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Eosinophilic Esophagitis: Pathogenesis and Role of Food Allergy

Norma Rubini, MD, PhD

Associate Professor of Allergy and Immunology
Federal University of the State of Rio de Janeiro

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Eosinophilic Esophagitis

History

- 1993 – Atwood et al – 11 adults with dysphagia, normal pH probe and eosinophilic infiltration in esophagus mucosa
- 1995 – Kelly et al – 10 children with severe GERD unresponsive to medicines
- ✓ Elemental diet => resolution of symptoms and reduction in eosinophils count
- ✓ Food challenges => recurrence of symptoms in 9/10

Atwood SE et al, Dig Dis Sci 1993
Kelly K et al, Gastroenterology 1995

Eosinophilic Esophagitis

Epidemiology

- Prevalence
 - ✓ Pediatric population – Hamilton County, Ohio - 4:10,000
 - ✓ Adult Swiss cohort – 2:10,000 adults
 - ✓ Recent studies in Europe and USA – 6:10,000 individuals
- Male to female rate – 3:1
- Caucasian (~ 80%)
- Atopy (~ 60%)

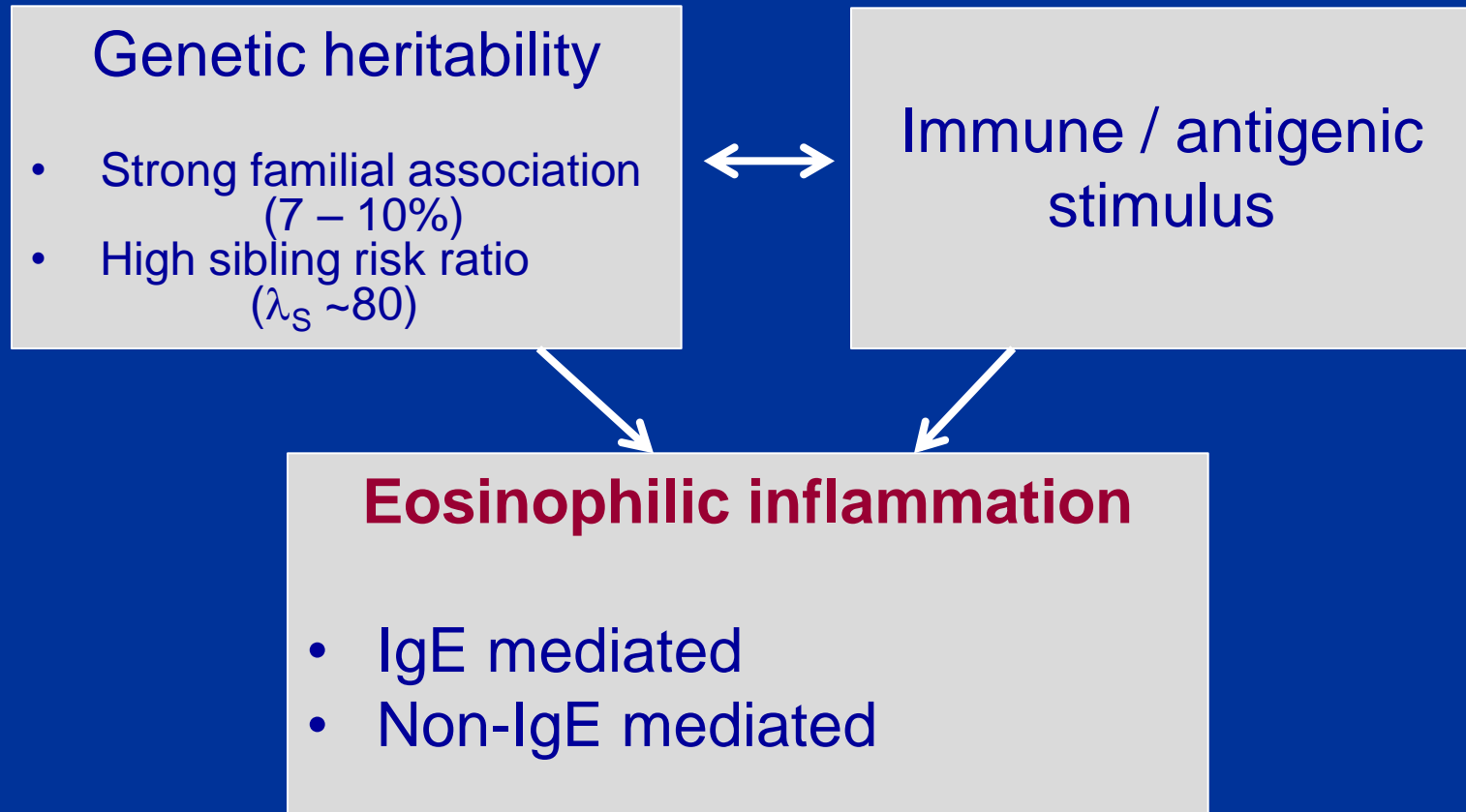
Eosinophilic Esophagitis

Definition

“Eosinophilic esophagitis represents a chronic immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation.”

Liacouros et al, Eosinophilic esophagitis: Updated consensus recommendations for children and adults, JACI 2011; 128: 3-20

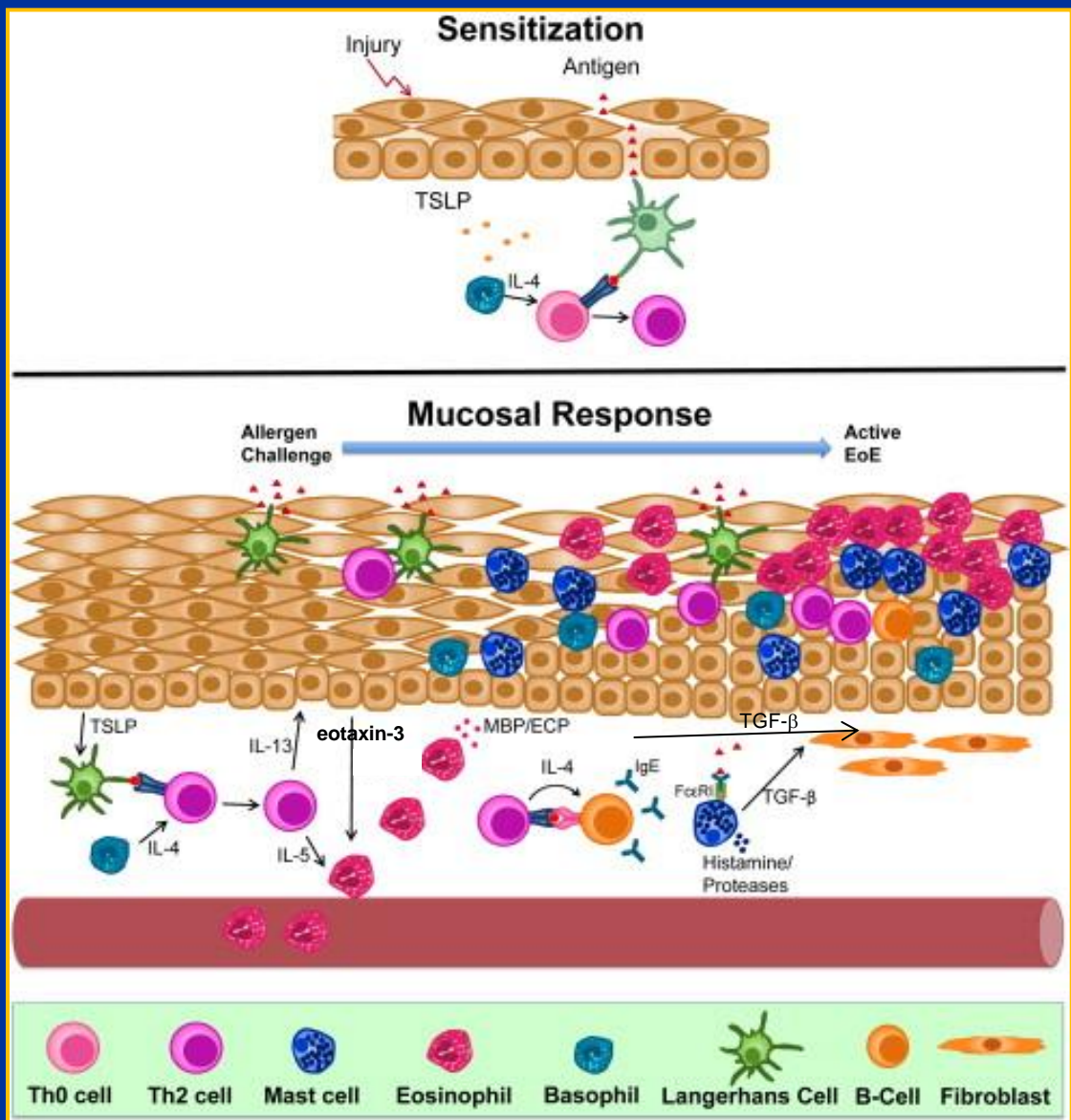
Pathogenesis of EoE



EoE – Pathological process

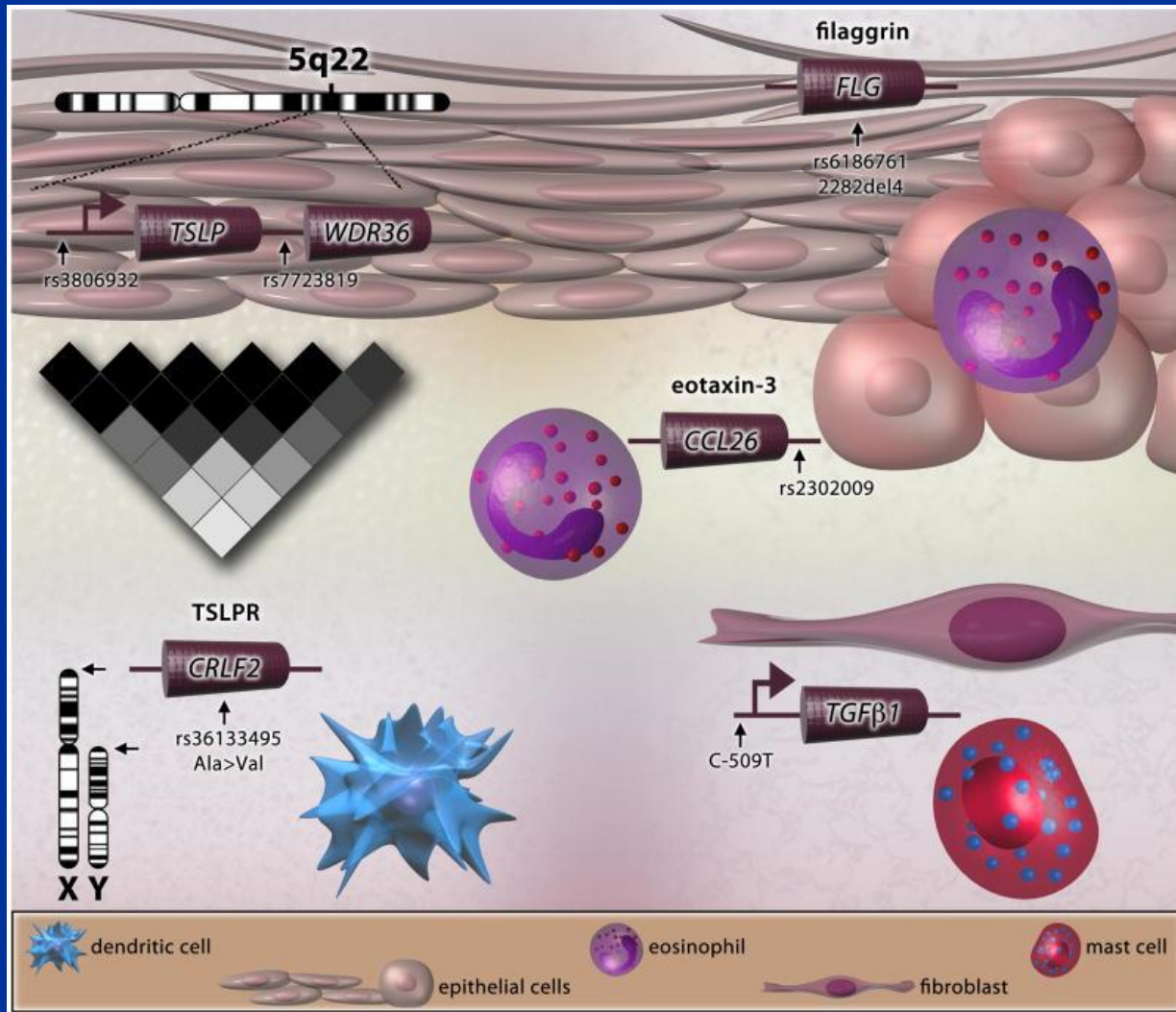
- Acute narrowing of the esophageal lumen by inflammation and oedema.
- Fixed narrowing and limited distensibility of the lumen by remodeling.
- Dynamic and variable narrowing caused by muscular contraction or spasm.

Pathogenesis of EoE



↓ barrier function
 ↑ proliferation
 ↑ fibrosis
 ↑ mastocytosis
 ↑ eosinophilia

Genetic risk variants in EoE



Eosinophilic Esophagitis

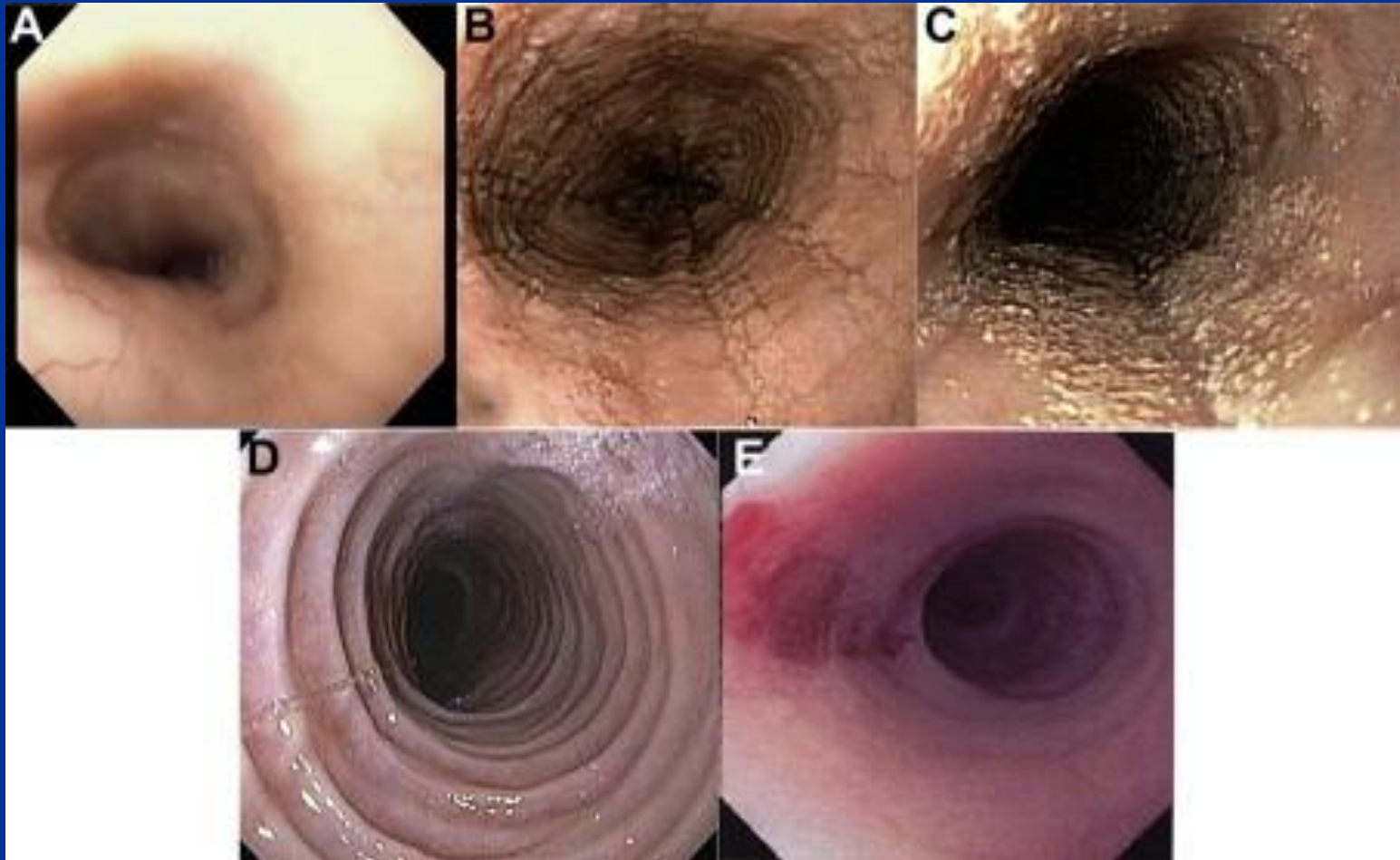
Established risk factors

| Risk Factor | Proposed mechanism(s) |
|-------------|--|
| Male gender | TSLP on sex chromosomes, Relaxin |
| Caucasian | Non-X linked SNP's (e.g. Filaggrin, Eotaxin-3) |
| Atopy | IgE mediated inflammatory infiltration |

Putative risk factors for EoE

| Risk Factor | Proposed mechanism(s) |
|---------------------------------------|--|
| Impaired barrier function | Increased antigen exposure |
| Impaired tolerance to food antigens | Timing and nature of food antigen exposure |
| Commercially prepared foods | Agglutined proteins incite immune reaction |
| Proton pump inhibitor use | Proteins are not denatured => greater antigen exposure |
| Aeroallergens in spring/summer | Exposure of air passages => inflammatory reaction and trafficking of eosinophils |
| Living in a temperate or arid climate | Low vitamin D and/or higher aeroallergen exposure |
| Migration as adult | Novel antigen incite immune reaction |
| Increased fibrotic remodeling | Decreased relaxin expression, SNP's for TGF- β and ACE |

Endoscopic features

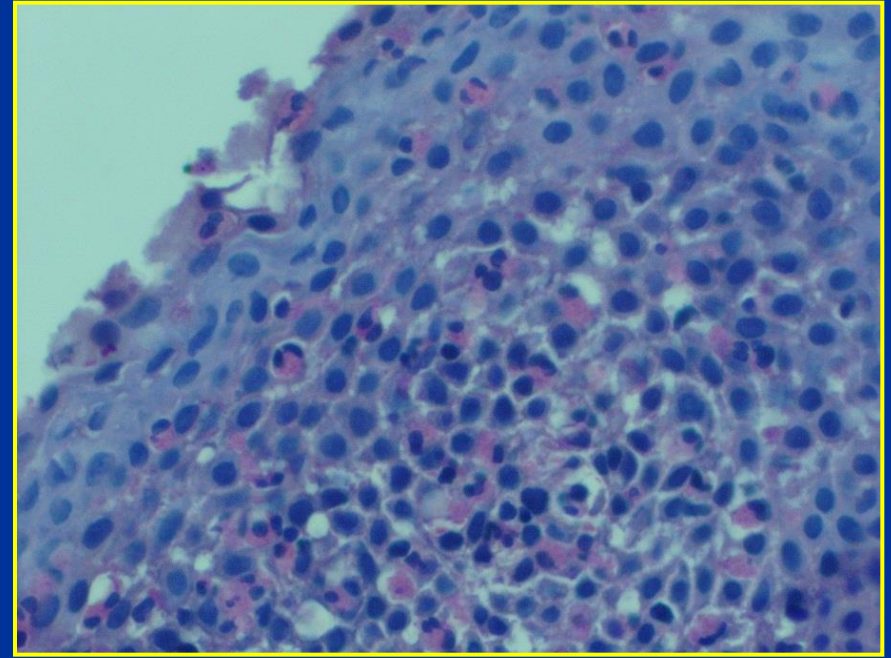
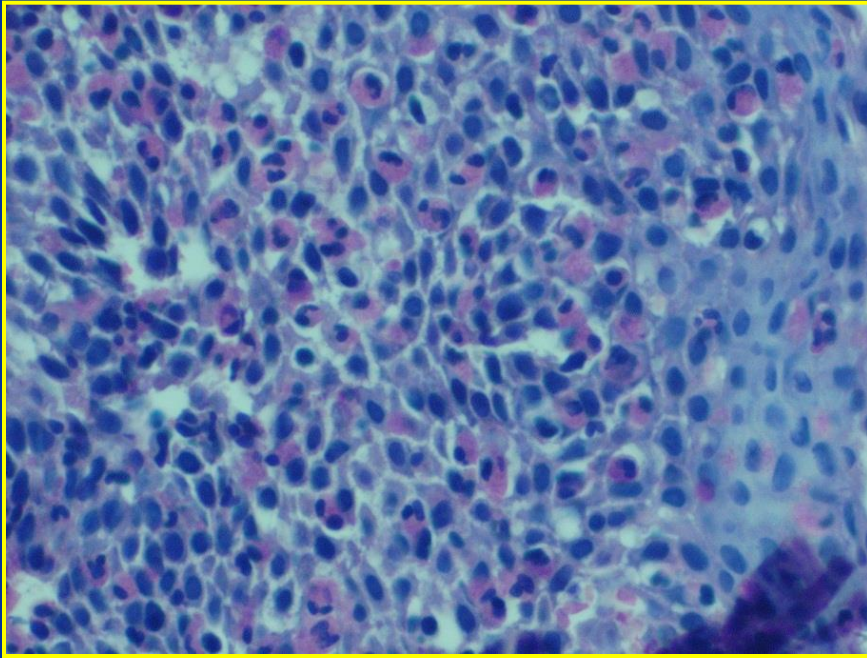


Eosinophilic Esophagitis

Histologic features

- Mucosal eosinophilia (>15 / hpf)
- Eosinophil microabscess formation
- Superficial layering of eosinophils
- Extracellular eosinophil granules
- Epithelial desquamation
- Basal zone hyperplasia
- Dilated intercellular spaces
- Subepithelial fibrosis / sclerosis
- Mastocytosis and mast cell degranulation
- CD8 lymphocytes and B cells

Histopathologic features



**Eosinophilic infiltration (110 eosinophils/hpf)
and superficial layering of eosinophils**

MBM, male, Caucasian, 22 years – EoE and milk allergy

N Rubini, 2012

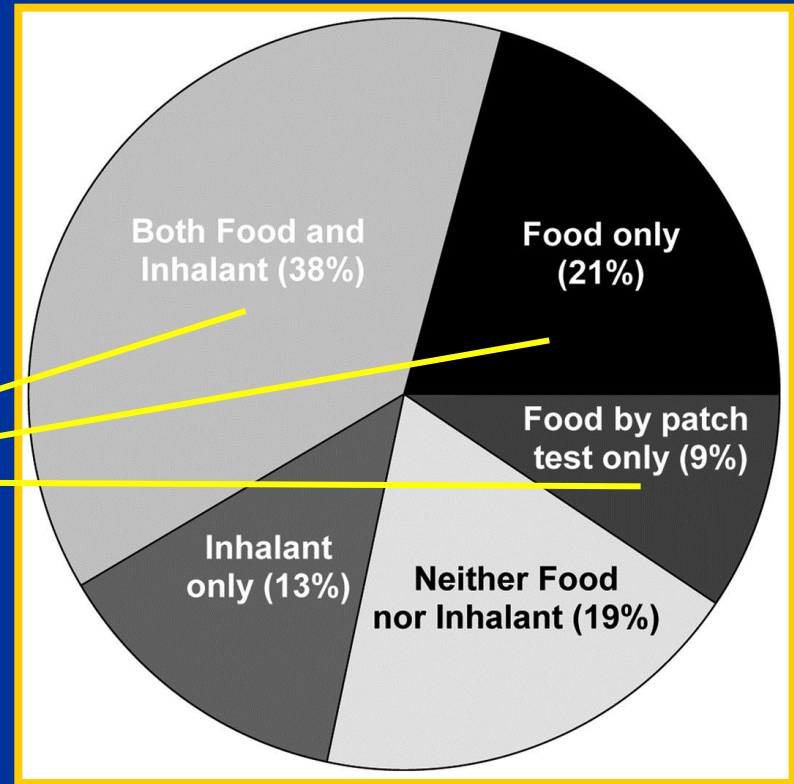
EoE and food allergy

- High prevalence of concomitant atopic diseases (>50%).
- Elevated serum IgE and blood eosinophilia – 50% to 60%.
- Food hypersensitivity has been reported in 19% - 73% of children and 13% - 25% of adults with EoE.
- Clinicopathological responsiveness to dietary therapy.
- De novo EoE has been observed with oral immunotherapy used for treatment of food allergies.

Allergic sensitization in pediatric patients with EoE

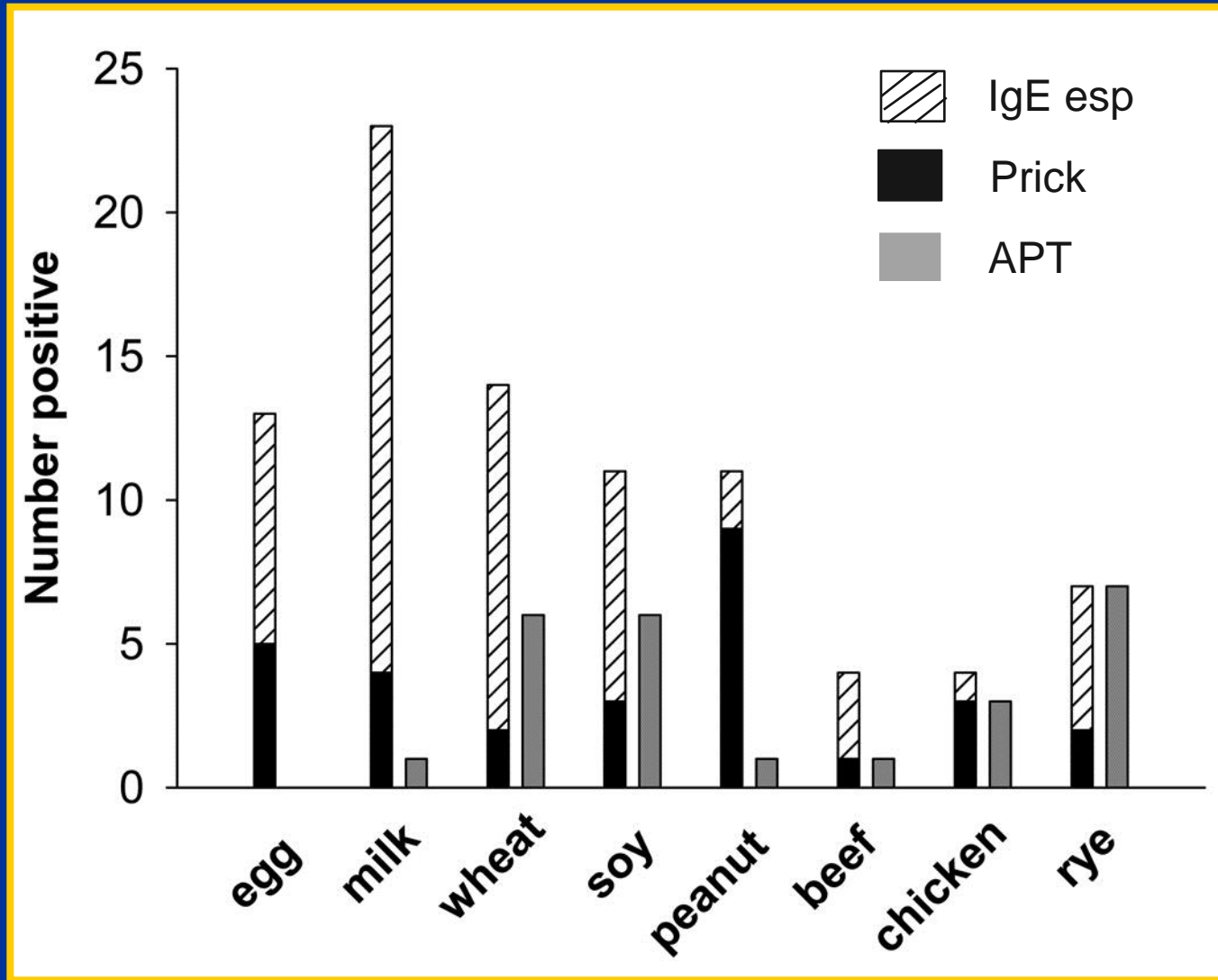
SPT – foods and inhalants
specific IgE – foods and inhalants
APT – foods

Foods – 68%



N = 53

Allergic sensitization in pediatric patients with EoE



N = 53

EoE and Food Allergy – Skin Prick test

| Food (n) | PPV (%) | NPV (%) | Sens (%) | Spec (%) |
|--------------|---------|---------|----------|----------|
| Milk (46) | 95,7 | 57,7 | 42,3 | 97,6 |
| Egg (39) | 84,8 | 75,4 | 65,1 | 90,2 |
| Soy (28) | 70,0 | 68,9 | 37,8 | 89,5 |
| Wheat (26) | 77,8 | 64,7 | 18,9 | 96,5 |
| Corn (26) | 57,1 | 71,3 | 13,8 | 95,4 |
| Beef (23) | 81,8 | 74,7 | 30,0 | 96,9 |
| Chicken (15) | 50,0 | 83,3 | 26,3 | 93,3 |
| Rice (14) | 50,0 | 85,6 | 13,3 | 97,5 |
| Potato (11) | 60,0 | 89,9 | 25,0 | 97,6 |

n = 316

Spergel JM et al, JACI 2007; 119:11

EoE and Food Allergy – Atopy Patch Test (APT)

| Food (n) | PPV (%) | NPV (%) | Sens(%) | Spec (%) |
|--------------|---------|---------|---------|----------|
| Milk (46) | 83,3 | 58,7 | 43,5 | 90,2 |
| Egg (39) | 78,3 | 82,8 | 62,1 | 91,4 |
| Soy (28) | 66,7 | 87,3 | 66,7 | 87,3 |
| Wheat (26) | 74,2 | 83,9 | 71,9 | 85,5 |
| Corn (26) | 65,8 | 93,9 | 89,3 | 78,0 |
| Beef (23) | 94,4 | 87,0 | 65,4 | 98,4 |
| Chicken (15) | 66,7 | 95,7 | 80,0 | 91,7 |
| Rice (14) | 59,1 | 96,9 | 86,7 | 87,5 |
| Potato (11) | 53,8 | 94,6 | 63,6 | 92,1 |

n = 316

Spergel JM et al, JACI 2007; 119:11

EoE and Food Allergy- APT + SPT

| Food | PPV (%) | NPV (%) | Sens(%) | Spec (%) |
|---------|---------|---------|---------|----------|
| Milk | 81 | 44 | 50 | 78 |
| Egg | 60 | 93 | 81 | 83 |
| Wheat | 42 | 88 | 65 | 74 |
| Soy | 33 | 93 | 71 | 73 |
| Peanut | 22 | 99 | 94 | 83 |
| Beef | 31 | 96 | 73 | 82 |
| Corn | 42 | 99 | 95 | 82 |
| Chicken | 32 | 98 | 88 | 80 |
| Potato | 36 | 98 | 81 | 90 |

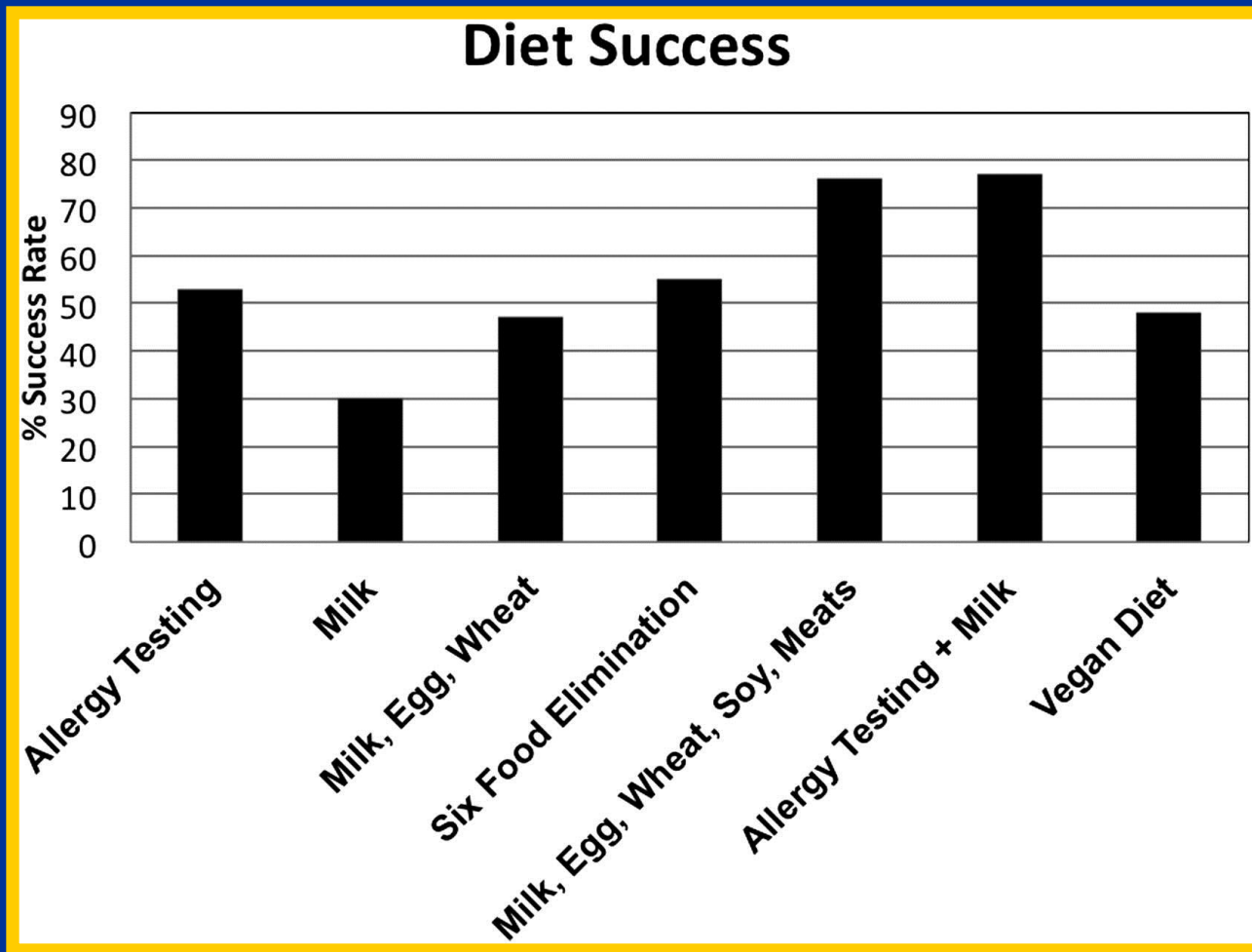
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Spergel JM et al, JACI 2012; 130: 461

Dietary modalities

| Item | Elemental diet | Allergy testing elimination diet | Empirical elimination diet |
|----------------------------------|---|--|----------------------------|
| Clinicopathological success rate | >80% | Children – 50% - 70% Adults – 20% - 30% | 50% - 70% |
| Number of elimination foods | All food groups eliminated | Typically \leq 4 foods eliminated | \leq 6 foods eliminated |
| Numbers of endoscopies required | ++++ | + | ++ |
| Drawbacks | Costly May require feeding tube Impact on QoL +++++ | Impact on QoL ++ | Impact on QoL ++ |

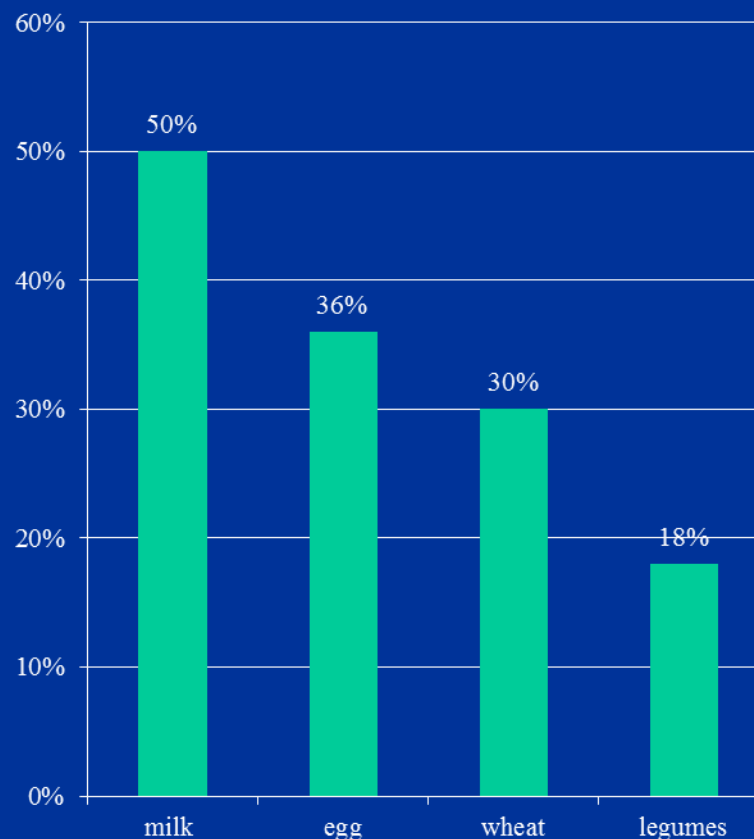
Identification of causative foods in children with EoE



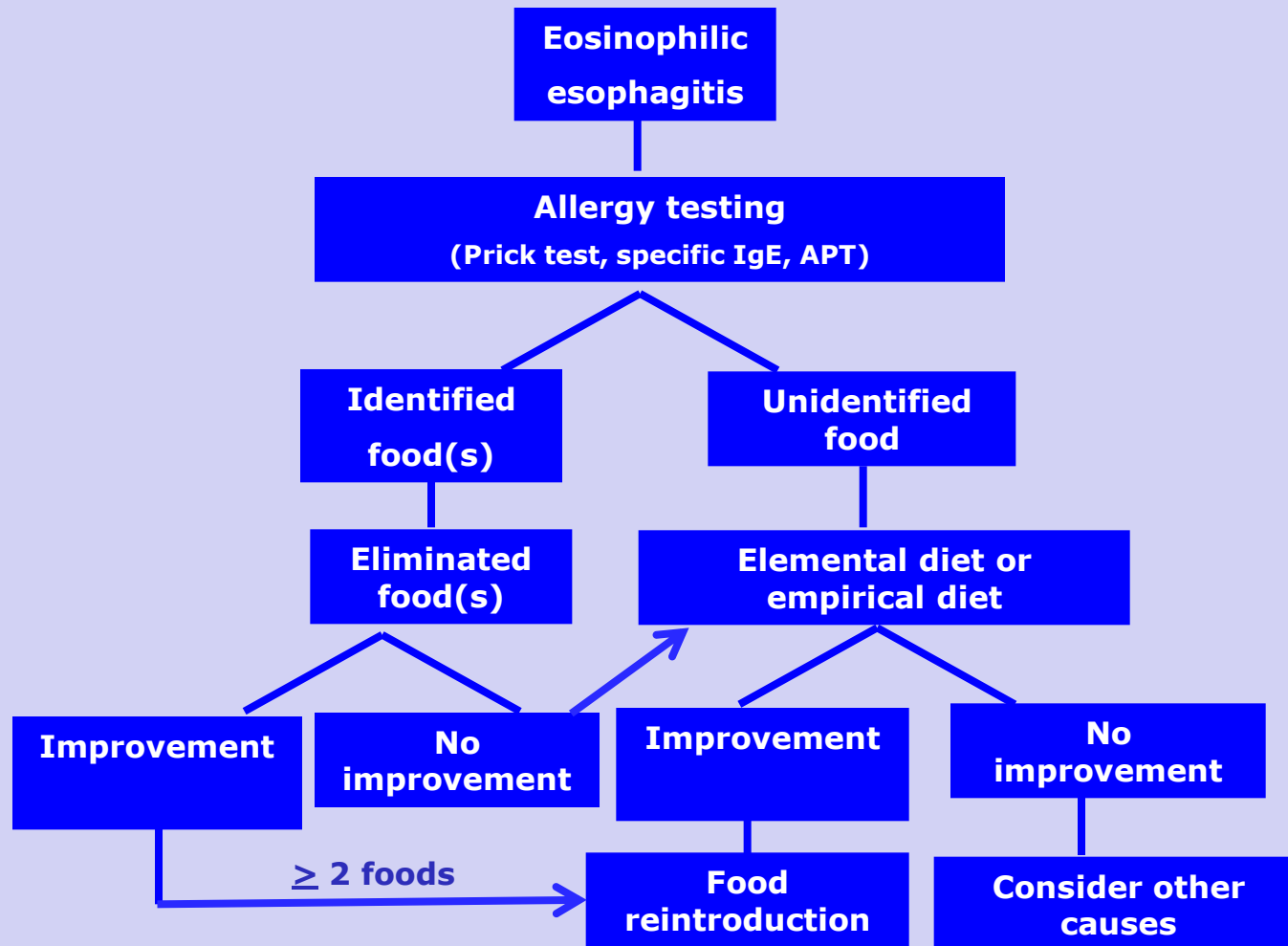
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Four-food elimination diet

- Prospective multicenter study in 4 Spanish hospitals between 2012 – 2014
- Population: 52 adults with EoE
- Four-food diet: milk, wheat, egg and soy/legumes
- Results: 28 patients (54%) achieved clinicopathological remission



Diagnostic investigation of food allergy in EoE



Conclusions

- Eosinophilic esophagitis (EoE) is an inflammatory disorder that is most likely initiated by a hypersensitivity reaction to allergic insult, with a late-phase characterized by eosinophil recruitment and subsequent tissue damage.
- The most clearly defined risk factors for EoE are gender (male predominance), race (Caucasians) and atopy.
- Most patients with eosinophilic esophagitis have compelling evidence of IgE-mediated hypersensitivity to foods, as determined by increased food-specific IgE or abnormal skin prick test.
- Removal of disease-exacerbating foods has proven to be successful in treating the disease and elimination diets have thus become the mainstay of therapy in EoE.
- Diet therapy, empiric or allergic test-directed, is an accepted and efficacious alternative to elemental diet that offers improved compliance, better food choices, less food reintroduction, and fewer endoscopies.