unnecessary dietary restrictions, saving endoscopies, and shortening the diagnostic process

Immunotherapy for EoE

Allergy Tests

Skin prick testing

Blood testing

- RAST - Radioallergosorbent
- ImmunoCAP
- ELISA - Enzyme-linked immunosorbent assay

Allergy Test Directed Food Elimination Efficacy

- Low in Adults
- Variable in Children

Luchendo. Meta-Analysis. J Clin Allergy Immunol. 2017.

Immunotherapy for EoE

Standard Subcutaneous Allergy Shots

- Limited data
- May benefit EoE pts with allergic rhinitis
- May be best in those sensitive to pollens containing allergens that cross react with food allergens
- Many of my patients seem to do well with SC Immuno-Rx

Egu. Immunother Immumod. 2018.

Immunotherapy for EoE

- Sub-lingual Immune Therapy
  - FDA-approval of two directed at different grass pollen, one for dust mites and one for short ragweed
- Evidence shows that EoE can occur after oral/sublingual immunotherapy
- SLIT contraindicated for pts w EoE

MC Rx for EoE

Prevalence of dysphagia in MCAS

58/175 MCAS pts (33.1%)

Prevalence of EoE in MCAS

2/175 MCAS pts (1.1%)

Limited experience in treating EoE with MC-directed therapy

Summary - 1

- Prevalence of EoE is increasing and seems related to allergic epidemic
- EoE easily diagnosed by history, risk factors, biopsy, and endoscopy
- Must always diagnose food bolus obstruction cases – Bx (often not done)
- At least 6 biopsies often needed
- Lymphocytic esophagitis &

Crohn's disease are in the DDx

Summary - 2

- No superiority of different topical steroids
- EoE rapidly returns after cessation meds
- EoE best treated with 3 D's plus
- The PCP/Integrative physician can help with diet, compliance, and possibly by certain types of immune modulation.
- The PCP can refer dysphagia pts early