

Eosinophilic Gastrointestinal Diseases

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Eosinophilic Esophagitis (EoE)

- *Eosinophilic esophagitis represents a chronic, immune / antigen mediated, esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation.*
- Diagnosed is based on clinical-pathologic findings on biopsy with greater than 15 eosinophils/HPF
 - Exclude other causes of esophageal eosinophilia
 - GERD, Celiac, IBD, Allergic Rhinitis
- EoE is a lifelong chronic condition



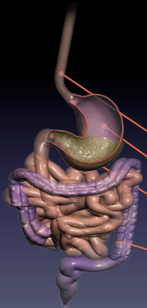
Liacouras, JACI 2011; Spergel et al J Pediatr Gastroenterol Nutr 2009



World Map of EoE



Gastrointestinal Eosinophils



Normal values, per 400x microscopic field:

- Esophagus (0)
- Gastric antrum (2-20)
- Duodenum (2-20)
- Colon (10- 50)



Other Causes of Eosinophilia

- GERD
- Celiac
- IBD
- Fungal Infection
- Allergic Rhinitis
- Drug Allergy



Symptoms of EoE

EoE – Clinical manifestations

- Symptoms similar to those of GERD
 - Histology does not respond to PPI's.
- Age related differences in symptoms
- Symptoms may be intermittent
- Male > Female
- May progress to esophageal fibrosis and esophageal dysfunction if not managed appropriately.

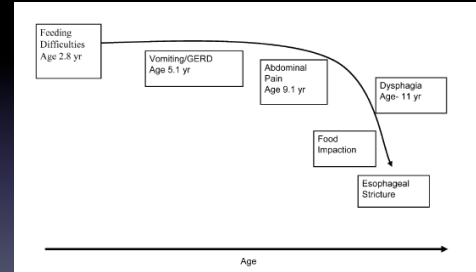
EoE patient	Common Symptoms
Infant	Food refusal, FTT, feeding intolerances/aversions, reflux
Children	Vomiting, dysphagia, abdominal pain, heartburn, regurgitation, feeding refusal/feeding aversions
Adult	Dysphagia, food impaction, heartburn, reflux



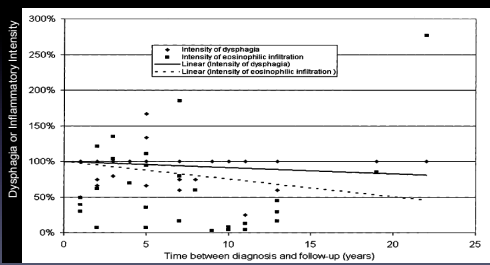
Funata et al. Gastroenterology 2007
Spiegel et al. J Pediatr Gastroenterol Nutr 2009



Symptom Progression in EoE



Chronic EoE: Adults



Straumann et al. Gastroenterology 2003

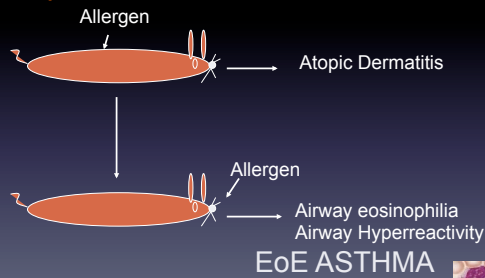


Pathogenesis

Similarities to Atopic Dermatitis
Asthma



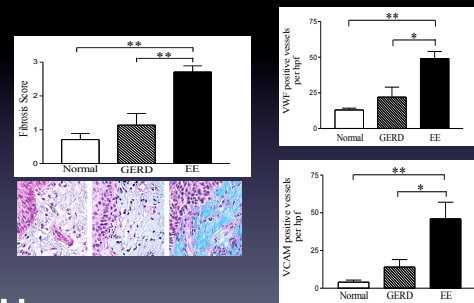
Mouse Model of Epicutaneous Sensitization



Spiegel et al. J. Clin. Invest. 1998; 101: 1614-1622.

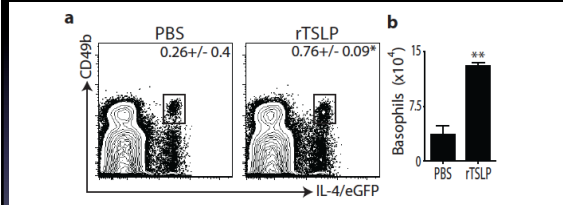


Esophageal Remodeling in Pediatric EoE



Aceves et al. JACI 2007

The role of basophils in EoE



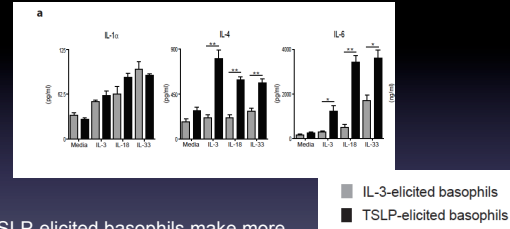
- TSLP promotes matured basophil survival and new basophil population with TSLP-R



Siracusa et al, Nature 2011



The role of basophils in EoE



TSLP-elicited basophils make more IL-4, IL-6, CCL3, CCL4 and CCL12 compared to IL-3-elicited basophils.

■ IL-3-elicited basophils
■ TSLP-elicited basophils



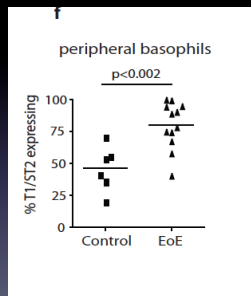
Siracusa et al, Nature 2011



The role of basophils in EoE

ST2/T1, also IL33 receptor, leads to basophil activation

IL-33 leads to Eosinophil, TH2, mast cells and basophil activation

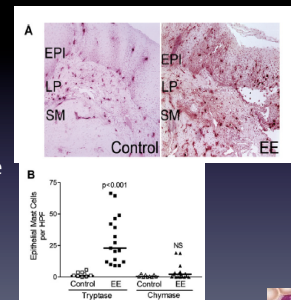


Siracusa et al, Nature 2011

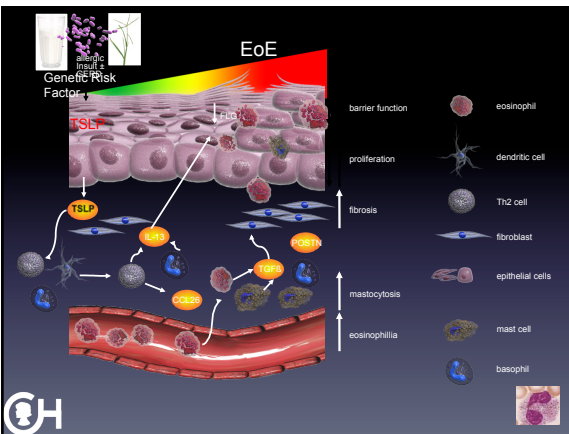


Role of Mast Cells

- Mast Cells invade Esophagus
- Secrete TGF- β 1
- Induce Smooth muscle contraction



Aceves et al J. Allergy Clin. Immunol 2010



The role of Atopy in EoE

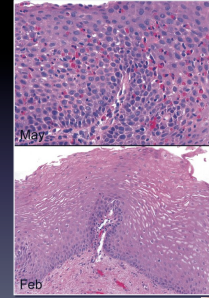
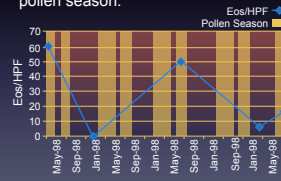


Association of Atopy with EoE

Ref	# of Pts	Age (Yrs)	Asthma	AR	AD	Food
General Population			10%	20-40%	5-20%	1-6%
Spergel	620	8m-20	50%	61%	21%	16%
Assad	89	3m-18 yr	39%	30%	19%	9%
Sugnamam	45	3m-16 yr	66%	93%	55%	24%
Guajardo	39	1m -31	38%	64%	26%	23%
Roy-Ghanata	23	18-57	26%	78%	4%	--

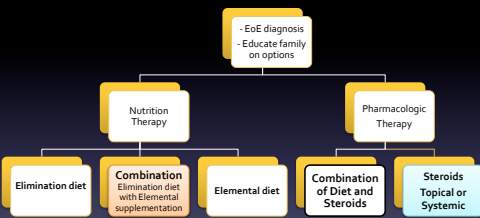
Seasonal Variation in EoE

20 year old female, history of multisensitization to aeroallergens. Symptoms of allergy and EE peaked during pollen season.



Fogg, et al; J Allergy Clin Immunol 2003; 112: 796-7.

Treatment Options



Pharmacologic Therapy

Systemic Steroids – effective at improving symptoms and histology of EoE in 95% of pts

- Upon discontinuation, 90% had recurrence of symptoms
- (Long term use) Side effects: bone abnormalities, poor growth, adrenal suppression
- May be needed short term for extreme cases

Topical/swallowed Steroids – less toxic to pt while still 50-85% effective

- A mainstay of EoE treatment in adults and children.
- Upon discontinuation almost all patients have a recurrence of symptoms
- Often, large doses needed
- Side effects: esophageal candidiasis

Liacouras et al, Clin Gastroenterol Hepatol 2005
Furuta et al, Gastroenterology 2007

Food Avoidance Therapy



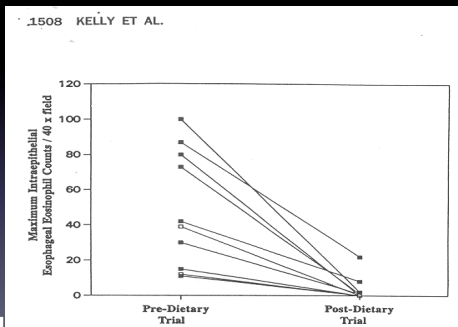
Link Between Food Allergy and EoE

- Dobbins (1977): 51 yo with GERD, food allergy and esophageal eosinophilia
- Kelly and Sampson (1995)
 - 10 patients (5 yr range: 8 mo-12.5 yr)
 - Given amino-acid based formula (> 6 weeks)
 - Neocate® or Neocate 1+®
 - 6 prior Nissen fundoplication
 - Endoscopy pre- & post-trial

Dobbins et al, Gastroenterology, 1977;72:1312-1316.
Kelly et al, Gastroenterology, 1995; 109: 1503-12
Van Rosendal et al, Am J Gastroenterol, 1997;92:1054-1056.

Kelly, 1995

Results



Dietary Management Amino Acid-Based Formula

160 Patients	Pre-Diet	Post-Diet	P value
Eosinophils/ H/PF	38.7 ± 10.3	1.1 ± 0.6	<0.001
Dysphagia	30	1	<0.01
GERD Symptoms	134	3	<0.01

- 172 patients (128 nasogastric tubes, 32 oral, 4 failed, 8 noncompliant)
- Patients evaluated 4-6 weeks after starting diet

Liacouras et al, Clin. Gastroenterol Hepatol 2005

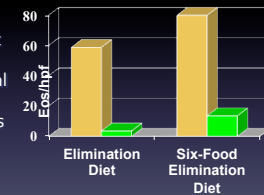


How to Select the foods?



Selective Diet: Guess

- 60 children
 - 35 children on elimination diet of milk, soy, wheat, egg, peanut and seafood
 - 25 children on elemental diet
- Repeat endoscopy-6 weeks later
- 74% of six-food diet had < 10 eos/hpf
- 88% of elemental diet had < 10 eos/hpf



Kagalawa et al. Clin Gastro Hepatol 2006



SFED follow-up

- Single Food Reintroduction in 36 children
- 74% to milk
- 26% to wheat
- 17% to egg
- 10% to soy
- 6% to peanut
- Single food in 72%, 2 foods in 8% and 3 foods in 8%



Kagalwalla et al. JPGN 2011



Food Testing in EoE

- 74% Atopic (asthma, ARC, or AD)
- 1/3 have negative skin tests
- Most common foods were
 - Egg, soy, milk, peanuts, beef, chicken, wheat, corn, peas, and potato
- 1/4 have negative APT
 - 1/8 have both negative SPT and APT
 - Wheat, corn, soy, milk, beef, rice, chicken, egg, rye, oat, and potato



Predictive Values: Combination of SPT and APT

Food	Combined SPT and APT			
	PPV	NPV	Specificity	Sensitivity
Milk (n = 99)	93.0%	32.4%	84.6%	52.9%
Egg (n = 38)	65.5%	86.6%	86.7%	85.7%
Wheat (n=37)	73.7%	99.1%	80.8%	85.7%
Soy (n = 25)	43.2%	92.6%	75.9%	67.9%
Beef (n=21)	48.4%	96.2%	84.9%	65.2%
Chicken (n=20)	46.3%	99.0%	83.3%	84.0%
Corn (n=17)	62.5%	98.6%	81.7%	95.0%
Potato (n=12)	47.4%	98.2%	91.5%	81.8%
Rice (n=11)	32.3%	99.0%	82.5%	90.9%
Pork (n = 11)	38.5%	97.5%	93.1%	62.5%

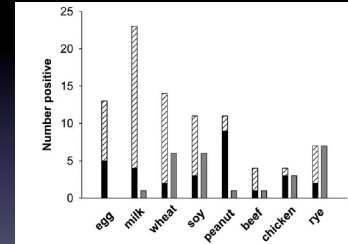


Spergel et al, JACI 2007 and unpublished data



Specific IgE

- 53 adult patients
- 80% had positive sIgE to food or aeroallergens
- sIgE was most sensitive



Hatched (sIgE), Black (SPT), APT (Gray)



Erwin et al, J Allergy Clin Immunol 2010



What method is best?

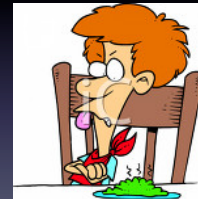
Method	SPT/APT	MILK	Milk, Egg, Wheat	SFED	SPT/APT + Milk
Rate of Resolution	57%	30%	48%	60%	77%

- Retrospectively examined all patients with defined food identified
- Excluded patients on ICS or anti-IL5
- Examined which diet method lead to normalization of histology



Nutrition Therapy

Common Challenge - Diet Adherence Nutritional Balance



Nutrition Therapy

Challen et al, JAMA 2010

Nutrition Therapy	Challenges/Barriers
6 Food Elimination	<ul style="list-style-type: none"> • May remove unnecessary foods • Increases risk of nutritional deficiencies • Potential growth problems • Symptoms may persist • Diet compliance • QOL • Cost
Tailored Elimination	<ul style="list-style-type: none"> • Increased risk of nutritional deficiencies • Potential growth problems • Lack of reliable allergen tests • Extensive allergy testing done on pt • Diet compliance • QOL • Cost
Elemental	<ul style="list-style-type: none"> • Diet compliance • QOL • Psychosocial developmental • Volume – NG or PEG tubes often needed • Cost



Summary: Treatment in EoE

- **Pharmacologic therapy** has been shown effective but long term use and possible side effects must be considered
- **Elimination diet** is effective - keeping in mind nutrient deficiencies may occur
- **Elemental diet** is the most effective nutrition therapy. Compliance/cost may be an issue for some patients
- **Combination of diet and steroids** for difficult to treat patient
- **Combination of elimination diet with elemental supplementation may be the best fit for patients and families dealing with EoE.**

“Dietary therapy should be considered as an effective therapy in all children diagnosed with EoE.”

Furuta et al, Gastroenterology 2007
Fouling & Noel, Nutr Clin Pract 2010



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