What to Eat or Not to Eat?

Palm Beach Pediatric Society
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Disclosures

Unfortunately, I have no financial relationships to disclose.

Learning Objectives

- Understand the basics of normal immune response to ingested food
- Understand the difference between IgE and non-IgE mediated food allergies
- Diagnose and manage “Milk Protein Allergy”
- Diagnose and manage FPIES
- Diagnose and manage Eosinophilic Esophagitis

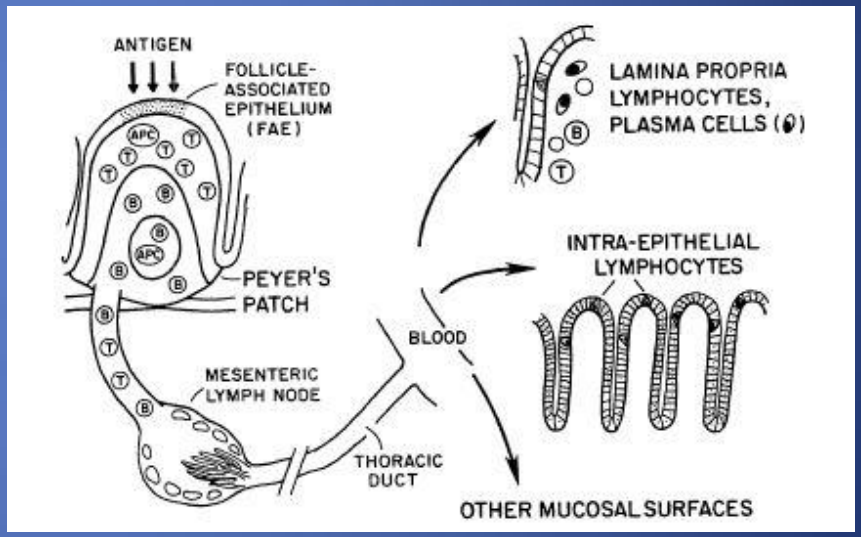
Normal immune response to ingested food

Mucosal Immunity: Anatomy

- Food enters the GI tract and encounters GALT
- GALT: gut associated lymphoid tissue
  - Largest antigenic load in the body
  - Different levels of protection
    - Mucous coat: physical barrier where potential pathogens get trapped and passed out in stool
    - Epithelium
    - Tight junctions:
      - Joining the adjacent enterocytes preventing even small peptides from passing through
      - Inflammatory processes can damage and allow free passage of gut content

Mucosal Immunity: Antigen Processing

- Specialized epithelium Antigen Presenting Cells (eg M cell) sample antigens and pass to PP
- Peyer's Patch (PP) processes antigen and turn B /T cells to sIgA committed cells
- These are released to lymphatics then to the blood
- These then migrate to rest of GI tract and mammary gland (less lung and GU)



Elson CO. The immunology of IBD. Philadelphia: Lea and Febiger, 1996.

Mucosal Immunity: sIgA

- Secretory IgA differs from serum IgA by the addition of the secretory component
- Secretory component
  - transports IgA from lamina propria to the gut lumen
  - protects IgA from degradation in the GI lumen
- Component of breast milk
- Antigen specific sIgA then binds pathogens so they cannot bind epithelium
- Pathogens get trapped in mucus and excreted in stool
- Can be reabsorbed in distal ileum and enter enterohepatic circulation

Mucosal Immunity: Oral Tolerance

- A state of downgraded immune response to innocuous dietary antigens (food)
- Mucosal tolerance: benign gut bacteria is tolerated in lumen but activates systemic immunity
- Mechanism is not fully known
- Antigen committed T cells suppress immune response
- Host of other cells/mechanisms play a role:
  - nonprofessional antigen-presenting cells, dendritic cells, and regulatory T cells, as well as lymphocyte anergy (cell turns off) or deletion
- Failure to induce tolerance to food protein is thought to result in food allergy

Mucosal Immunology (2012) **5,** 232–239
JPGN (2000) 30, S13-S19

Food Allergy (FA)

- An adverse food reaction can be either a food allergy (an immune mediated response) or nonimmune related (eg lactose intolerance)
- A food allergy is an abnormal response to food exposure (usually orally) via IgE, non-IgE or mixed processes
- There are multiple types of FA each with its own clinical and pathophysiologic processes

FA: IgE and Non-IgE

- Urticaria/ angioedema
- Oral allergy syndrome
- Resp/GI symptoms
- Anaphylaxis

- Eosinophilic Esophagitis
- Eosinophilic Gastroenteritis
- Atopic Dermatitis

- Food protein-induced enterocolitis syndrome (FPIES)
- “MPA”
- Celiac disease

FA: nonimmune related (DDX)

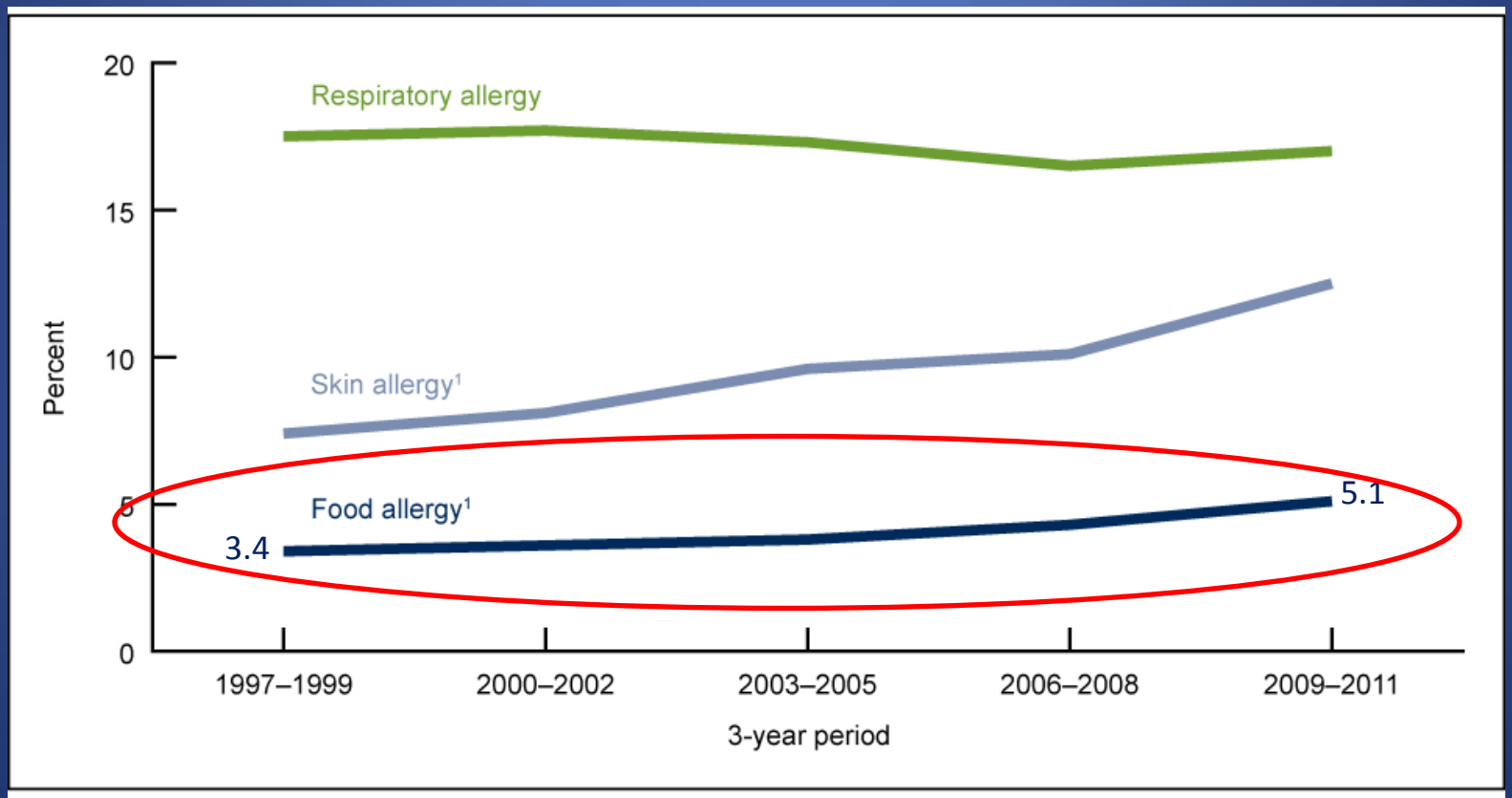
- Malabsorption
  - Carbohydrate: Lactose intolerance
  - Fat: Pancreatic insufficiency
- Anatomic
  - GERD, pyloric stenosis
- Toxic
  - Seafood: scromboid poisoning (fresh tuna)
  - Clostridium botulinum and staph aureus
- Intolerances
  - Alcohol
  - Caffeine
- Psychological: food aversions/phobias

FA: Epidemiology

- Most acquired in the first 2 yrs of life
- Highest prevalence is at 1 yr old (6 to 8%)
- Rate fall progressively until late childhood where it remains stable at 3-4%
- Parental perceived FA in childhood has been found to be as high as 30%
- More than 170 foods reported to cause FA but 6 food groups are responsible for most of this

FA: Prevalence

The increasing of FA in childhood (0-17 years) in the united States from 1997 to 2011



[1]Significant increasing linear trend for food and skin allergy from 1997–1999 to 2009–2011.
SOURCE: CDC/NCHS, Health Data Interactive, National Health Interview Survey.

FA: 6 Major allergen groups

- Cow's milk
- Soy
- Eggs
- Wheat
- Fish/Shellfish
- Peanut/Tree nut

FA: IgE Mediated

- Rapid in onset from minutes to 2 hrs
- Protein based not fat or carbohydrate
- One to two allergens > multiple
- Six major allergen groups (>85% of allergens)
- Baked/cooked versions of some allergens are tolerated (e.g. Eggs)
- Most are outgrown except fish/shellfish and peanut/tree nut
- Retested every year or two

FA: IgE Mediated Clinical Presentaion

- Skin: urticaria and angioedema
  - FA accounts for about 20% of cases
  - Generally rapid appearing
  - FA are an uncommon cause of chronic urticaria
- Oropharyngeal:
  - By itself or part of systemic reaction
  - Oral allergy syndrome
- Respiratory: Asthma, allergic rhinitis and conjunctivitis common in children with FA but uncommon as isolated response to a food allergen
- Anaphylaxis: serious allergic reaction that is rapid in onset and may cause death

FA: IgE Mediated Clinical Presentaion

- Gastrointestinal:
  - Rarely the sole manifestation of FA
  - Symptoms include nausea, vomiting, abdominal pain/cramping, and diarrhea
  - Upper GI symptoms are usually minutes to 2 hrs
  - Lower GI symptoms (eg diarrhea) usually occur after 2 to 6 hrs

FA: IgE Mediated Clinical Presentaion

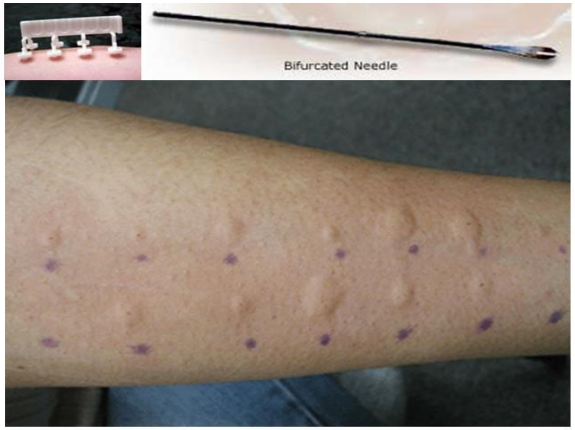
- Oral allergy syndrome (pollen-food allergy syndrome):
  - Fresh uncooked fruits and vegetables (cooked do not induce symptoms)
  - Becomes cross reactive with allergic pollen antigen
  - Immediate oropharynx pruritus with mild swelling of lips, tongue, throat
  - Usually resolve in minutes with withdrawal of food but can progress
- Food-dependent, exercise-induced anaphylaxis:
  - Anaphylaxis only if exertion within 2-4 hrs of ingested food
  - Most in adolescents and young adults
  - MC foods are wheat, celery and seafood
  - Can be ingested without issues if no exertion

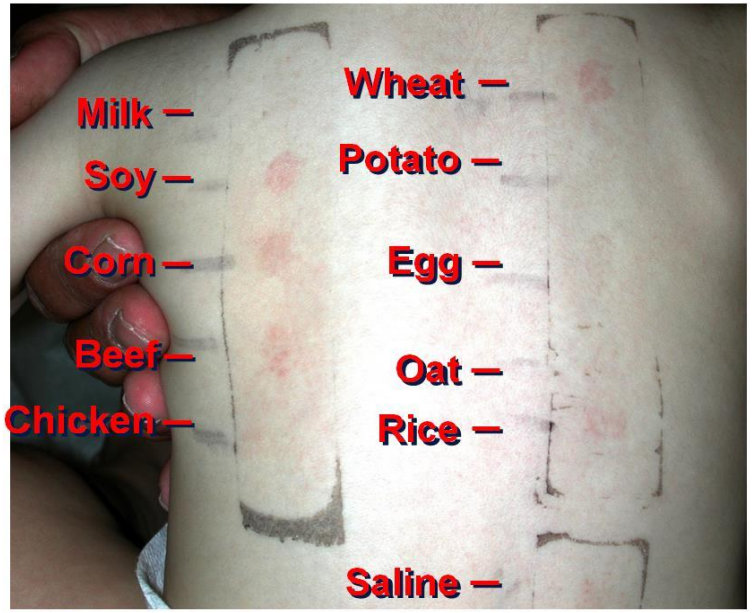
FA: IgE Mediated Diagnosis

- History is critical: pretest probability needs to be high to help with diagnosis
  - Symptoms , timing, reproducibility
  - Skin test or in vitro tests alone are NEVER diagnostic
- Double Blind, Placebo Controlled, Oral Food Challenge
  - Gold standard
  - Single blind or Open challenge is also diagnosis if compatible with the history and tests
- Skin prick test (SPT)
  - Used to detect IgE mediated FA (>3 mm positive)
  - Only done where they are trained to handle anaphylaxis
  - Low specificity and high sensitivity
  - Thus if used as a screening test can yield FP results
  - Negative test will usually exclude IgE mediated allergy
- Atopy Patch testing (APT)
  - Topical application of antigen for 48hrs
  - For detecting Non-IgE mediated FA
  - Not standardized (reagents, methods, or interpretation) not recommended

FA: IgE Mediated Diagnosis

Methods of Direct Allergy Testing





FA: IgE Mediated Diagnosis

- In Vitro testing
  - Considered less sensitive than SPT
  - Usually more costly than SPT
  - Useful in known anaphylaxis and eczema patients
- Radioallergosorbent test (RAST): older version
- Fluorescent enzyme immunoassay
  - ImmunoCAP version is now well studied and most used
  - Very high positive predictive value **in children** when compared to clinical history and results of SPT and/or DBPCFC for select antigens

FA: IgE Mediated Diagnosis

ImmunoCAP

Rating	IgE level (kU/l)	comment
0	< 0.35	ABSENT OR UNDETECTABLE ALLERGEN SPECIFIC IgE
1	0.35 – 0.69	LOW LEVEL OF ALLERGEN SPECIFIC IgE
2	0.70 – 3.49	MODERATE LEVEL OF ALLERGEN SPECIFIC IgE
3	3.50 – 17.49	HIGH LEVEL OF ALLERGEN SPECIFIC IgE
4	17.50 – 49.99	VERY HIGH LEVEL OF ALLERGEN SPECIFIC IgE
5	50.00 – 100.00	VERY HIGH LEVEL OF ALLERGEN SPECIFIC IgE
6	> 100.00	Very HIGH LEVEL OF ALLERGEN SPECIFIC IgE

https://en.wikipedia.org/wiki/Radioallergosorbent_test

FA: IgE Mediated Diagnosis

- ImmunoCAP (kU/L)
- 95% PPV*
  - Egg 7 [2]
  - Milk 15 [5]
  - Peanut 14
  - Tree nuts 15
  - Fish 20
  - Soy 30**
  - Wheat 26**

- SPT (wheal diameter)
- 95% PPV*
  - Milk 8 mm [6 mm]
  - Egg 7mm [5mm]
  - Peanuts 8 mm [4 mm]

*With appropriate history
** less well studied, much lower PPV
[ ] for children < 2 yrs old

Sampson JACI 2001
Boyano etal. Clin Exp Allergy 2001
Garcia-Ara etal. JACI 2001
Clark etal. Clin Exp Allergy 2003
Maloney etal. JACI 2008

Sporik etal. Clin Exp Allergy 2000

FA: IgE Mediated Treatment

- Educate the patient
  - Strict adherence to food allergen avoidance
  - Nutritionist to help identify foods, hidden foods, and learning to read labels
  - Learning to recognize early signs of reaction
- Emergency treatment plans
  - Liquid antihistamine
  - Self injectable epinephrine
    - Always with them (not in a hot car)
    - School, relatives , etc
- Go to emergency facility/ call for help (911)

FA: IgE Mediated: Prognosis

- Majority of cow's milk, eggs, wheat and soy are outgrown in childhood and adolescence
- Fish/shellfish and peanut/tree nut tend to persist into adulthood
- Decreasing levels of IgE in immunoCAP testing is encouraging for resolution
- Medically supervised food challenge is recommended for confirmation

FA: Milk Allergy

- Both IgE mediated and non-IgE mediated
- IgE mediated was the type addressed previously
- Non-IgE mediated is what we typically refer to as cow's milk allergy/ intolerance, allergic colitis, milk protein allergy/intolerance
- Now called Food protein-induced proctocolitis of infancy (FPIPI)
- Renamed in 2010 by expert panel (J Allergy Clin Immunol. 126(6) 2010)

FPIPI: Epidemiology

- Overall prevalence is unknown but one population based study looking at RECTAL bleeding attributed to cow's milk: 1.6 per 1000 infants
- Cow's milk is main trigger at >65% (soy and egg next)
- It is more common with FH of atopy than general population

FPIPI: Clinical Presentation

- Exclusively in young infants (typical onset 2-8 wks old)
- Infants are generally healthy but pass blood tinged stools and mucus
- Some are fussy with increased BM frequency but usually not frank diarrhea
- Half of infants are breast fed (unknown why)
- Eliminating the antigen from diet (or mother's diet) usually results in resolution in 3 days (up to 2 weeks)
- Recurrence seen with maternal inadvertent ingestion

FPIPI: Diagnosis

- Mainly based on H&P (clinical diagnosis)
  - Elicit typical history
  - Check for fissure (main cause of rectal bleeding in pts under 1 yr old but can delay the dx at times if blood is though to originate from fissure)
  - Typical stools are soft to loose with blood specks or streaks with/without mucus
- SPT or in vitro IgE test are negative (not recommended)
- Flex Sig is reserved for atypical presentations
  - Mild colitis with LNH frequently observed
  - Inflammation is limited to rectum and distal sigmoid
  - Bx reveal eosinophils, NOT cryptitis/crypt abscesses
- Fecal calprotectin (don't test lactoferrin) elevated
- Occult blood can take weeks to clear and not recommended
- DDX: anal fissure, NEC, infection, FPIES, etc

FPIPI:
Management: Breast Fed

- Continue BF
- Eliminate all dairy and other mammalian milks
- If severe symptoms, consider amino acid based (AA) formula while mom pumps and discard for 3-5 days
- Careful reading of all food labels
- If fails and was done correctly for 2 weeks, then soy and eggs (some moms will eliminate more but most will not)
- Counselling can be time consuming
- Multiple allergens unlikely but can be seen in up to 8%
- 8% will fail and need extensively hydrolyzed or AA based formula

FPIPI:
Management: Formula Fed

- Change to extensively hydrolyzed (EH) formula
- Note that partially hydrolyzed formulas are NOT hypoallergenic
- AA based lacks allergenicity
- Soy not recommended (cross sensitivity with cow's milk- up to 50%)
- 5-10% do not respond so will need and amino acid based formula
- One study suggest that infants on an EH formula with probiotic (LGG) recover more rapidly

FPIPI: Management

- Standard time table for reintroduction is at one year old (usually successful)
- Expert experience* suggest 50% breast fed tolerant of antigen in mom's diet at 6 months and 95% at nine months (formula also tolerant at nine months)- no formal studies on this
- Reintroduction can be done at home, unless initial presentation was severe
  - AA based formula to EH formula
  - BF to have mom add small amounts of cow's milk to her diet each day
  - EH formula fed with cow's milk added in a stepwise fashion
  - Pts with milder symptoms can introduce faster
- If symptoms recur then strict diet again for 6 months before reattempt
- No need to restrict subsequent siblings as low risk BUT IgE mediated are at a somewhat higher risk for allergic disease
- Prognosis: excellent as nearly all infants resolve at a yr and progression is rare

* Lake/Sicherer, UpToDate 2015)

Food protein-induced enterocolitis syndrome: FPIES

- Epidemiology:
  - Not know but in Israeli study*, 44 of 13019 (0.34%) babies confirmed with FPIES; far less common than FPIPI
  - Rare in siblings
- Pathogenesis
  - Not fully known but non-IgE mediated
  - Food specific IgE antibodies (serum levels or SPT) are not detected in the majority of pts but up to 25% may have evidence of specific IgE to the FPIES inducing foods
  - Cow's milk and soy are the most common triggers with studies showing 40-50% reactivity to both though none of the 44 babies above reacted to soy
  - Rare in exclusively breast fed Infants
  - Can occur with solids with rice being the most common and also the antigen that may elicit the most severe reactions (requiring IVF)

* J Allergy Clin Immunol. 2011 Mar;127(3):647-53

FPIES: Clinical Presentation

- Classic FPIES begins in early infancy, usually 1-4 weeks following cow's milk or soy introduction (the 44 babies were in first 6 mths)
- Reactions to solids occur later at 4- 7 mths when they are introduced
- Rare after 1 yr old with introduction of foods
- Respiratory and skin manifestations are absent
- 30% develop atopic diseases and many have FH of atopy
- 75% appear seriously ill and 15% are hypotensive and require hospitalization, esp after acute episodes
- Two presentations are seen: Acute and chronic (see next slide)
- Atypical FPIES: up to 25% of FPIES have/develop IgE antibodies to a food and illness is more protracted and have potential of developing IgE mediated allergy (eg Anaphylaxis) as well

FPIES: Chronic vs Acute

	Chronic* FPIES	Acute FPIES
Food ingestion	Food ingested on a regular basis, initially described in young infants being fed with milk or soy-based formulas; food ingestion after a period of avoidance results in the symptoms of acute FPIES	Food ingested on an intermittent basis or after a longer period of avoidance
Onset of symptoms	Intermittent vomiting without clear temporal association with food ingestion, chronic diarrhea that may contain blood or mucous; may lead to weight loss or failure to thrive	Typical onset of vomiting in one to three hours, accompanied by pallor, lethargy; may be followed by diarrhea in five to eight hours in some patients
Symptoms and signs	Intermittent vomiting Diarrhea Lethargy Pallor Weight loss Failure to thrive Severe Bilious vomiting Bloody diarrhea Abdominal distention Dehydration Limpness Dusky appearance	Repetitive, vomiting (95%–100%) Lethargy (75%–85%) Pallor Dehydration Diarrhea (25%–40%) Severe Repetitive, projectile vomiting, up to 10–20 times Bilious vomiting Bloody diarrhea Abdominal distention Limpness Dusky appearance Hypotension (15%–20%) Temperature, less than 36°C
Laboratory findings	Anemia Hypoalbuminemia Leukocytosis with left shift Eosinophilia Metabolic acidosis Methemoglobulinemia Stool reducing substances	Neutrophilia, more than 3500 cells/mL peaking at approximately six hours Thrombocytosis more than 500 × 10^9/L Elevated gastric juice leukocytes more than 10/hpf at three hours (research setting) Metabolic acidosis Methemoglobulinemia Fecal leukocytes and eosinophils

*FPIES = food protein-induced enterocolitis syndrome; FPIAP = food protein-induced allergic proctocolitis; * = chronic FPIES phenotype has been reported in young infants continuously fed with milk or soy-based formula. It is unclear whether chronic FPIEs can be caused by solid foods in older children.*

Nowak-Węgrzyn, Konstantinou G. Non-IgE-mediated food allergy: FPIES. Curr Pediatr Rep 2:135–143, 2014

FPIES: Diagnosis

- History with the typical symptoms with clinical improvement upon withdrawal of causative antigen
- Other etiologies, esp in acute setting, must be excluded
- No specific laboratory or radiographic findings
- Often multiple episodes and extensive evaluation before diagnosis is made
- Oral food challenge is gold standard but high risk and recommended to do in inpatient setting and only if needed to confirm dx

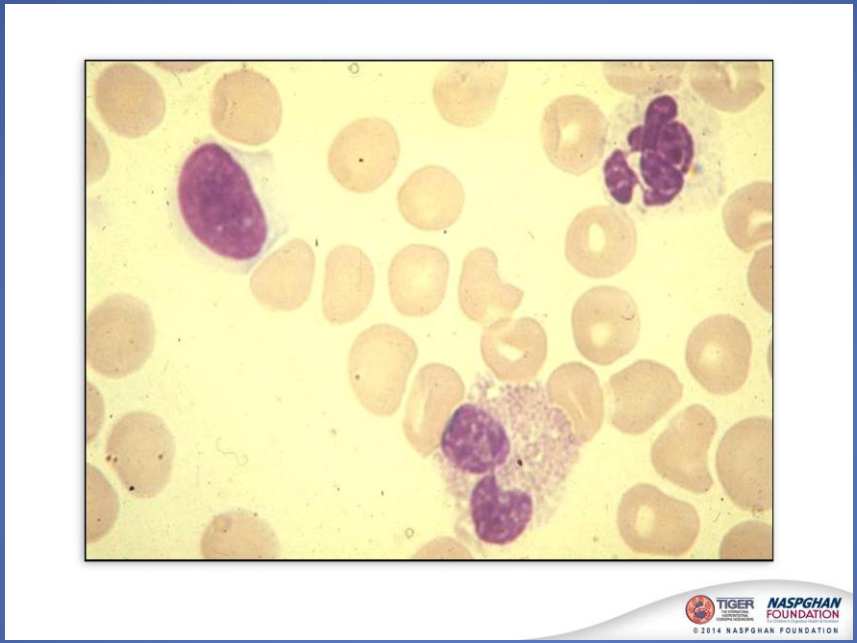
FPIES: Treatment

- Strict elimination of the food (antigen)
  - Infants on formula switched to EH formula (10-20% will need AA based formula)
  - Rare for BF infant but try to avoid suspected food if able else as above
  - Chronic symptoms usually improve in 3-10 days
  - When starting solids skip cereals/grains as 1/3 of cow's milk and soy FPIES develop solid-food FPIES (delay until a year but poor evidence for this)
- Emergency treatment plan
  - Taken to ER for moderate to severe reactions
  - Started on IVF and treated as there situation dictates based on level of dehydration/vital signs
  - Steroids and epinephrine (no study done to confirm true benefit)
  - IV/IM ondansetron has been effective with vomiting and abd pain
  - Outpatient ondansetron has not been studied
  - If never had a severe episode, a mild episode of minimal vomiting can be handled at home

FPIES: Prognosis

- Cow's milk and soy usually resolve by 3 yrs old (90% in the Israeli study)
- Solid-food and/or those with IgE detected antigens, may have a more protracted course
- Oral food challenge is used to determine if offending food can be reintroduced into the diet but when to do it is unsure (must be done in a protected environment, not at home!)

Eosinophilic Esophagitis (EoE)



- A chronic, immune mediated esophageal inflammatory disease associated with esophageal dysfunction resulting from severe eosinophil predominant inflammation

EoE: Epidemiology

- Reported throughout the world, except Africa
- First reported in late 1960s and 1st reported in a child in 1983 but not until 2007 were the first guidelines published
- Estimated prevalence of 4/10,000 (Ohio 2003), 5.5/10,000 (Minnesota 2006)
- Incidence seems to be increasing (Ohio study claims the incidence is now higher than IBD in children- in Switzerland study as well)
- More common in boys (3:1), Caucasians and FH of atopy
- No ICD code prior to 2008: ICD-9: 530.13, ICD-10: K20.0
- As far as is known, does not progress to neoplasia or general eosinophilic gastrointestinal d/o, hypereosinophilic syndrome, or eosinophilic leukemia.

JPGN 2013; 57(1): 72-80
Gastro 2014; 147: 1238-1254

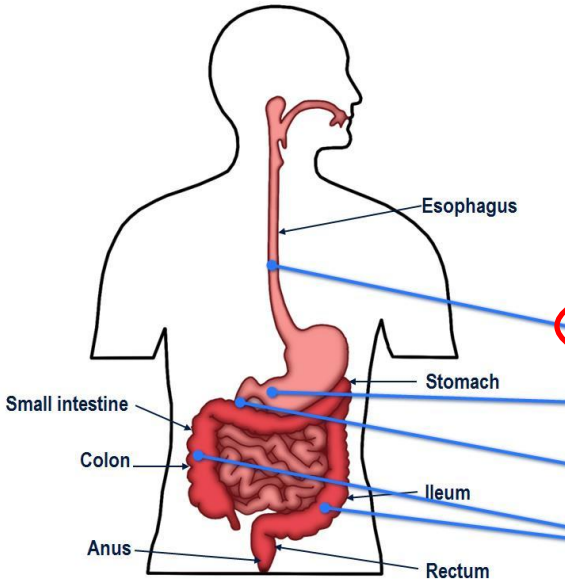
EoE: Epidemiology

- Onset from infancy to adulthood with bimodal distribution, one peak in childhood (5-10 yrs) and the other in adulthood (30s)
- Strong familial association
  - Higher incidence btw siblings than general population
  - Almost 10% of patients have parents with hx of stricture or EoE
- Higher rate of atopy (asthma, eczema, AR)
- 10-20% IgE mediated FA
- 50% have another family member with allergy hx

CGH 2005;12:1198-206
Gastro 2003;125:1660-9
Gastro 2009;137:1238-49
Gastro 2014;147:1238-54

EoE: Pathophysiology

Gastrointestinal Eosinophils



Normal eosinophil values, per high power field (hpf):

- Esophagus (0)
- Gastric antrum (2-10)
- Duodenum (10-20)
- Colon (15-30)

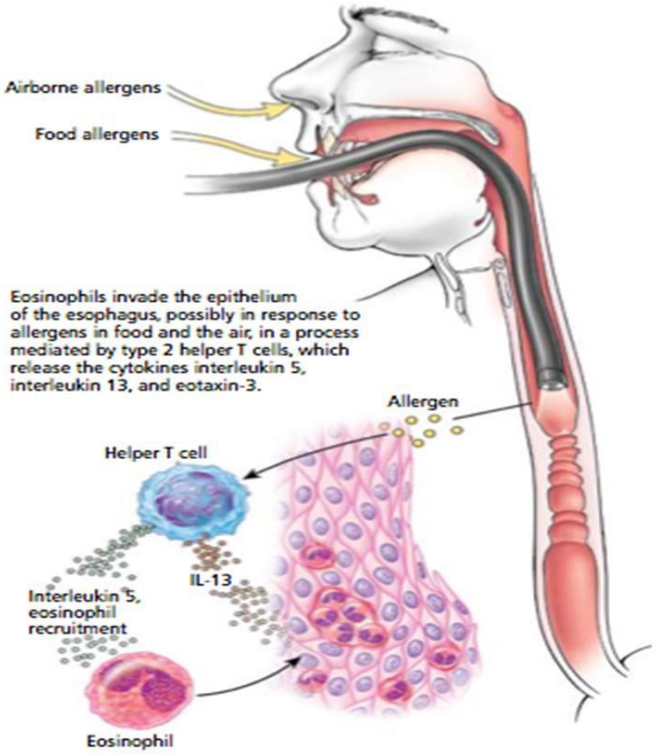
Average accepted values

DeBrosse CW et.al. *Pediatr Dev Pathol.* 2006;9(3):210-8.

EoE: Pathophysiology

Potential Pathophysiology of EoE

- Intraluminal allergen exposure
  - Predominately food antigens
- Mucosal production of eosinophilic chemoattractants
- Influx of eosinophils
- Release of inflammatory mediators
- Esophageal dysfunction



Noneveski et al; *Clev Clin J.* 2008:75(9):623-633.

EoE:
Clinical Presentation: Definitions

- Esophageal eosinophilia: Finding eosinophils in the squamous epithelium of the esophagus
- EoE (2013 ACG guidelines):
  - Symptoms of esophageal dysfunction
  - Eosinophil predominant inflammation with peak eosinophil count > 15 per HPF (1 or more bx)
  - Persists after 2 months of PPI
  - Exclude other causes of eosinophilia
  - Response to tx supports the dx but not required
- PPI responsive esophageal eosinophilia: EoE that clears the eosinophils with use of a PPI only

EoE: DDX of Esophageal Eosinophilia

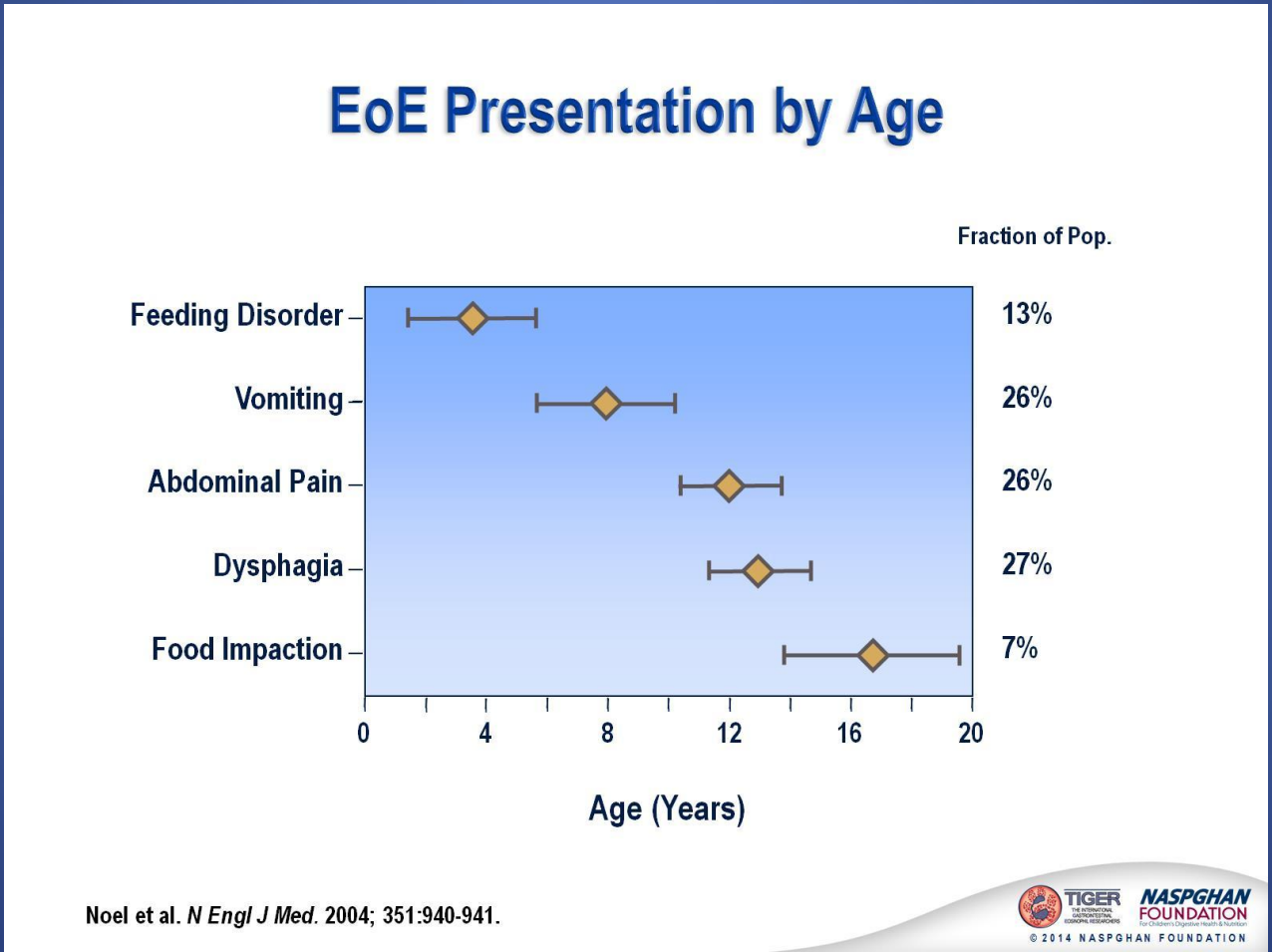
- GERD
- EoE
- PPI responsive esophageal eosinophilia (PPI-REE)
- Eosinophilic gastrointestinal diseases
- Celiac disease
- Crohn's disease
- Infection
- Hypereosinophilic syndrome
- Achalasia
- Drug hypersensitivity
- Vasculitis
- Pemphigoid vegetans
- Connective tissue disease
- Graft-versus-host disease

EoE:
Clinical Presentation

- Symptoms are similar to GERD

Patients	Symptoms
Infants/toddlers	Food refusal, FTT, feeding intolerance/ aversion (choking/gagging), regurgitation, vomiting
Children	Vomiting, abdominal pain (epigastric), dysphagia, nausea, regurgitation, heartburn, Feeding refusal
Adolescence	Dysphagia, food impaction, reflux, heart burn

EoE:
Clinical Presentation

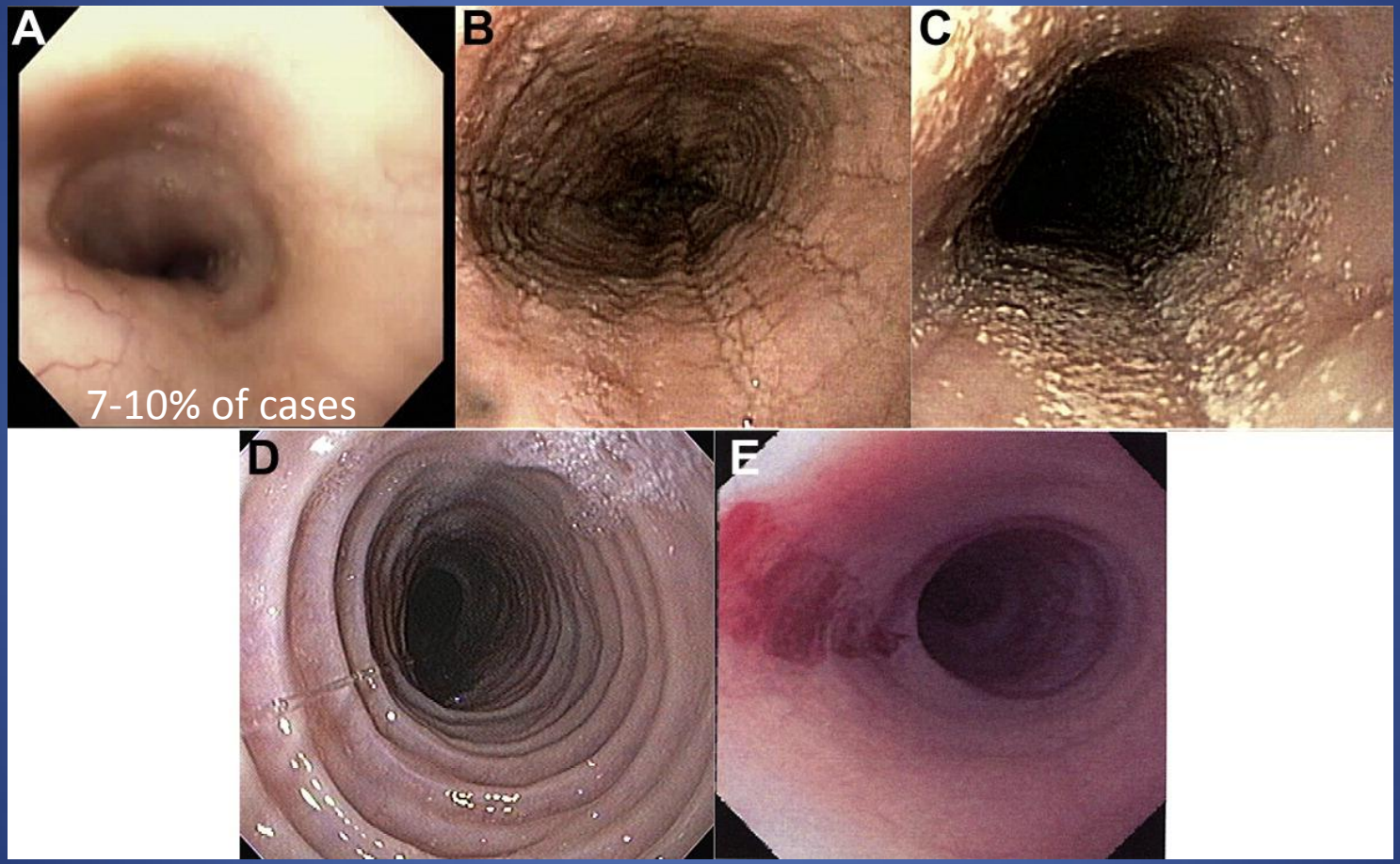


These not the sole symptom reported, but the primary complaint at referral. Most kids are referred for vomiting, abdominal pain and dysphagia.

EoE:
Diagnosis

- Must distinguish EoE from GERD and PPI-REE
- When GERD tx does not resolve symptoms or the symptoms return, then EoE should be considered
- EoE should be considered in all cases or dysphagia
- I go as far as to say that EoE should be evaluated in all cases of food impaction even if the bolus cleared
- EoE always requires endoscopy and esophageal bx for the diagnosis along with clinical presentation

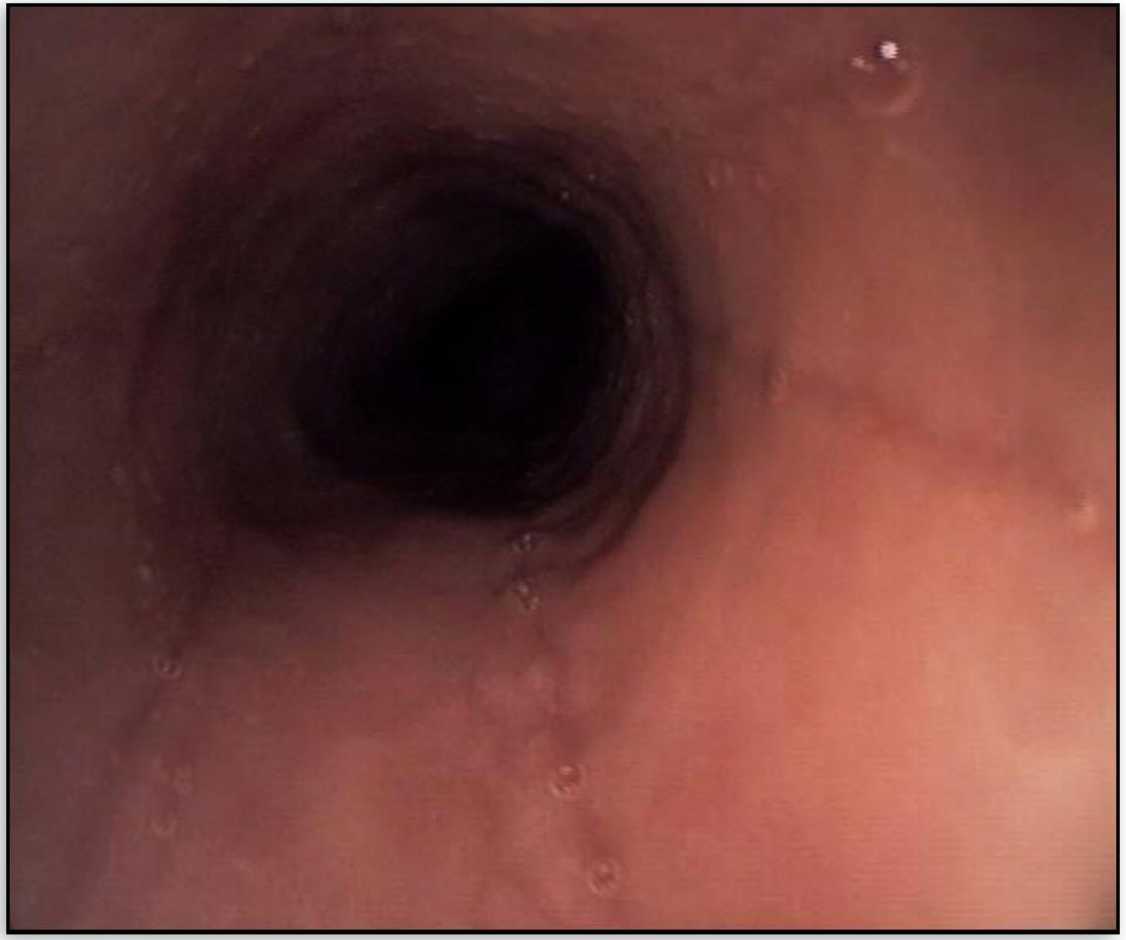
EoE: Endoscopic Features



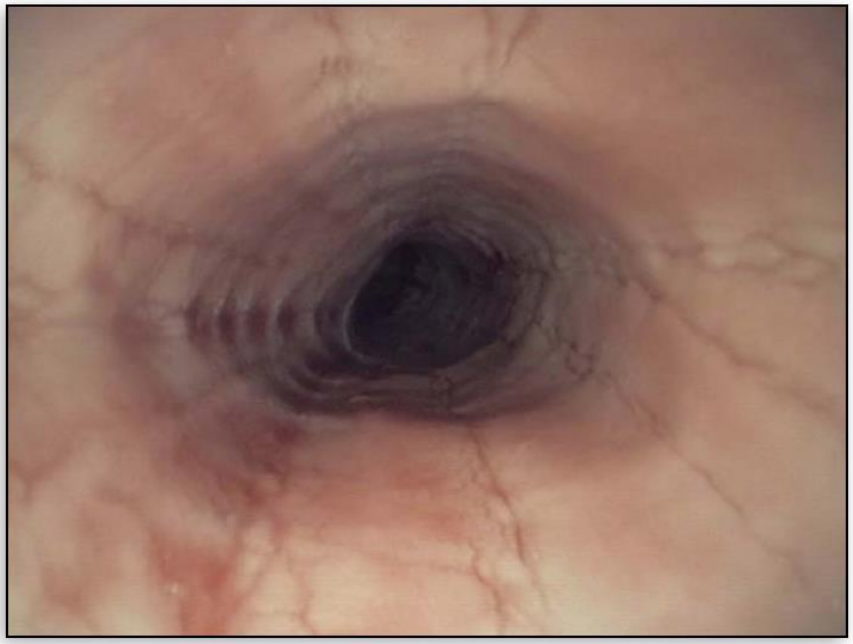
A: Normal esophagus **B**: Esophageal furrowing **C:** White mucosal plaques **D:** Esophageal ring trachealization **E**: Small-caliber esophagus with mucosal tearing after endoscopy.

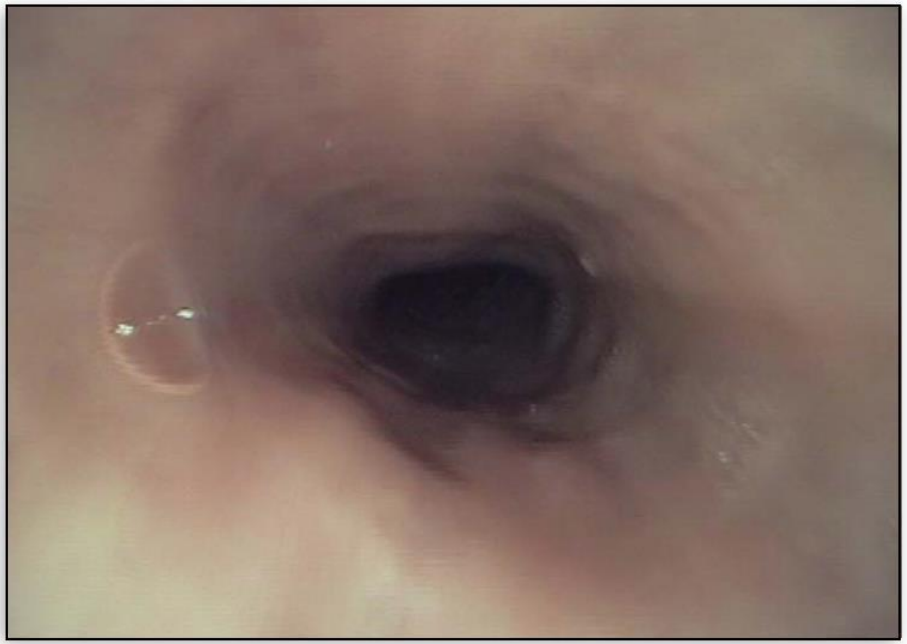
Journal of Allergy and Clinical Immunology 2011 128, 3-20.e6DOI:

Esophageal Furrowing

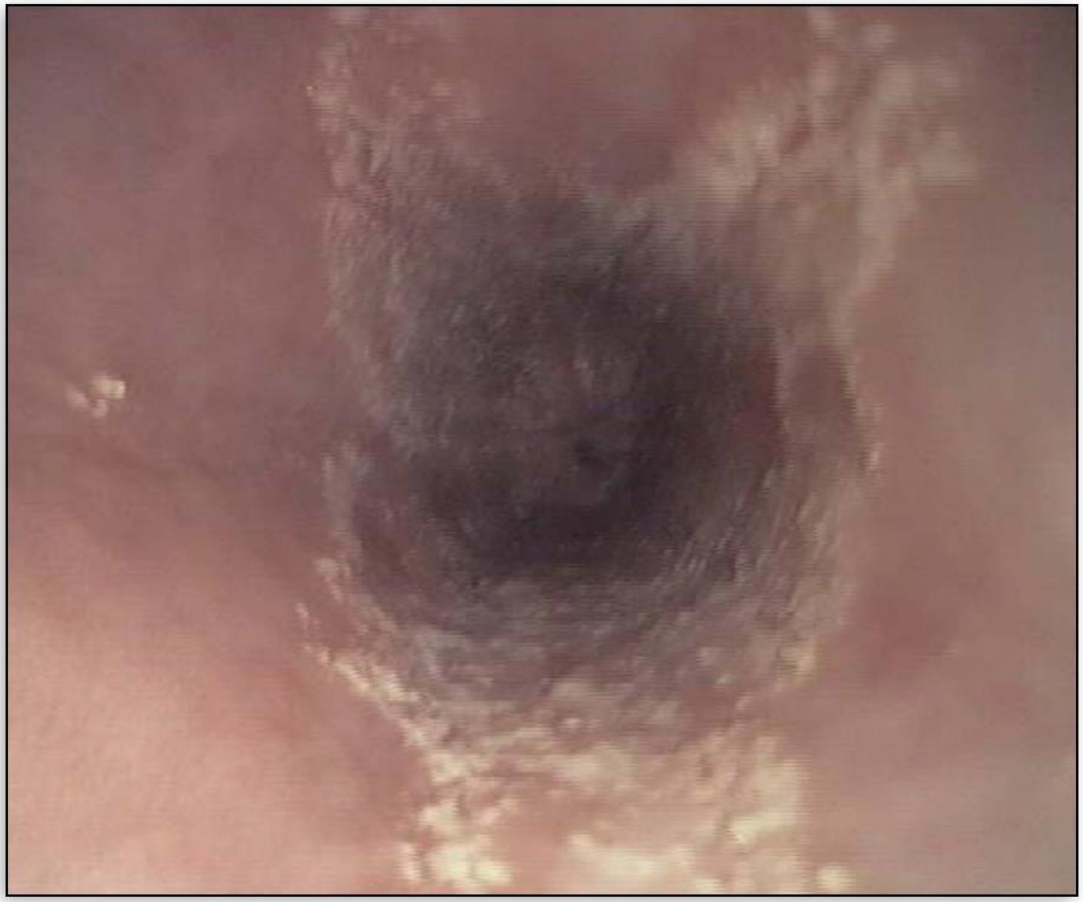


Esophageal Furrowing
Before & After Treatment

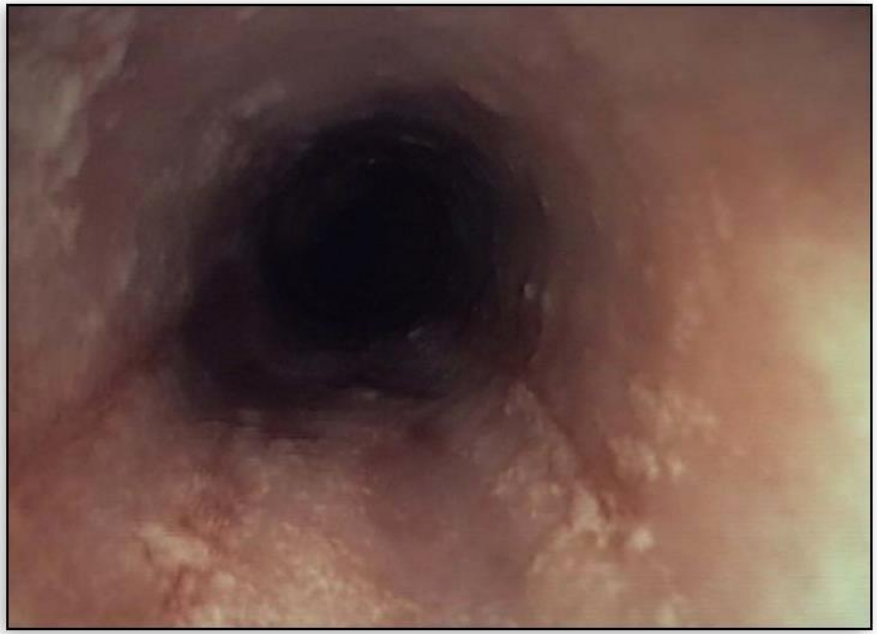


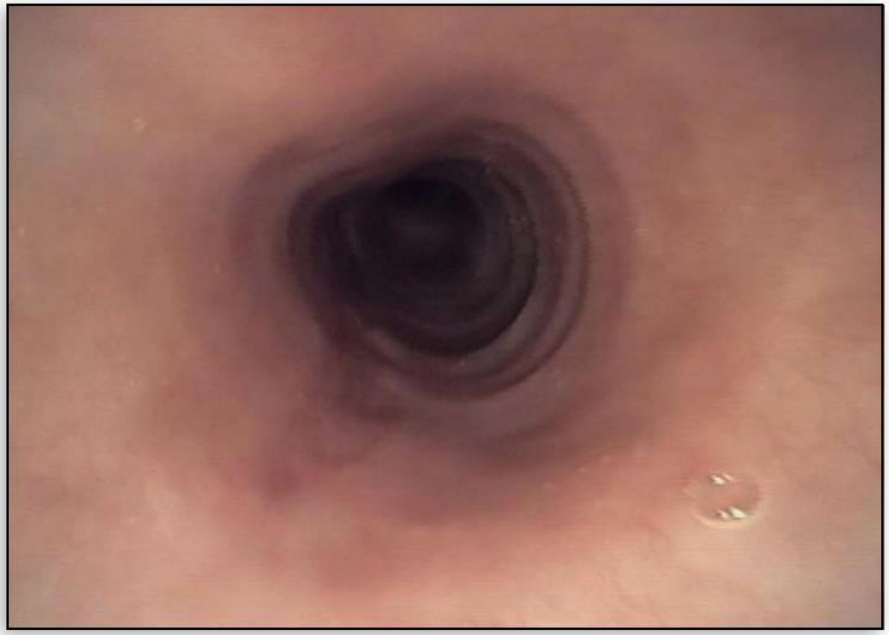


White Plaques

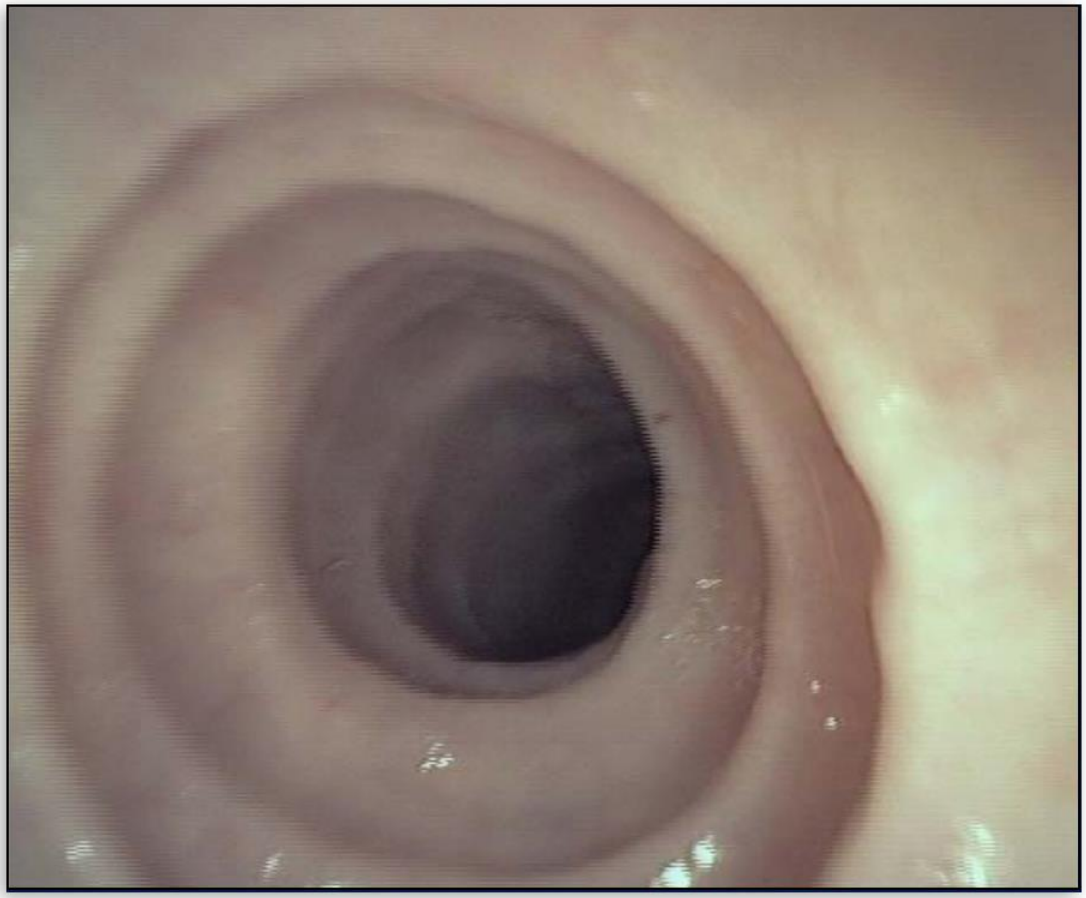


White Plaques
Before and After Treatment

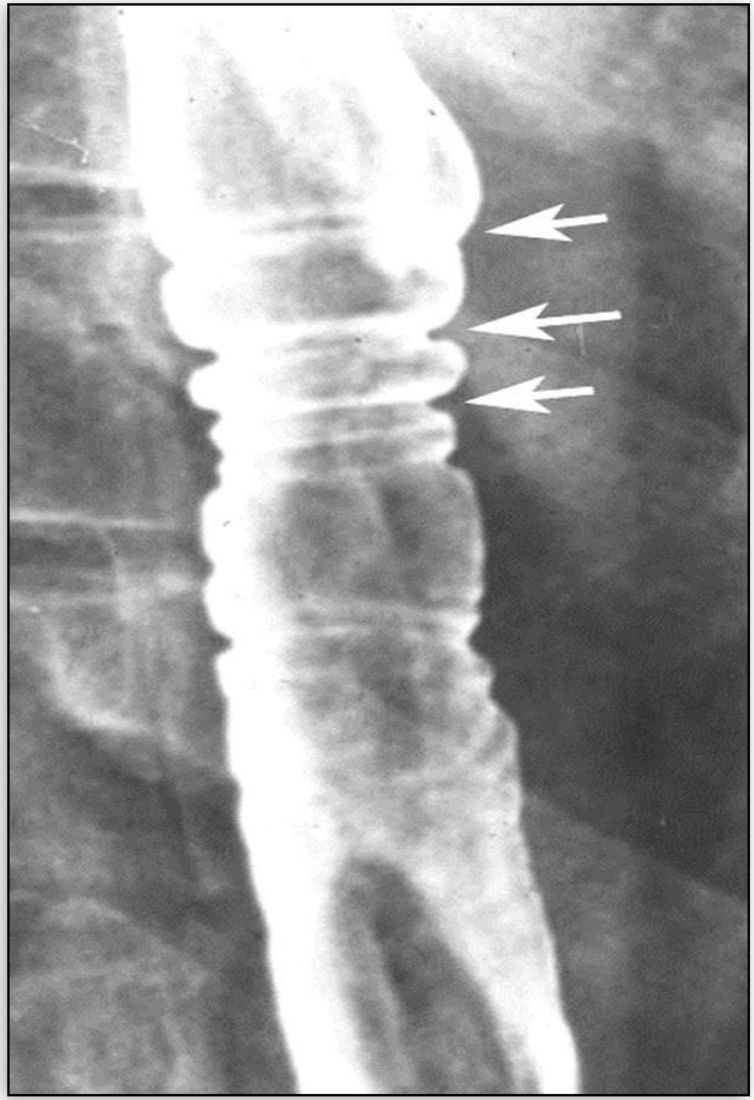




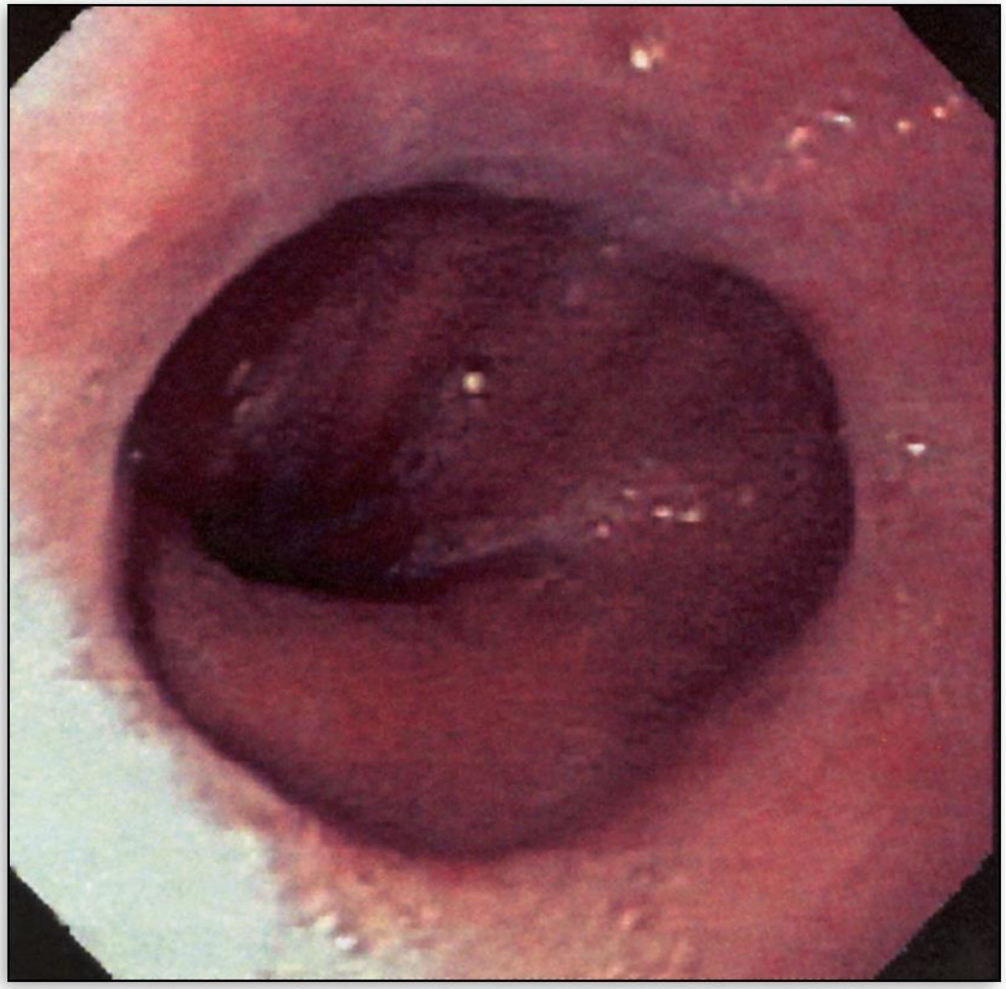
Esophageal Rings



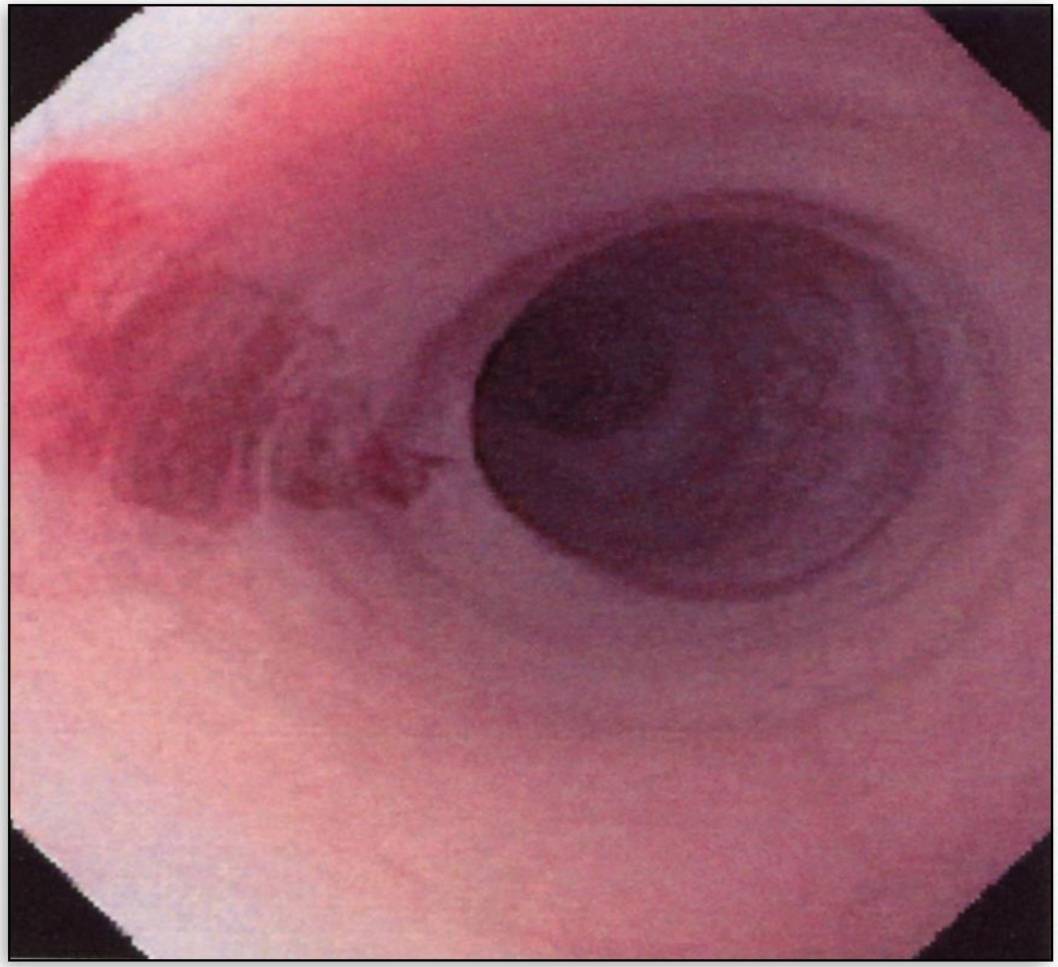
Esophageal Rings



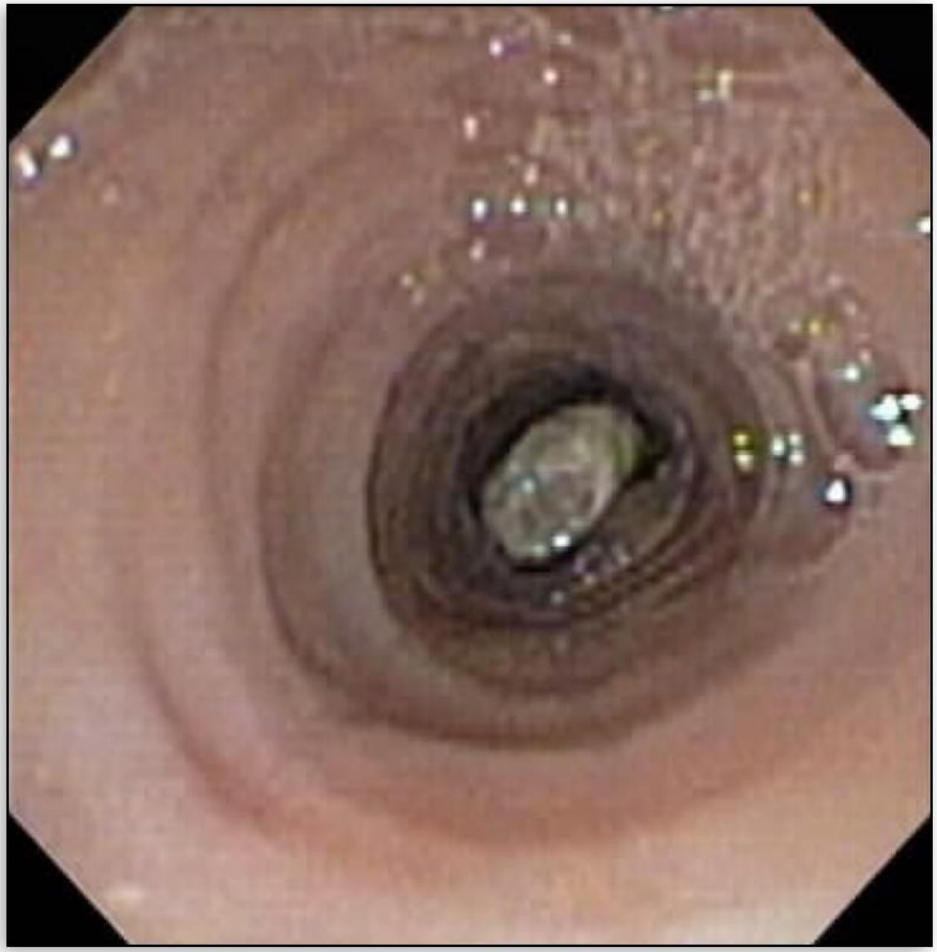
Distal Esophageal Stricture



Small Caliber Esophagus



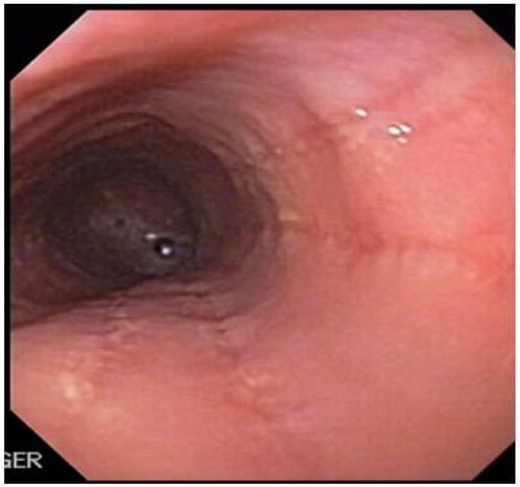
Pill Impaction



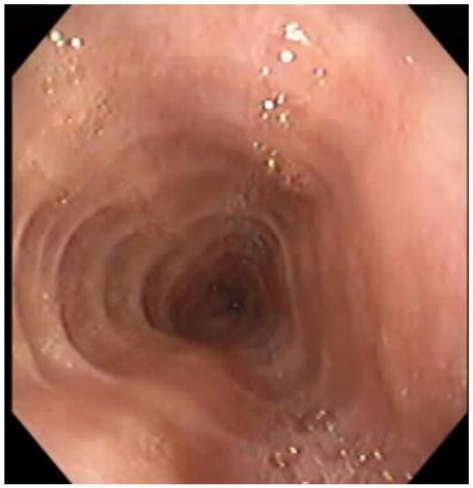
EoE: Endoscopic Features

- Children tend to have milder findings of furrowing and white plaques while adults have rings and narrowing
- These milder symptoms are mostly inflammatory while more severe symptoms represent fibrotic disease
- There is speculation that untreated childhood disease could lead to adult presentation of fibrostenotic disease

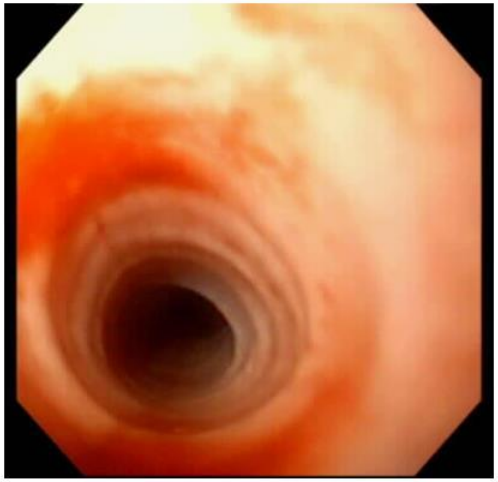
Endoscopic Progression in an Untreated EoE Patient



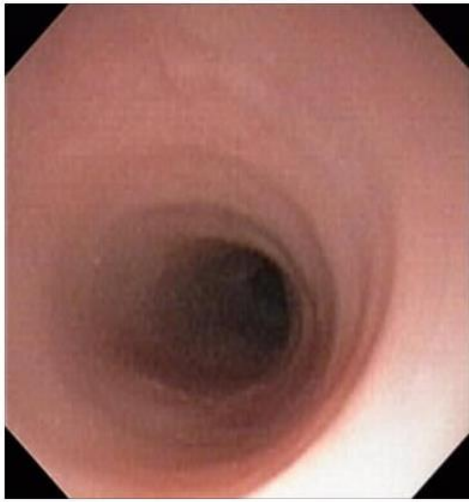
Initial presentation, age 7, with GER symptoms, refused therapy



3 years later; intermittent dysphagia; refused therapy

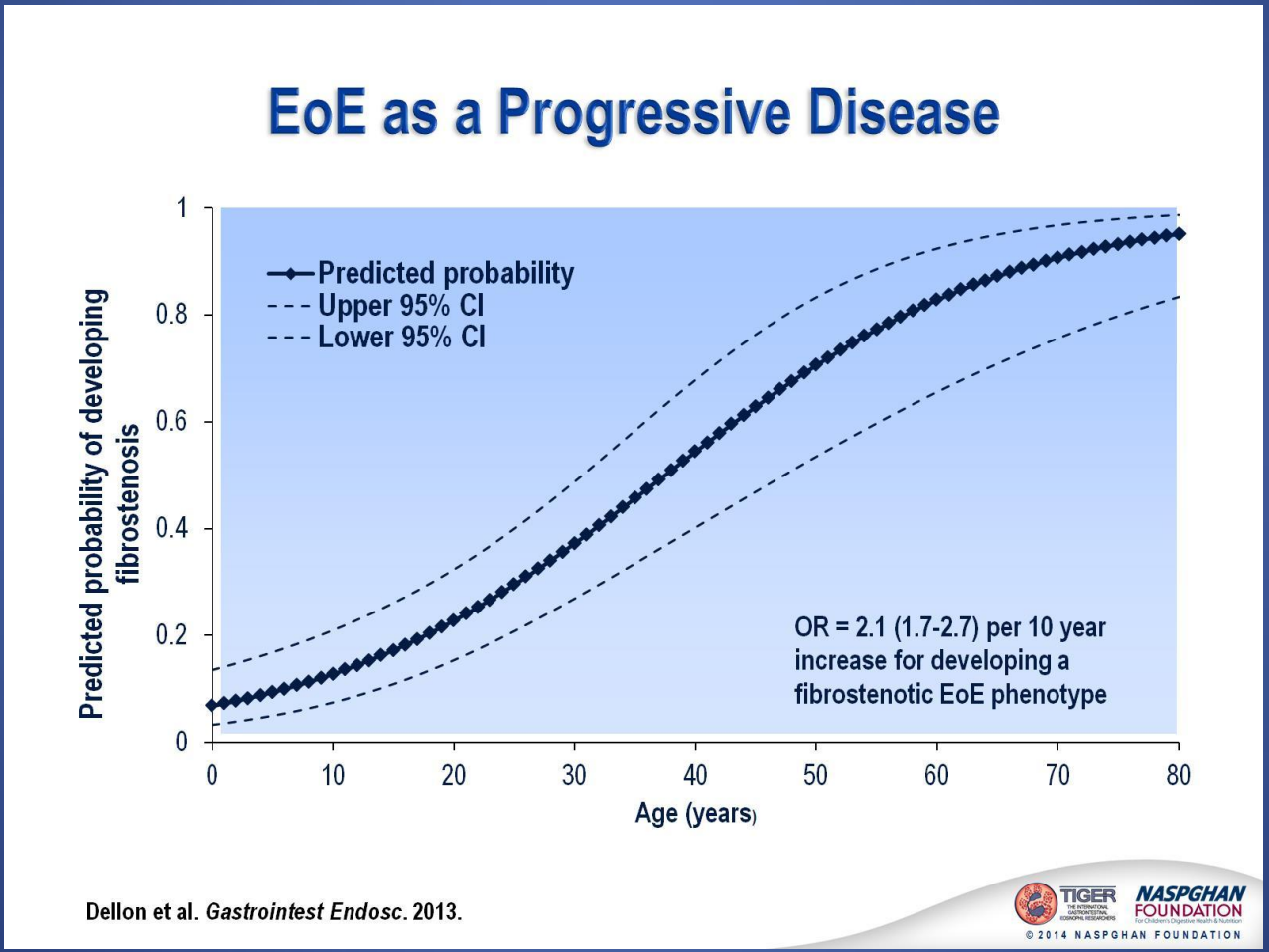


5 years after initial presentation; severe daily dysphagia – treated with systemic steroids



1 week after treatment with solumedrol - symptoms and histology significantly improved

EoE: Endoscopic Features



EoE: Endoscopic Features

Operating Characteristics

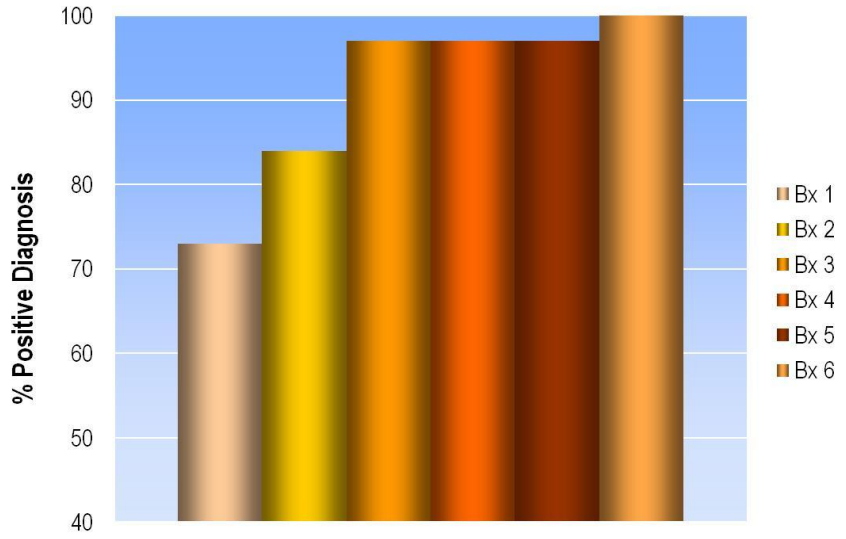
	Rings	Stricture	Linear furrows	White plaques	Decreased vasculature	Abnormal endoscopy
Sensitivity (%)	48	15	40	27	43	87
Specificity (%)	91	95	95	94	90	47
PPV (%)	64	51	73	67	65	42
NPV (%)	84	76	83	74	79	89

- Even with all these endoscopic findings, none is specific enough to dx EoE. Even an abnormal endoscopy does not predict it. Thus bx is needed.

Kim et al. *Clin Gastroenterol Hepatol*. 2012;10(9):988-986.

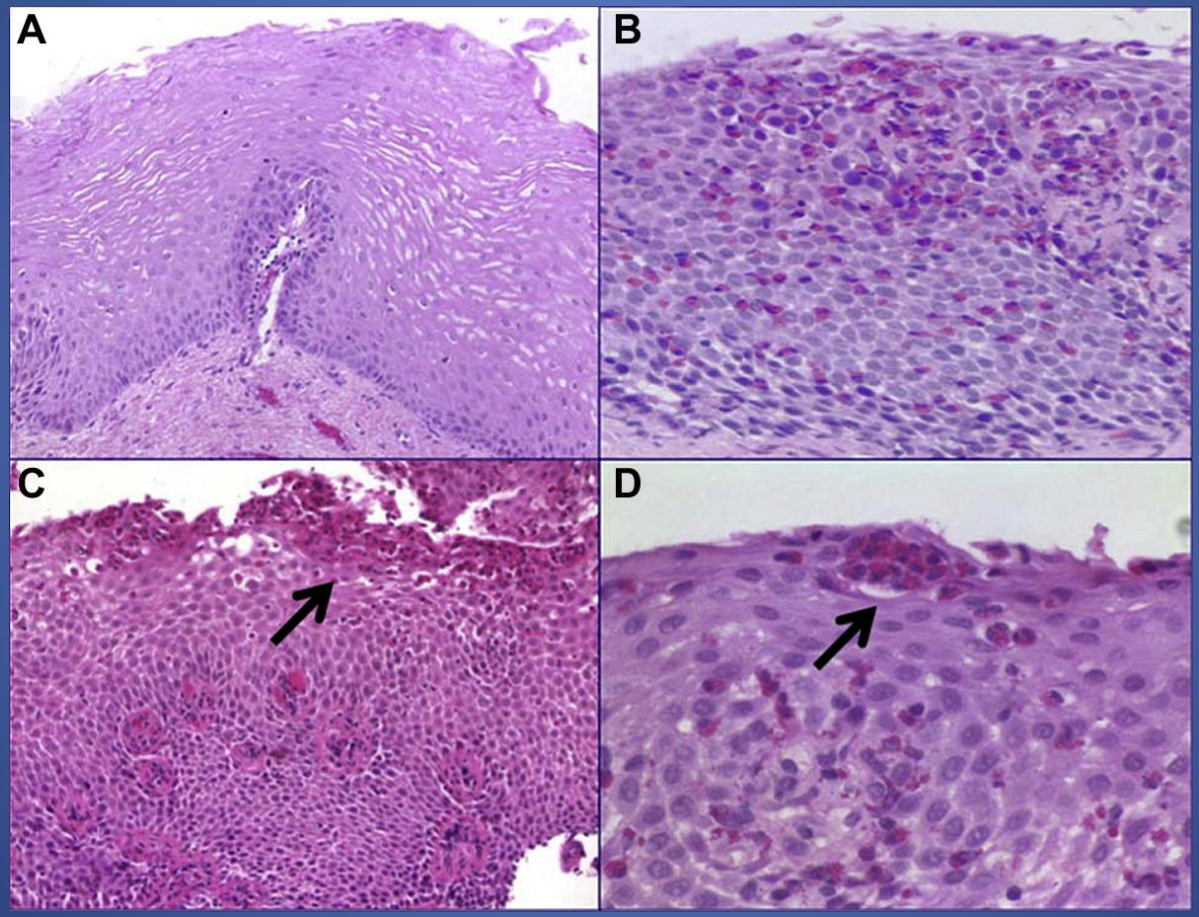
EoE: Histology

Typically 1-2 bx are taken for GERD if suspected. EoE requires multiple biopsies from multiple sites (2-4 from 2 separate locations (DE and ME/PE)), with optimal number being 4-6 biopsies.



Shah et al. *Am J Gastroenterol*. 2009; 104:716-721.

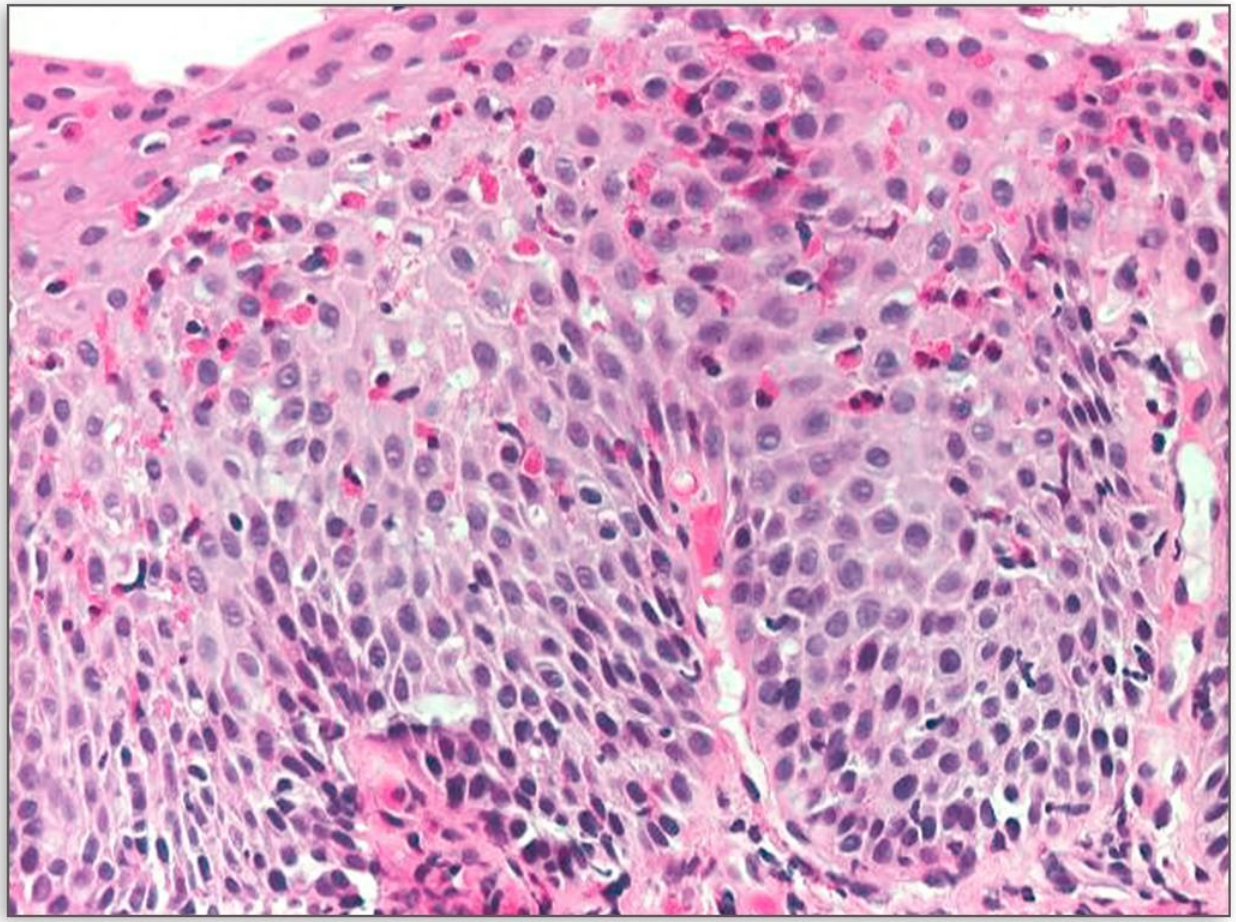
EoE: Histology



Esophageal mucosal biopsy specimens. **A:** Normal esophagus. **B;** EoE. **C:** EoE, superficial layering of surface eosinophils *(arrow)*. **D:** EoE, microabscess *(arrow)*.

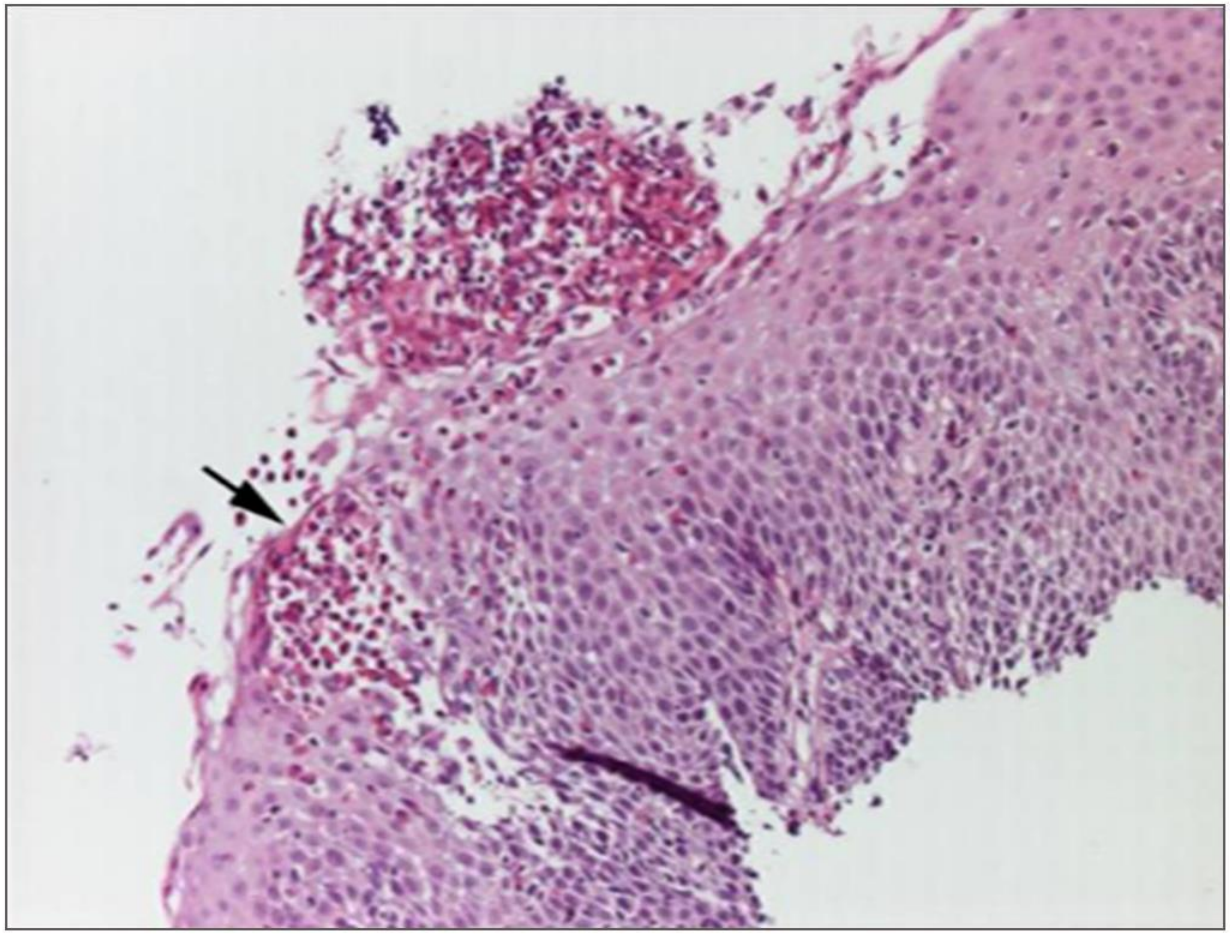
Journal of Allergy and Clinical Immunology 2011 128, 3-20.e6DOI:

EoE Histology



There are numerous intraepithelial eosinophils (IEE), and many are degranulated.

EoE Histology



Intraepithelial eosinophilic abscess (arrow). Eosinophilic abscess on the surface of the epithelium in the center of the photograph. Such foci of eosinophils may shed or become partially detached from the surface epithelial cells which correlates with the white flecks, plaques or exudates seen during endoscopy.

EoE: Diagnosis

- Pts can undergo multiple EGDs, even in one year
- A novel test being evaluated called the esophageal string test to try to limit that
- Swallow a capsule with a string attached and the end is taped to face
- As it stretches thru the esophagus, the string is coated with the degranulated products of the eosinophils in the esophagus
- Analysis of the string proteins mimic the levels of IEE on bx

EoE: Treatment

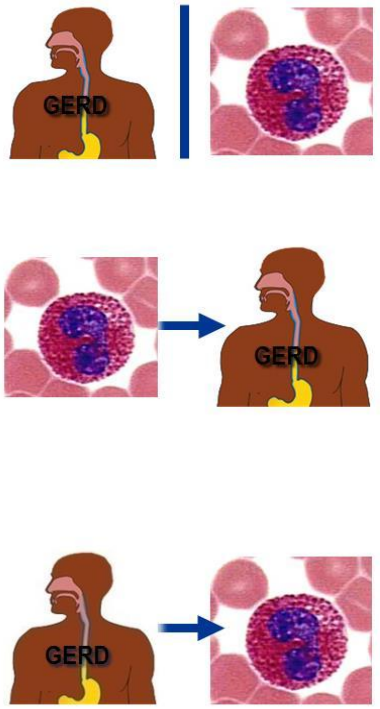
- Treatment is complex and very individualized
- Goals
  - Resolution of current symptoms
  - Prevention of recurrence
  - Avoid future fibrostenotic sequela
- Treatment consists of the three D,s
  - Drugs
  - Diet
  - Dilation
- No drugs are approved by FDA for EoE treatment (All are off label uses)

EoE: Treatment Drugs

- PPI
  - useful in making the diagnosis of EoE (vs PPI-REE vs GERD)
  - useful for treating GERD symptoms associated with EoE
  - PPI alone is insufficient for treatment; symptoms will continue and so will IEE
- Steroids :Oral/ systemic
  - Rapid resolution (w/i 1 week for symptoms and 4 weeks for histology)
  - Usual side effects (dosed like in IBD)
  - Upon tapering, EoE returns
- Steroids: “Topical”
  - Fluticasone and Budesonide
  - They work as well with systemic having little to no typical steroid side effects with the short term use (only superficial candidal infection see and rare)
  - Upon tapering, EoE returns
- Others
  - Infliximab (Remicade): doesn’t work
  - Montelukast: Mixed- initial high dose work but f/u studies failed
  - Cromolyn: doesn't work
  - 6MP: In 3 pts yes, but high side effects so not recommended currently

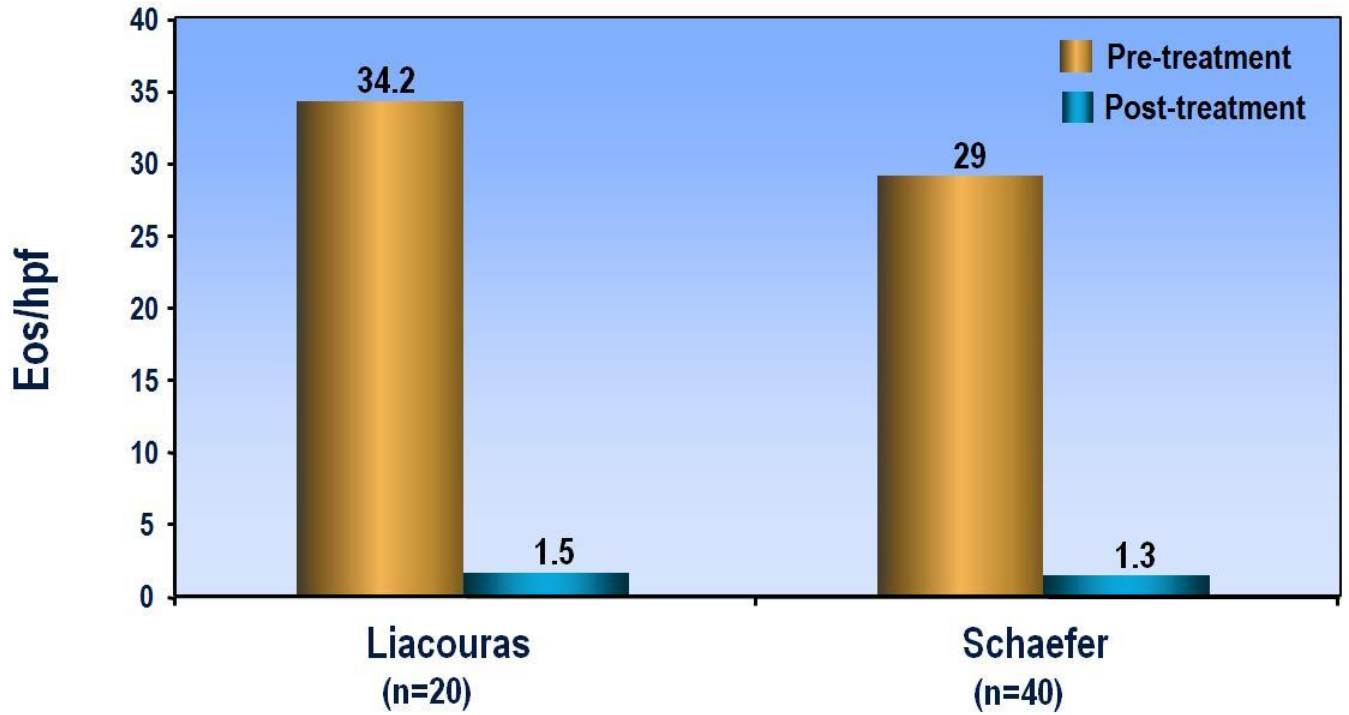
EoE: Treatment
Drugs: PPI

- GERD causes eosinophilia
  - Usually less than 7 eosinophils/hpf but can be greater
- GERD and EoE co-exist but are unrelated
  - 20% to 40% of adults have GERD
- EoE contributes to or causes GERD
  - Eosinophil secretory products alter esophageal motility, permeability, and fibrosis causing secondary GERD
- GERD contributes to or causes EoE
  - Increased esophageal permeability results in exposure of deep epithelial layers to antigens
- A trial of proton pump inhibitors (PPI's), even when diagnosis of EoE appears clear-cut, is always recommended



Spechler et al. *Am J Gastroenterol.* 2007; 102:1301-1306.

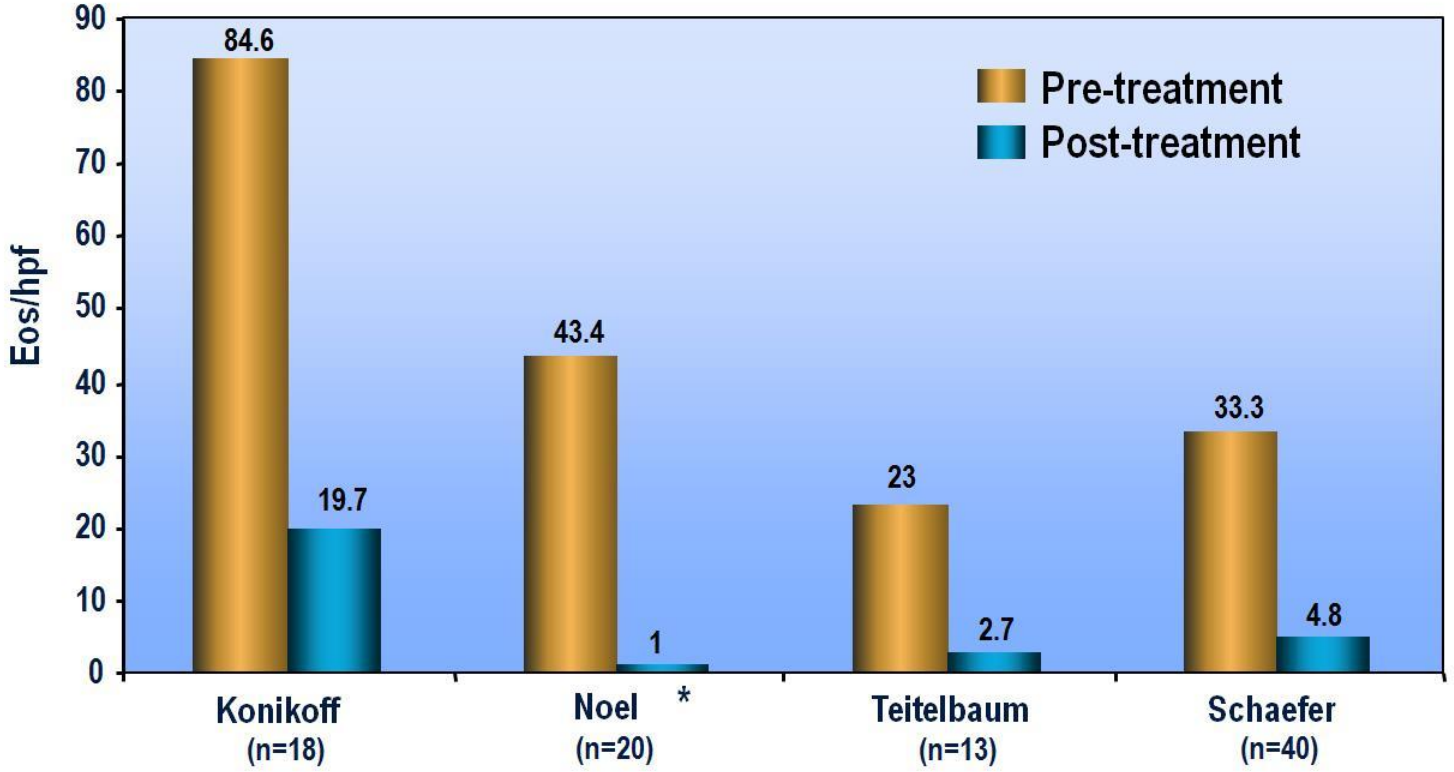
Oral Steroid Studies



1 mg/kg BID; max 30 mg BID

Liacouras et al. *J Pediatr Gastroenterol Nutr.* 1998; 27:90-93.
Schaefer et al. *Clin Gastroenterol Hepatol.* 2008; 6:621-629.

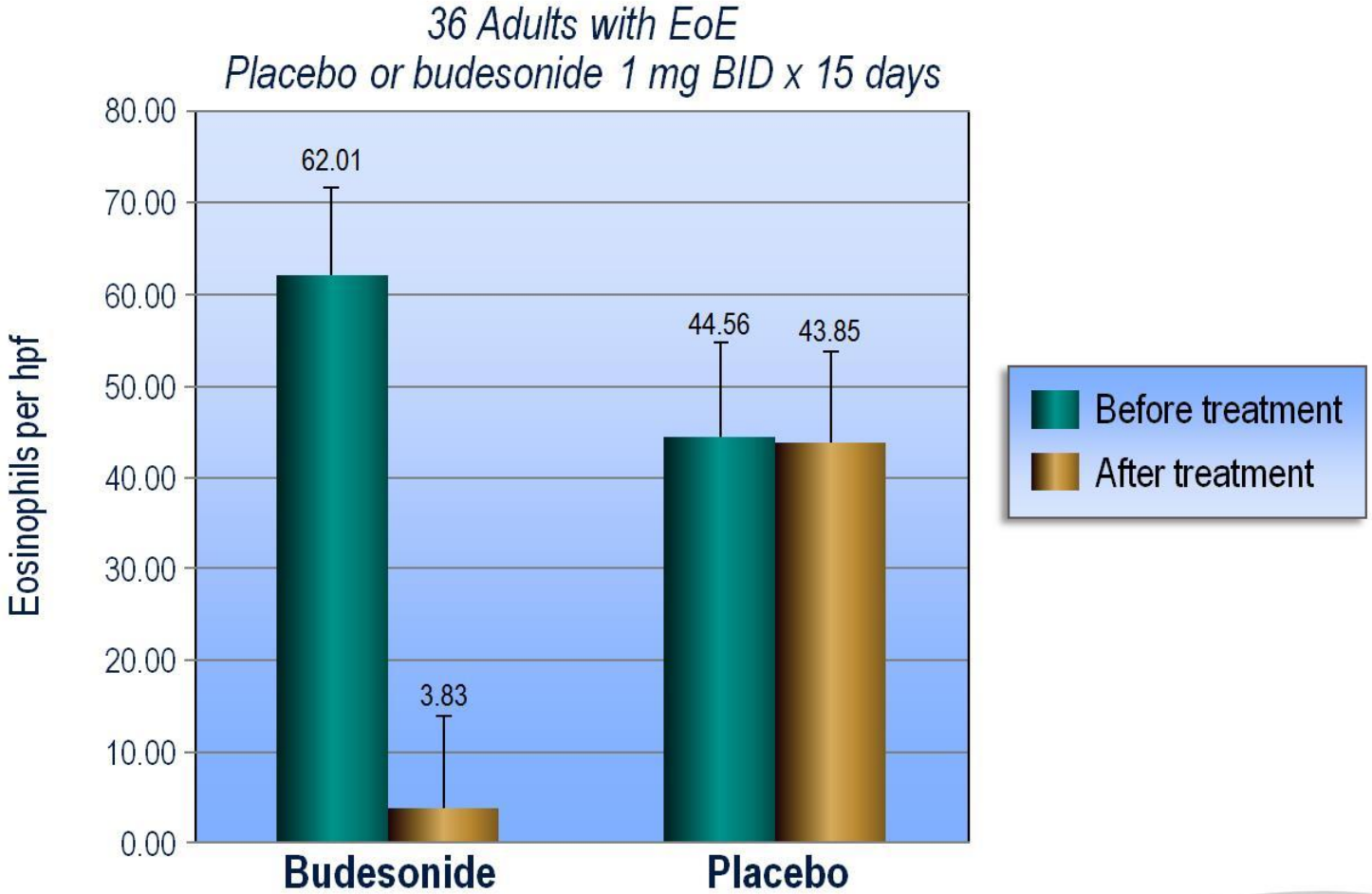
Topical Steroids *(Swallowed Fluticasone)*



*Post treatment data on 16 patients.

Konikoff et al. *Gastroenterology.* 2006; 131:1381-1391.
Noel et al. *Clin Gastroenterol Hepatol.* 2004; 2(7):523-530.
Teilbauam et al. *Gastroenterology.* 2002; 122:1216.
Schaefer et al. *Clin Gastroenterol Hepatol.* 2008; 6:621-629.

Randomized, Double-Blind Placebo Controlled Trial Budesonide (BEE Trial)



Straumann et al. *Gastroenterology*. 2008; 134(Suppl):A104.

EoE: Treatment
Drugs

- Fluticasone
  - MDI is dispensed directly into the mouth then swallowed
- Budesonide
  - Ampule is mixed with sucralose (Splenda) and swallowed
  - Termed oral viscous budesonide (OVB)
  - Neocate Nutra has been reported as well as effective
- No food for 30 mins after
- Typically given for 2-3 months
- Return of symptoms typically 4-9 months
- Maintenance studies with lower doses are being conducted

EoE: Treatment
Diet

- 1995 Kelly et al showed that in 10 pts with refractory GERD and high IEE, an AA diet resolves IEE
- Since then, three main diets are used
  - Elemental diet
  - Six food elimination (empiric) diet (6FED)
  - Targeted/directed elimination diet (TED)

Gastro 1995;109:1503-12

Diet Choice

Approach	Definition	Pros	Cons
Elemental >90%	Diet exclusively consisting of amino acid–based formula	• Hypoallergenic • Nutritionally comprehensive • Reduces symptoms and eosinophil counts	• Taste (may require feeding tube) • Expense • Age appropriateness • Excludes all food • May have adverse impact on quality of life
Empiric diet 72%	Diet that eliminates the major food allergens from the diet (typically milk, egg, wheat, soy, peanut/tree nut, and fish/shellfish, though variants exist)	• Allergy testing not required • Studied across all ages • Reduces symptoms and eosinophil counts	• Some avoidance may be unnecessary • Only four foods may be necessary • Expense • May be nutritionally incomplete
Targeted diet 45% As low as 10% in some studies	Diet that eliminates foods on the basis of allergy skin testing (skin prick test and/or atopy patch test)	• Most specific therapy • Can preserve diet • Established sensitivity, specificity, and NLR/PLR to assist with add-back • Reduces symptoms and eosinophil counts	• Testing precision and technique is inconsistent across centers • Milk testing precision very poor when negative • Empiric milk elimination as an addition greatly improves response • Some avoidance may be unnecessary (sensitization without clinical allergy)

Resolution rates meta-analysis Gastro 2014;146(7):1639-1648

Greenhawt et al. *J Allergy Clin Immunol.* In Practice 2013;1(6):602-607.

Food

Study	N	Age (y)	Foods*						
			Milk, %	Egg, %	Soy, %	Wheat, %	Peanut/tree nut, %	Fish/Shellfish, %	Legumes, %
Gonsalves	20	22-55	50	5	10	60	10		
Kagalwalla	36	3-18	74	17	10	26	6		
Lucendo	42	17-57	62	26.2	14.3	28.6	16.7	19	23.8
Henderson	26	0.9-22	65	40	38	37			
Spergel	319	1-18	66.1	24.5	16.3	22.6	5.0	0	
Total†	442		64.0	22.2	15.4	24.9	5.9	1.8	

*Foods that cause changes in esophageal eosinophil counts on reintroduction; multiple foods were reintroduced in the same patient.
†Total percentages represent an average of all 5 studies.

Greenhawt et al. *J Allergy Clin Immunol.* In Practice 2013;1(6):602-607.

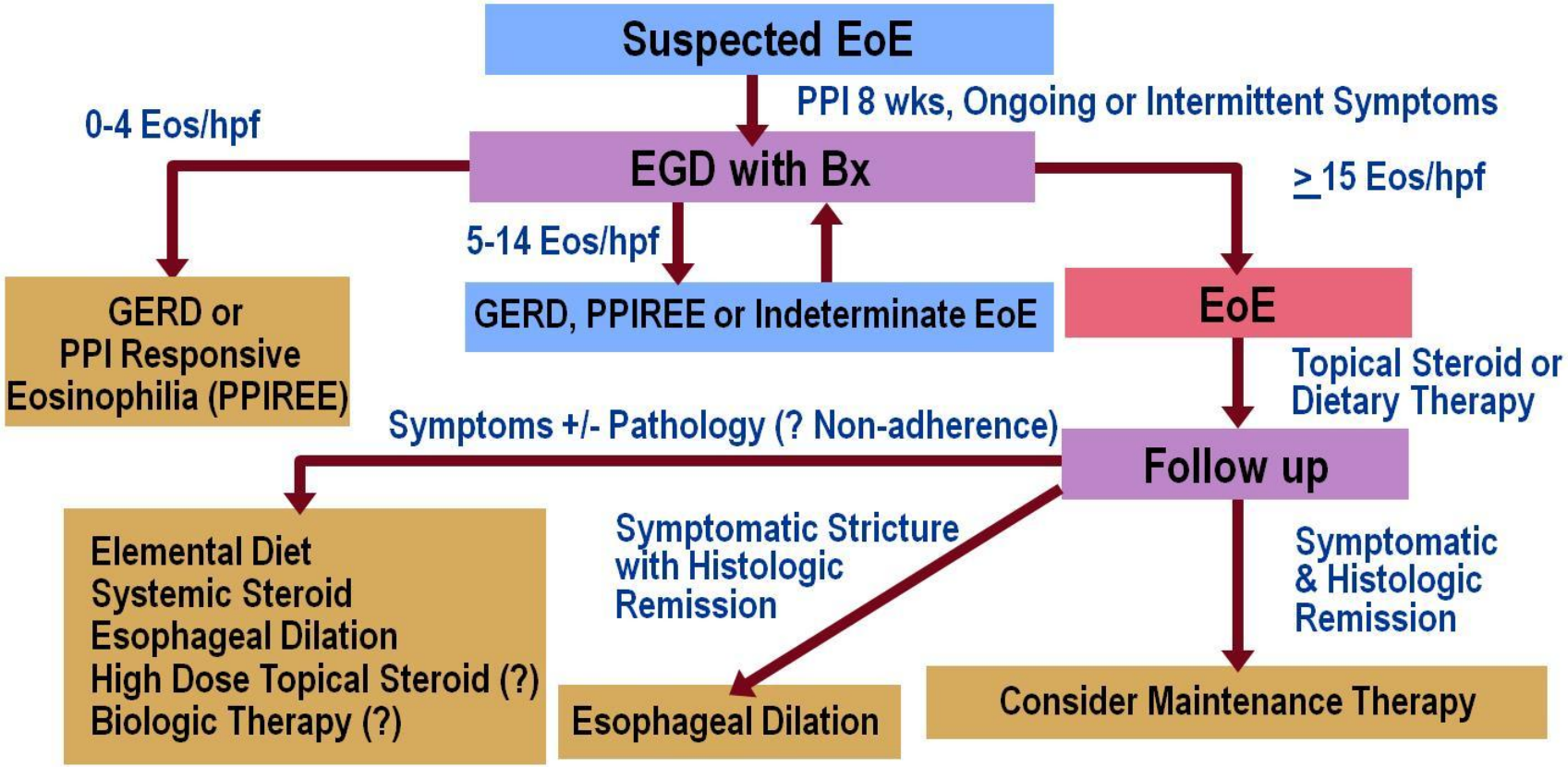
EoE: Treatment
Diet

- TED uses skin prick and atopy testing to attempt to get the IgE and non-IgE mediated allergens
- Milk now recommended to add to TED because of the high reactivity to it regardless of APT or SPT results (NPV <30% in EoE)
- APT and SPT when combined has high NPV for most common foods and poor PPV
- If a causative food is found, then the treatment for EoE is simply to avoid this antigen but low probability to find such a food antigen
- Nutritional consultation maybe needed

EoE: Treatment
Dilations

- Prior to 2008 high complication rate
- After, gentle EoE techniques used and now no different from current rates without EoE
- Rare in peds and used when severe stricture
- Does not affect the eosinophilic inflammation
- 75% chest pain after dilation
- 50% symptom free at 1 year
- If possible, always use steroids and/or diet first

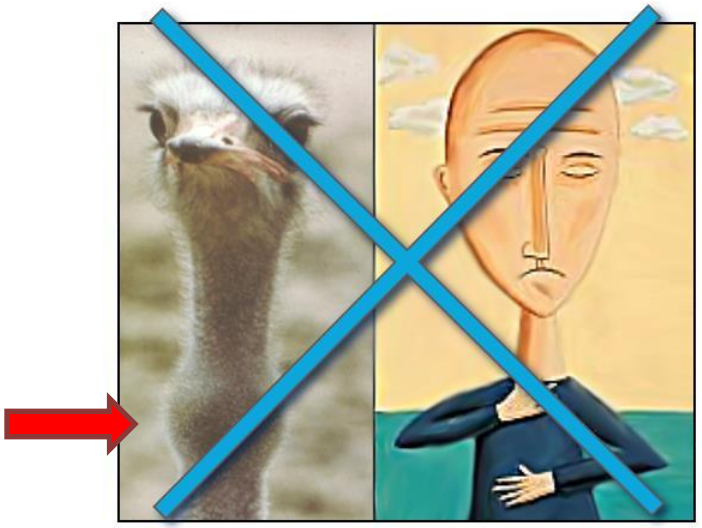
Suggested Algorithm for Management of Eosinophilic Esophagitis



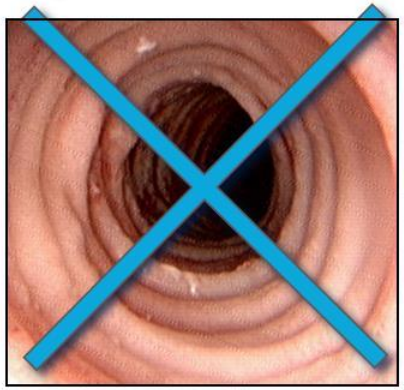
Hirano, I. *Eosinophilic Esophagitis.* 2012. Ed C. Liacouras. 2011.

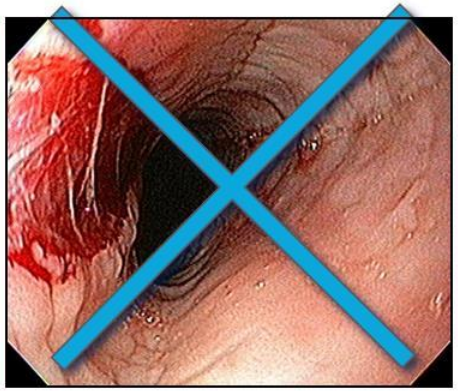
Treatment Goals of EoE

- Eliminate symptoms
  - Dysphagia
  - Heartburn



- Prevent complications
  - Esophageal stenoses
  - Esophageal fragility





Endoscopic photos from Dr. Ikuo Hirano

Questions?

Thank You