Le forme gastrointestinali di allergia alimentare

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UOC Allergologia OPBG
EiC, WAO Journal

Benevento
15 gennaio 2016

1. Allergie gastrointestinali ed EGID
2. Meccanismi delle EGID
3. Sintomi delle EGID
4. EGID, perché è una malattia allergica
5. EGID, quando è un'allergia alimentare
6. EGID ed allergia ambientale
7. Conclusioni

Gastrointestinal milk allergies

IgE-mediated, immediate-onset

- Oral allergy syndrome (OAS)
- Immediate GI allergy
- CMA in short-bowel syndrome

Non IgE-mediated, early-onset

- Milk protein-induced enterocolitis syndrome (FPIES)

Fiocchi A, Schunemann H. Diagnosis and Rationale for Action against Cow's Milk Allergy. The WAO DRACMA guideline. WAO Journal 2010; .

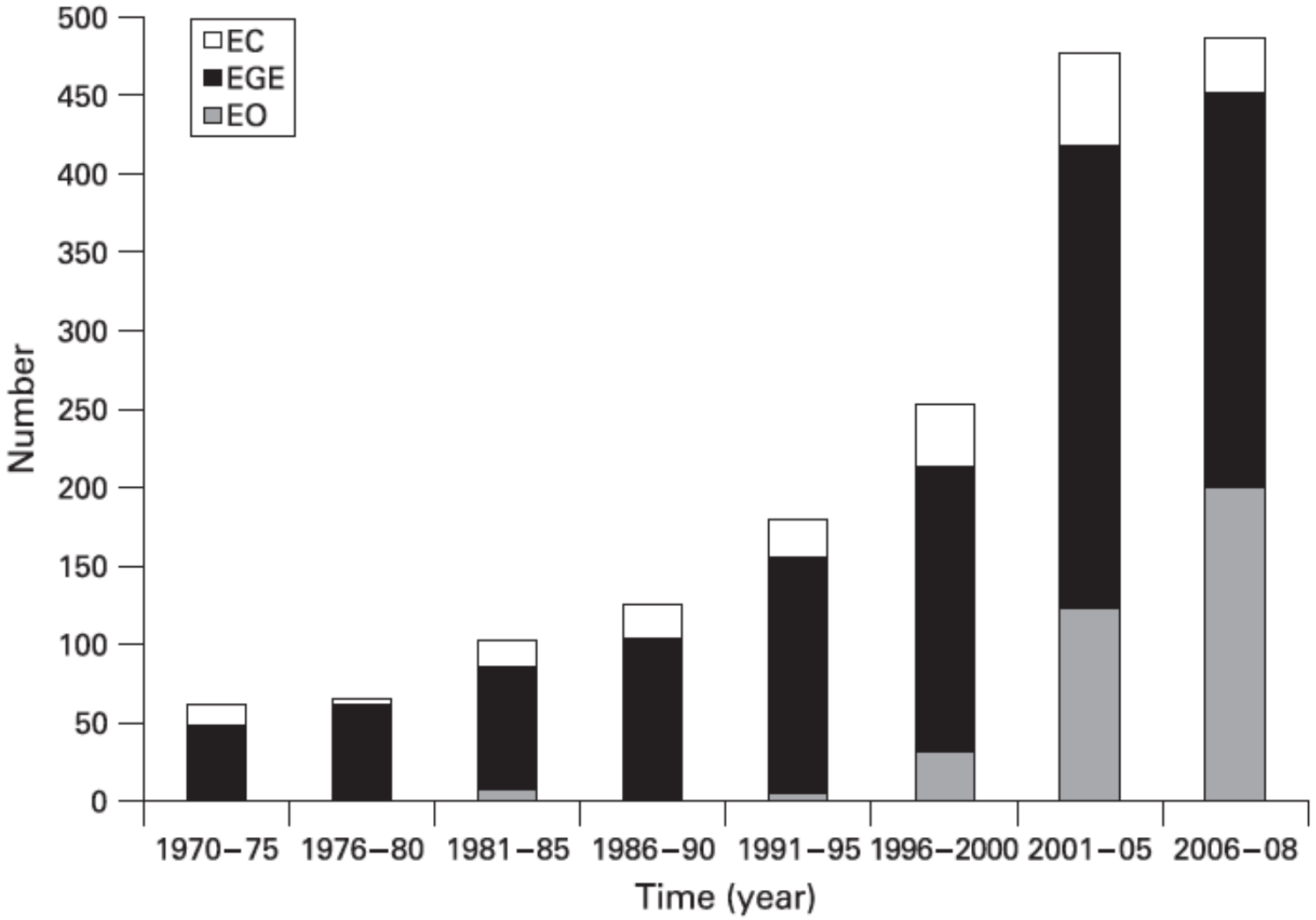
Gastrointestinal milk allergies

Non IgE-mediated, late-onset

- Gastroesophageal reflux disease (GERD)
- Crico-pharyngeal spasm
- Pyloric stenosis
- Eosinophilic esophagitis (EoE)
- Milk protein-induced enteritis/proctocolitis
- Constipation
- Severe irritability (colic)

Fiocchi A, Schunemann H. Diagnosis and Rationale for Action against Cow's Milk Allergy. The WAO DRACMA guideline. WAO Journal & Pediatr Allergy Immunol 2010; *in press*.

PubMed search for “eosinophilic oesophagitis” (EO), “e. gastroenteritis” (EGE) and “e. colitis” (EC)



Yan BM. Primary eosinophilic disorders of the gastrointestinal tract. Gut 2009;58:721-32

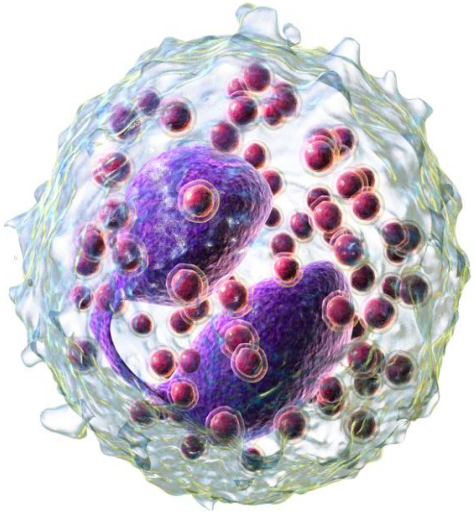
Eosinophilic gastrointestinal disorders (EGID)

DEFINITION

Disorders that selectively affect the gastrointestinal tract with eosinophil-rich inflammation in the absence of known causes for eosinophilia. Their features seem more related to cellular-mediated hypersensitivity from eosinophils rather than humoral (IgE) hypersensitivity

CLINICAL PATTERN

- Localisation
- Extension
- Depth

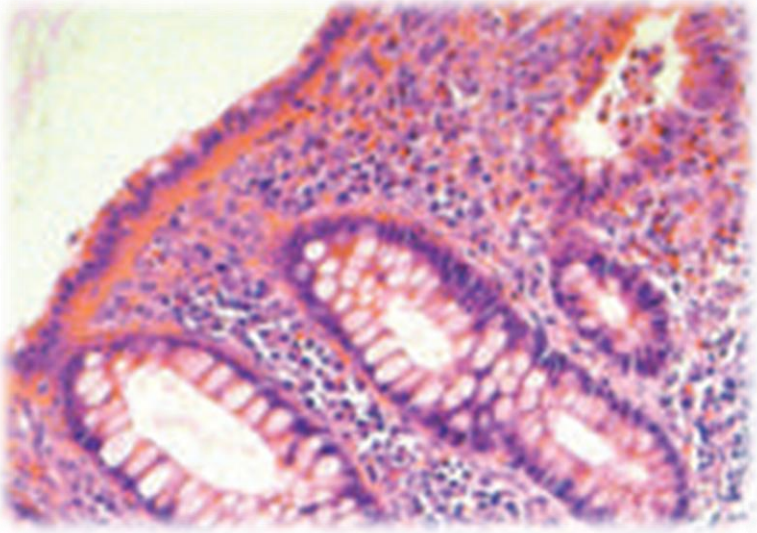


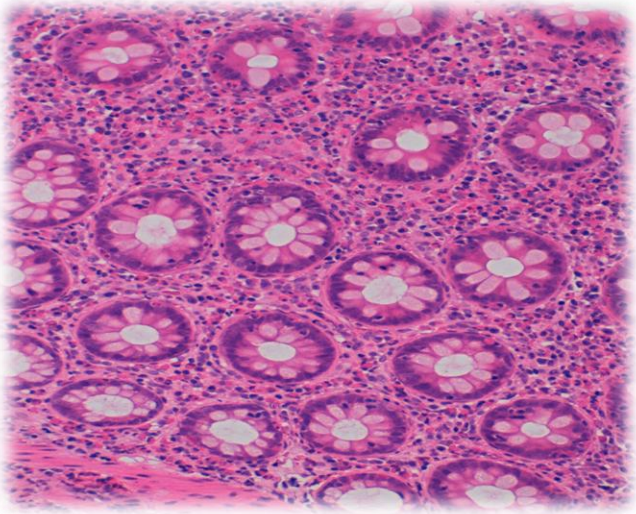
Jung Y, Rothenberg ME. Roles and regulation of gastrointestinal eosinophils in immunity and disease. J Immunol. 2014;193:999-1005

Primary vs. secundary EGID

Eosinophilic esophagitis
Eosinophilic gastritis
Eosinophilic gastroenteritis
Eosinophilic enteritis
Eosinophilic colitis
HyperEo syndrome with GI involvement

Food allergies
Celiac disease
Gastrointestinal infection
IBD
Connective tissue disease
Asthma and allergic rhinitis
GERD
Drug reaction





Jung Y, Rothenberg ME. Roles and regulation of gastrointestinal eosinophils in immunity and disease. J Immunol. 2014;193:999-1005

The spectrum of GI inflammatory disorders involving eosinophils

IgE-MEDIATED ⟷ NON-IgE-MEDIATED

Food Anaphylaxis

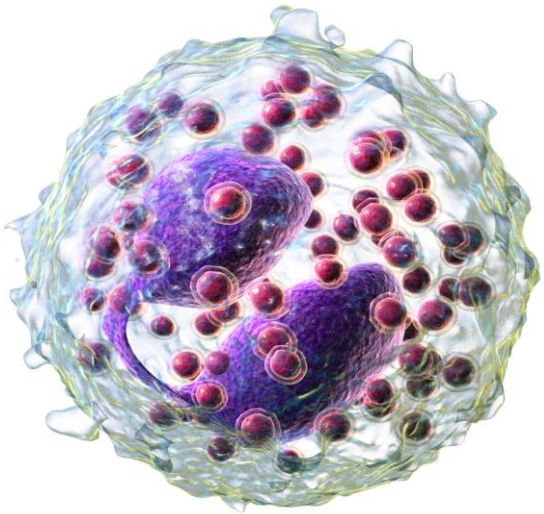
Protein Hypersensitivity Enteropathy

EGID

Eosinophilic Esophagitis
Eosinophilic Gastritis
Eosinophilic Gastroenteritis
Eosinophilic Enteritis
Eosinophilic Colitis

Celiac Disease

IBD



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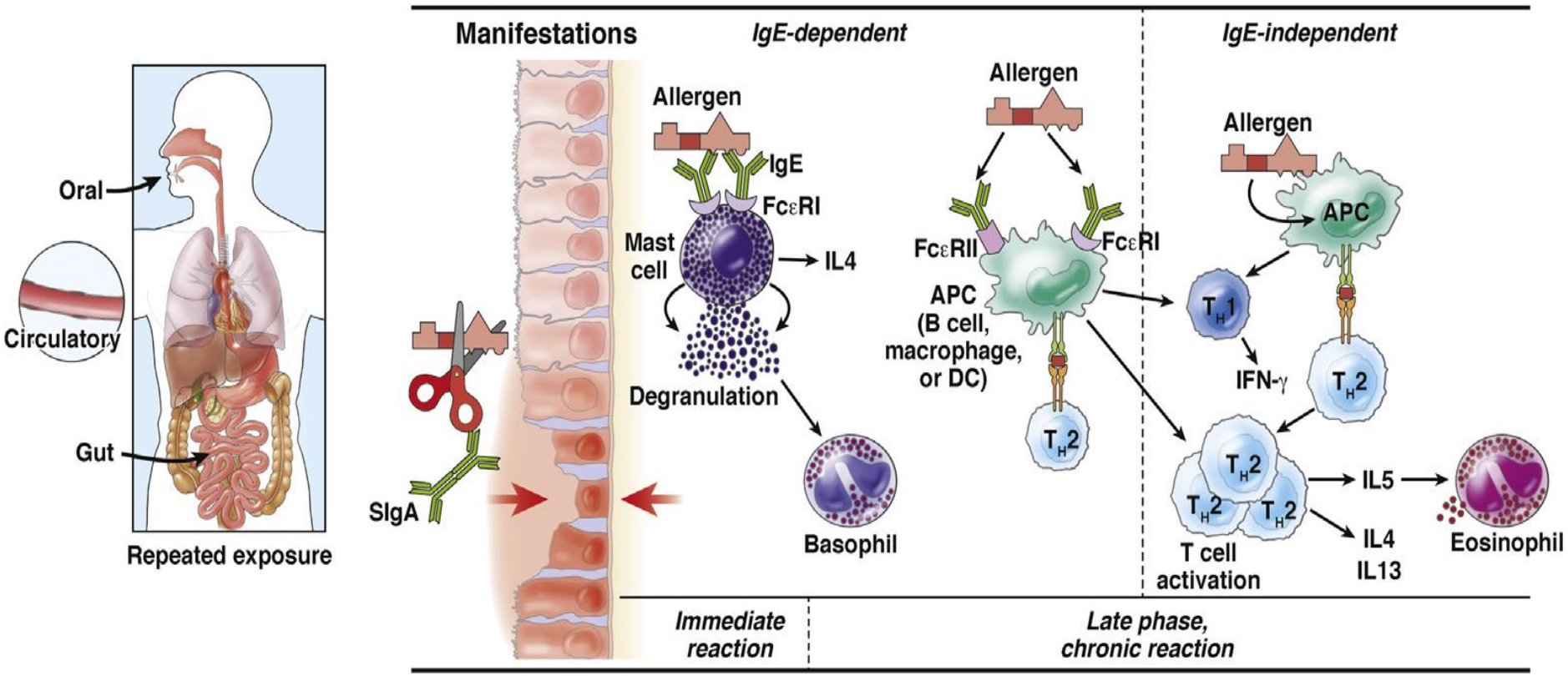
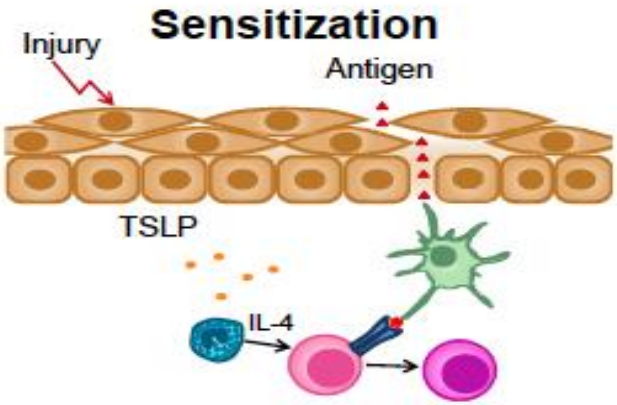
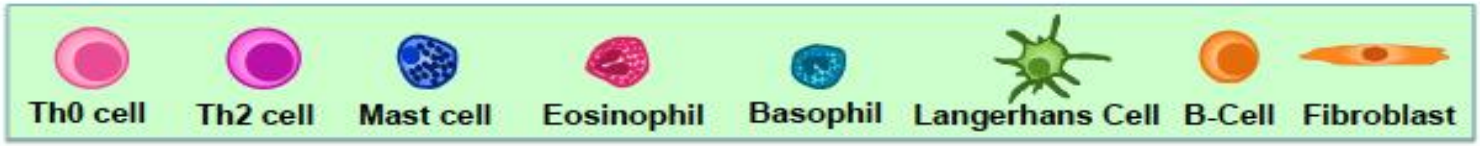
The IgE reaction from immediate to late phase



Wechsler JB, Bryce PJ. Allergic mechanisms in eosinophilic esophagitis. Gastroenterol Clin North Am. 2014;43:281-96





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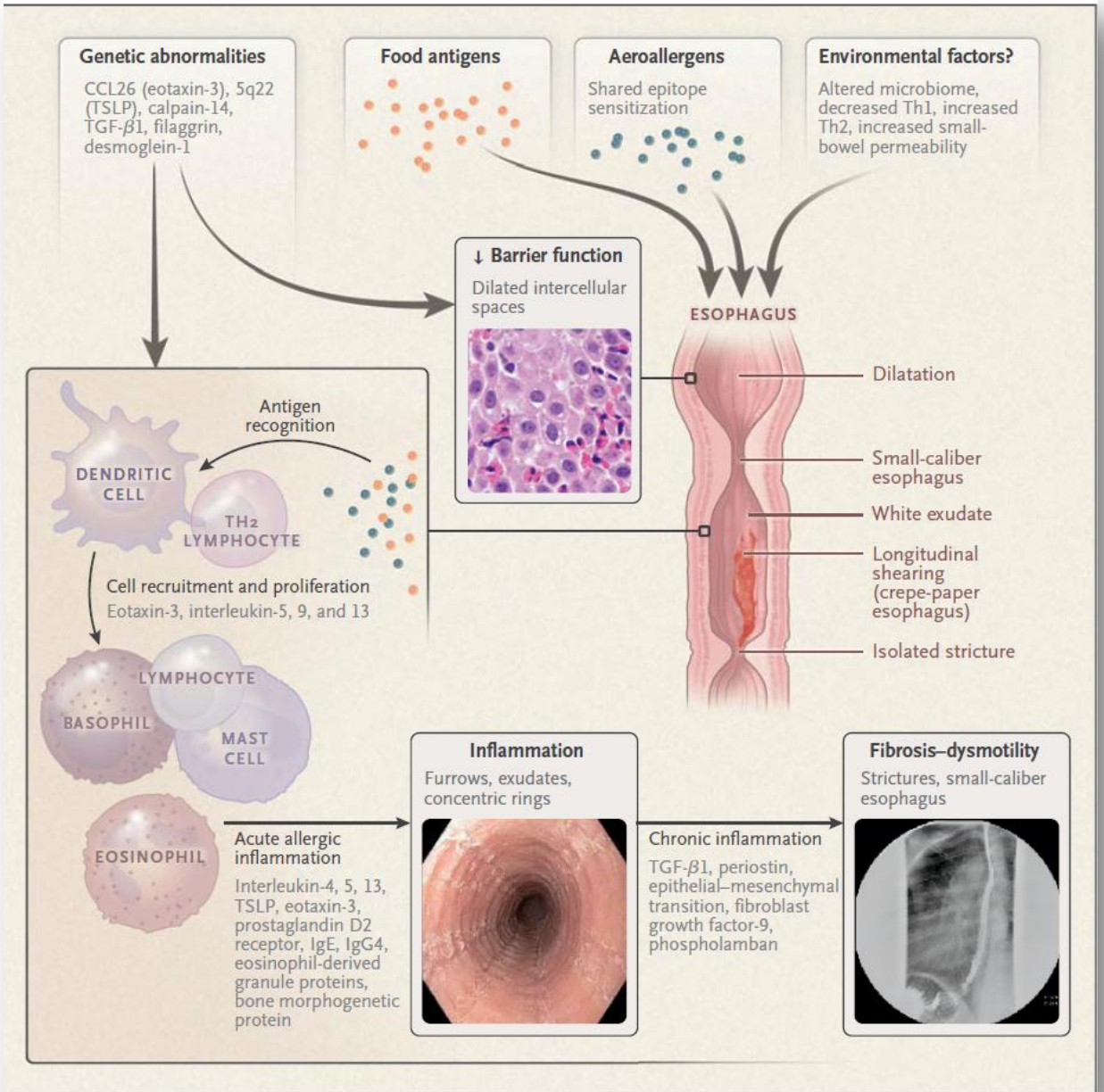
Pathophysiological Mechanisms of Eosinophilic Esophagitis.



Furuda N. Eosinophilic Esophagitis . N Engl J Med 2015;373:1640-8.

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EGID: clinical manifestations based on topographical location

- ESOPHAGUS
- STOMACH
- DUODENUM
- ILEUM
- LARGE BOWEL
- BILE CONDUCT/PANCREAS

ESOPHAGEAL DYSUNCTION
Feeding refusal
GORD symptoms
Dysphagia
Food impaction

Shah N. Histological findings in infants with Gastrointestinal food allergy are associated with specific gastrointestinal symptoms. BMC Clin Pathol. 2015;15:12

EGID: clinical manifestations based on topographical location

- ESOPHAGUS
- **STOMACH**
- DUODENUM
- ILEUM
- LARGE BOWEL
- BILE CONDUCT/PANCREAS

Dyspepsia
Nausea, Vomiting
Epigastric pain
Gastric Outlet obstruction
Ascities

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EGID: clinical manifestations based on topographical location

- ESOPHAGUS
- STOMACH
- **DUODENUM**
- ILEUM
- LARGE BOWEL
- BILE CONDUCT/PANCREAS

Gastric Outlet obstruction,
Nausea, Vomiting
Abdominal Pain
Diarrhoea
Weight Loss
Perforation
Ascities

Shah N. Histological findings in infants with Gastrointestinal food allergy are associated with specific gastrointestinal symptoms. BMC Clin Pathol. 2015;15:12

EGID: clinical manifestations based on topographical location

- ESOPHAGUS
- STOMACH
- DUODENUM
- **ILEUM**
- LARGE BOWEL
- BILE CONDUCT/PANCREAS

Abdominal Pain
Small Bowel Perforation
Small Bowel Obstruction
Ascities

Shah N. Histological findings in infants with Gastrointestinal food allergy are associated with specific gastrointestinal symptoms. BMC Clin Pathol. 2015;15:12

EGID: clinical manifestations based on topographical location

- ESOPHAGUS
- STOMACH
- DUODENUM
- ILEUM
- **LARGE BOWEL** → Diarrhoea, Bloody Diarrhoea, Abdominal Pain, Constipation
- BILE CONDUCT/PANCREAS

Shah N. Histological findings in infants with Gastrointestinal food allergy are associated with specific gastrointestinal symptoms. BMC Clin Pathol. 2015;15:12

EGID: clinical manifestations based on topographical location

- ESOPHAGUS
- STOMACH
- DUODENUM
- ILEUM
- LARGE BOWEL
- BILE CONDUCT/PANCREAS

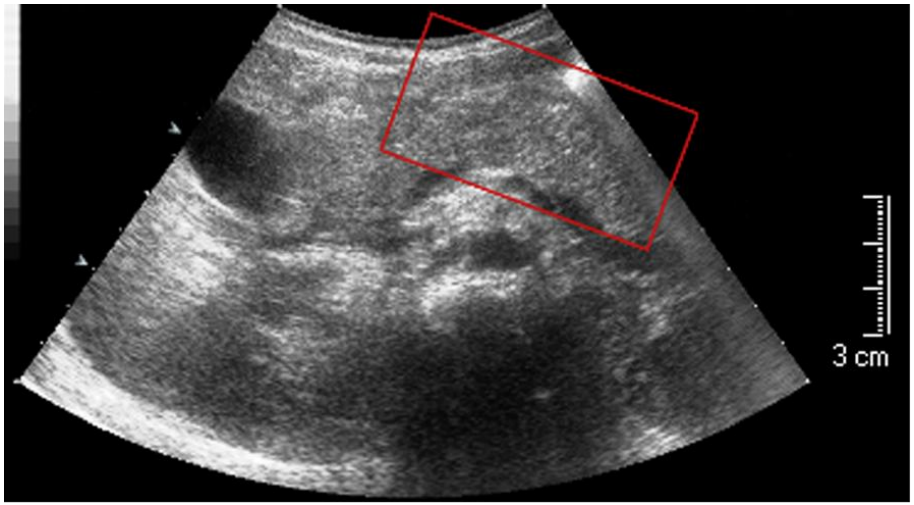
Jaundice,
Cholestasis
Epigastric pain
Abnormal Liver tests
Pancreatitis
Pancreatic mass

Shah N. Histological findings in infants with Gastrointestinal food allergy are associated with specific gastrointestinal symptoms. BMC Clin Pathol. 2015;15:12

Food allergy in digestive system

- An 8-year-old child with recurrent pancreatitis.
- Fish-free diet; SPT: cod, 4 mm, sIgE ImmunoCAP: cod, 1.30kU/l
- Food challenge with cod negative.
- Open cod administration → anaphylactic reaction + abdominal pain Pancreatitis! (↑ amylase, ↑ tryptase)

Parenchymal oedema at ultrasonography



Pellegrino K. Severe reaction in a child with asymptomatic codfish allergy: food challenge reactivating recurrent pancreatitis. Ital J Pediatr. 2012;38:16

EoE: presenting symptoms & history of atopy

Table 1. Presenting Symptoms among 103 Pediatric Patients with Eosinophilic Esophagitis.*

Symptom	Median Age (Interquartile Range)	No. (%)
Feeding disorder	2.0 (1.2	
Vomiting	8.1 (3.1	
Abdominal pain	12.0 (9.(	
Dysphagia	13.4 (10	
Food impaction	16.8 (13	

Table 2. History of Atopy in the 103 Pediatric Patients.

Variable	Percent of Patients
Rhinoconjunctivitis	57.4
Wheezing	36.8
Possible food allergy*	46
Family history of atopic disease	73.5
Family history of eosinophilic esophagitis†	6.8
Family history of esophageal dilatation	9.7

Noel RJ. Eosinophilic esophagitis. N Engl J Med 2004; 35:940-1

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EoE is an atopic disease.

Atopic mechanisms

1. Altered epithelial barrier dysfunction
2. Activated TH2 cells
3. Classical atopic cytokines:
   - Thymic Stromal LymphoPoietin (TSLP)
   - Atopic cytokines (IL-4, IL-13, TNFa)
   - Eotaxin-3 (CCL-26)
4. Similar histology, from TH2 to fibrosis via eosinophils

Spergel JM. An allergist's perspective to the evaluation of Eosinophilic Esophagitis. Best Pract Res Clin Gastroenterol. 2015;29:771-81

EoE is an atopic disease.

Epidemiology

1. prevalence dramatically increased in the last decade
2. a 70-fold increase from 1994 to 2011
3. 30-50% of individuals with EoE have asthma
4. 50-75% have allergic rhinitis
5. 10-20% have IgE-mediated food allergy
6. rates of atopic dermatitis three times higher than in the general population

These data suggests EoE is a super-atopic phenotype.

Spergel JM. An allergist's perspective to the evaluation of Eosinophilic Esophagitis. Best Pract Res Clin Gastroenterol. 2015;29:771-81

EoE is an atopic disease.

Aeroallergens

1. Esophageal eosinophilia develops in mice following intranasal exposure to Aspergillus fumigatus
2. 26% of patients with allergic rhinitis without GERD had esophageal eosinophilia when biopsied during a time of active allergy symptoms
3. Seasonality of EoE symptoms
4. Decreased EoE diagnosis in the winter and increased diagnosis in the spring, summer, and fall.
5. EoE after starting SLIT for pollen and grass allergies
6. Resolution of esophageal eosinophilia after 2 year SCIT to dust mite

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EoE is an atopic disease.

Dietary treatment

Foods meet the classic Koch's postulate:
- removing food resolves disease
- the same food causes disease.

How to determine what foods cause the disease?
- empiric removal of food
- allergy test-driven removal of food.

Common food allergens: milk, egg, soy, and wheat

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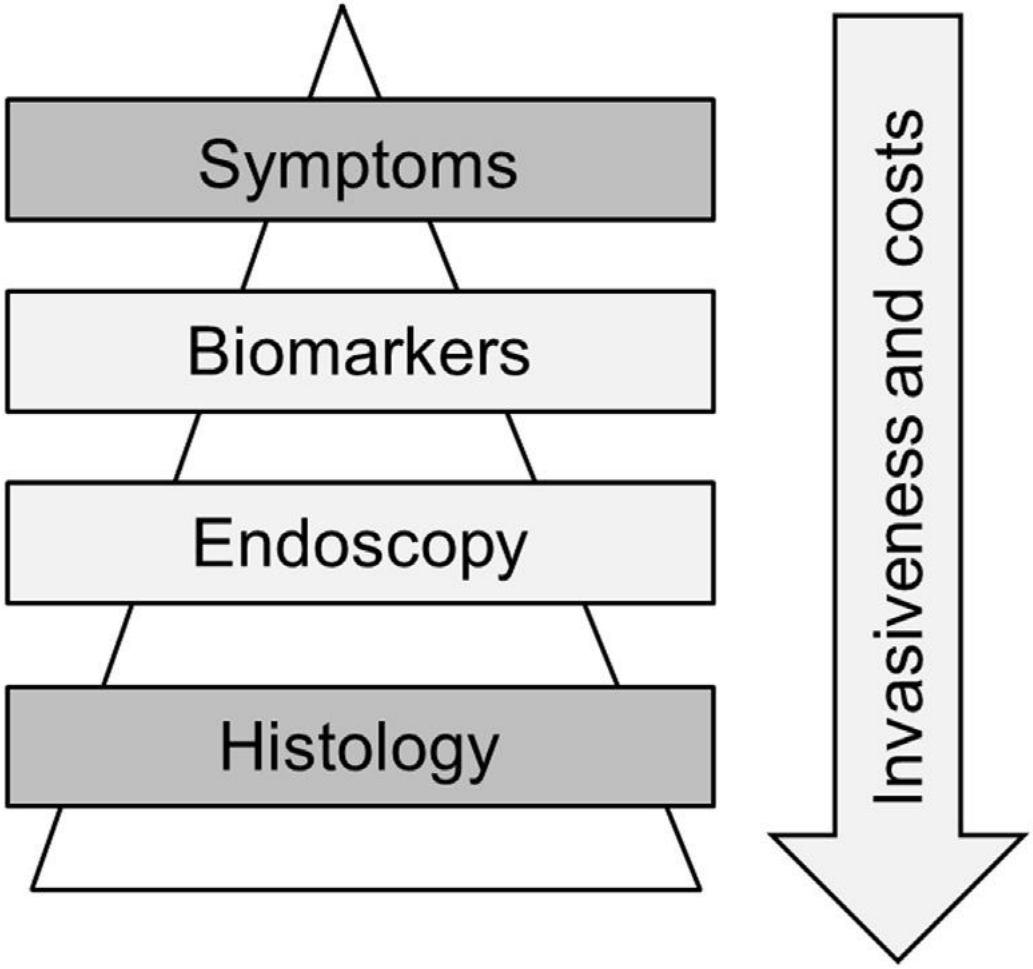
Diagnosis of eosinophilic esophagitis.



Schoepfer A. Diagnostic approach to eosinophilic oesophagitis: Pearls and pitfalls. Best Practice & Research Clinical Gastroenterology 2015; 29:783-92

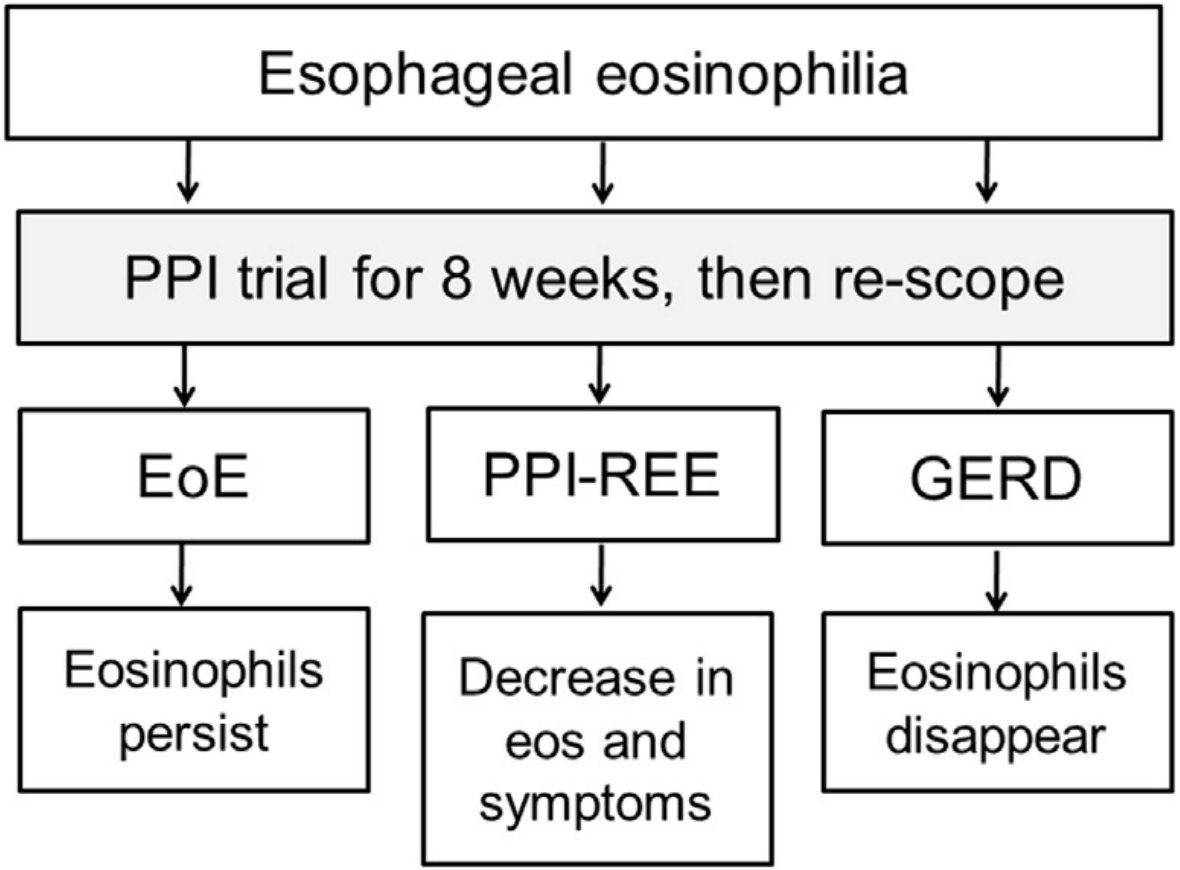
Medical treatment of active eosinophilic esophagitis.

Table 1. Medical Treatment of Active Eosinophilic Esophagitis.

Omeprazole (proton-pump inhibitor)†	Children with body weight 10 to 20 kg: 10 mg twice a day Children with body weight >20 kg: 20 mg twice a day Adults: 40 mg once or twice a day
Glucocorticoids	
Fluticasone	Children: 220 to 440 μg twice a day Adults: 440 to 880 μg twice a day
Budesonide	Children: 0.25 to 0.5 mg twice a day Adults: 1 to 2 mg twice a day

Furuda N. Eosinophilic Esophagitis . N Engl J Med 2015;373:1640-8.

Treatment of eosinophilic esophagitis.



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Medical treatment of active eosinophilic esophagitis.

Table 1. Medical Treatment of Active Eosinophilic Esophagitis.

Method	Specific Recommendation or Dosage
Elemental diet therapy	—
Elimination diet therapy	
Six-food elimination	Elimination of milk, wheat, eggs, soy, seafood, and nuts
Four-food elimination	Elimination of milk, wheat, eggs, and soy
Allergy testing–based	Elimination of foods on the basis of results of radioallergosorbent testing, skin-prick testing, or atopy-patch testing*
Glucocorticoids	
Fluticasone	Children: 220 to 440 μg twice a day Adults: 440 to 880 μg twice a day
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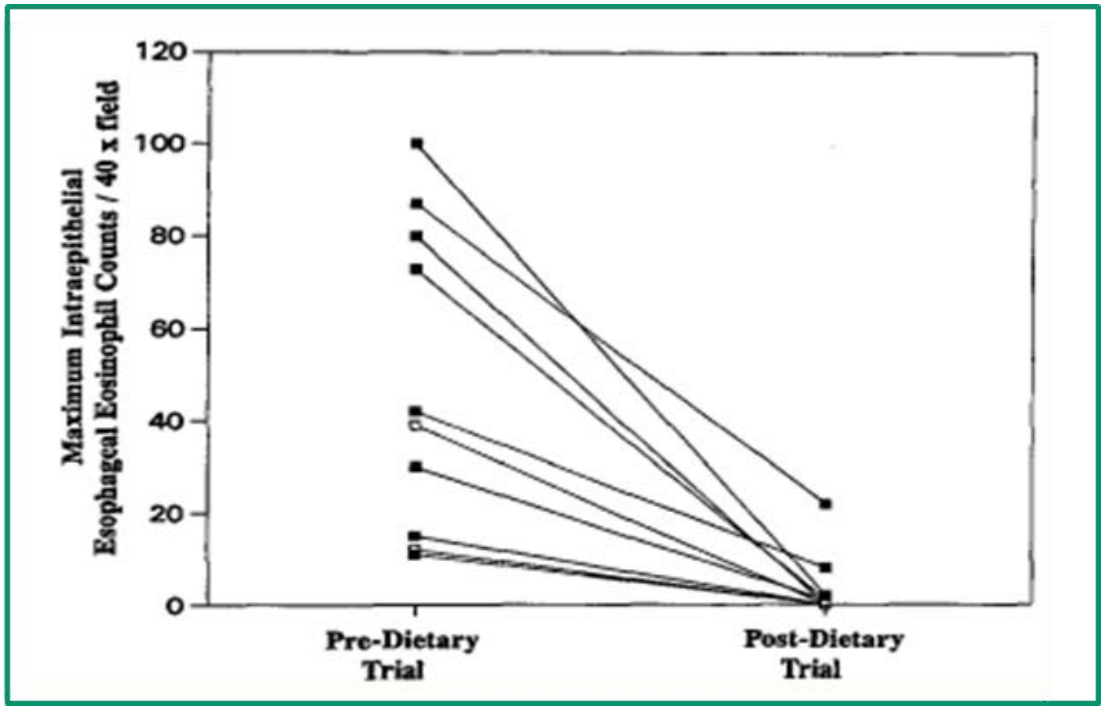
Furuda N. Eosinophilic Esophagitis . N Engl J Med 2015;373:1640-8.

Neocate® decreases eosinophil count in EoE attributed to gastroesophageal reflux

- Ten children previously diagnosed with GERD
- Neocate for a minimum of 6 weeks.
- Resolution (n = 8)
- Improvement (n = 2)
- Intraepithelial eosinophil counts decreased from 41 to 0.5 (P = 0.005)
- Patients redeveloped their previous symptoms on open food challenges



Kelly KJ. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an aminoacid-based formula. Gastroenterology. 1995;109:1503-12

Elementary diets and EoE

- 381 patients with EoE
- Corticosteroids significantly improved clinical symptoms and esophageal histology
- Such improvement was temporary
- Dietary restriction or amino acid-based formula improved both the clinical symptoms and/or esophageal histology in 98% patients.

160 patients	Pre-diet	Post-diet	p
Eos/HPf	38.7±10.3	1.1±0.6	<0.001
Dysphagia	30	1	<0.01
GERD	134	3	<0.01

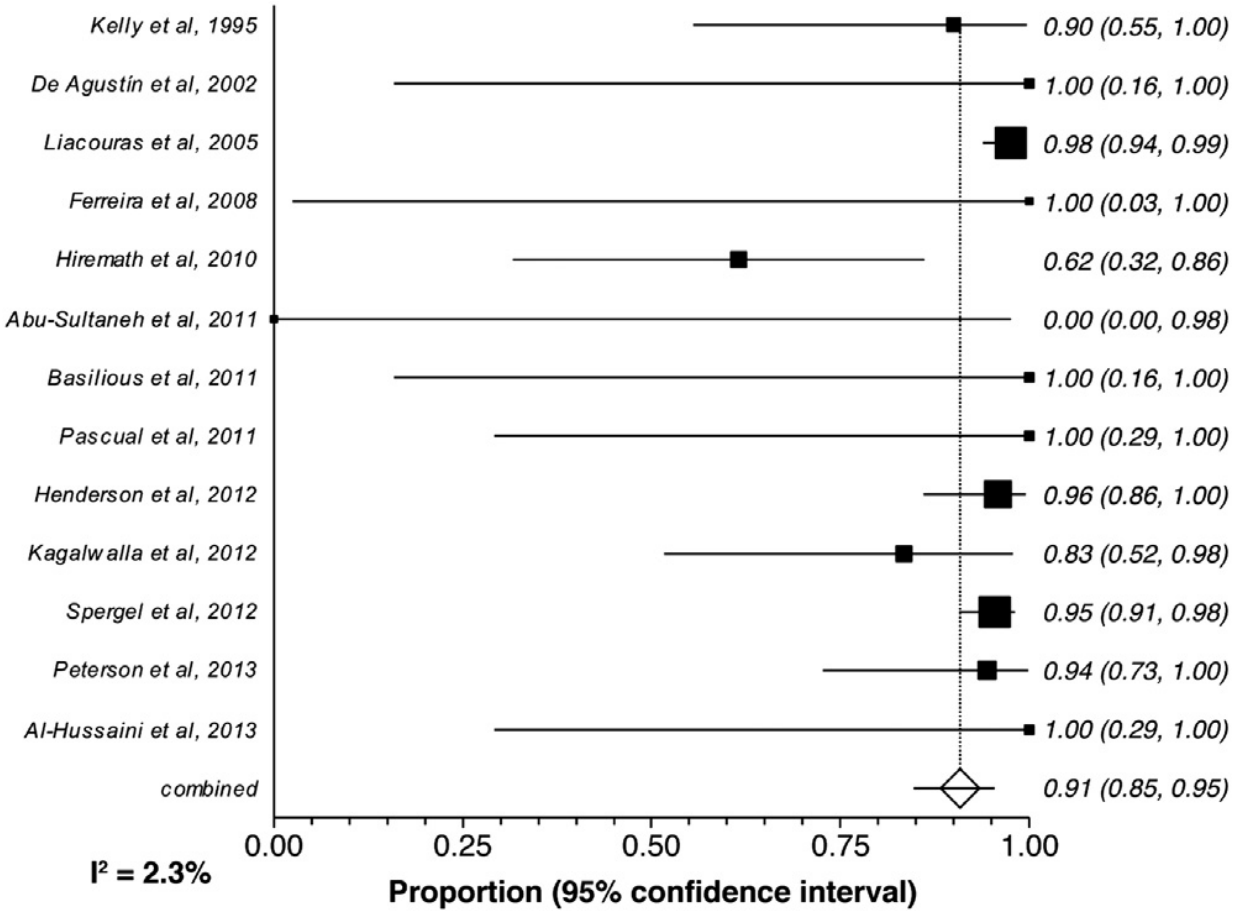
Liacouras CA. Eosinophilic esophagitis: a 10-year experience in 381 children. Clin Gastroenterol Hepatol 2005;3:1198-206

Elemental diets and EoE: a metanalysis

Elemental diet as the most effective option to induce disease remission, but with a limited application in clinical practice. Drawbacks:

- need to avoid all table food
- unpleasant taste
- high cost
- psychological effects
- social limitations

Restricted almost exclusively to pediatric patients.



Arias A. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. Gastroenterology 2014;146:1639–1648

Six-foods empiric elimination diet (SFED).

60 EoE patients.

1) 35 selective elimination of milk, soy, wheat, egg, peanut/nut and fish;
2) 25 were strict elemental diet (amino acid based formula)

Clinical symptoms significantly improved in both groups.

Group 2) clinically improved with almost complete histologic resolution in 90%
Group 1) improved clinically and histologically in 75%

Kagalwalla AF. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. Clin Gastroenterol Hepatol 2006; 4:1097-102

Six Food Elimination Diet (SFED) Adults

SFED highly effective in the treatment of both symptoms and histopathology

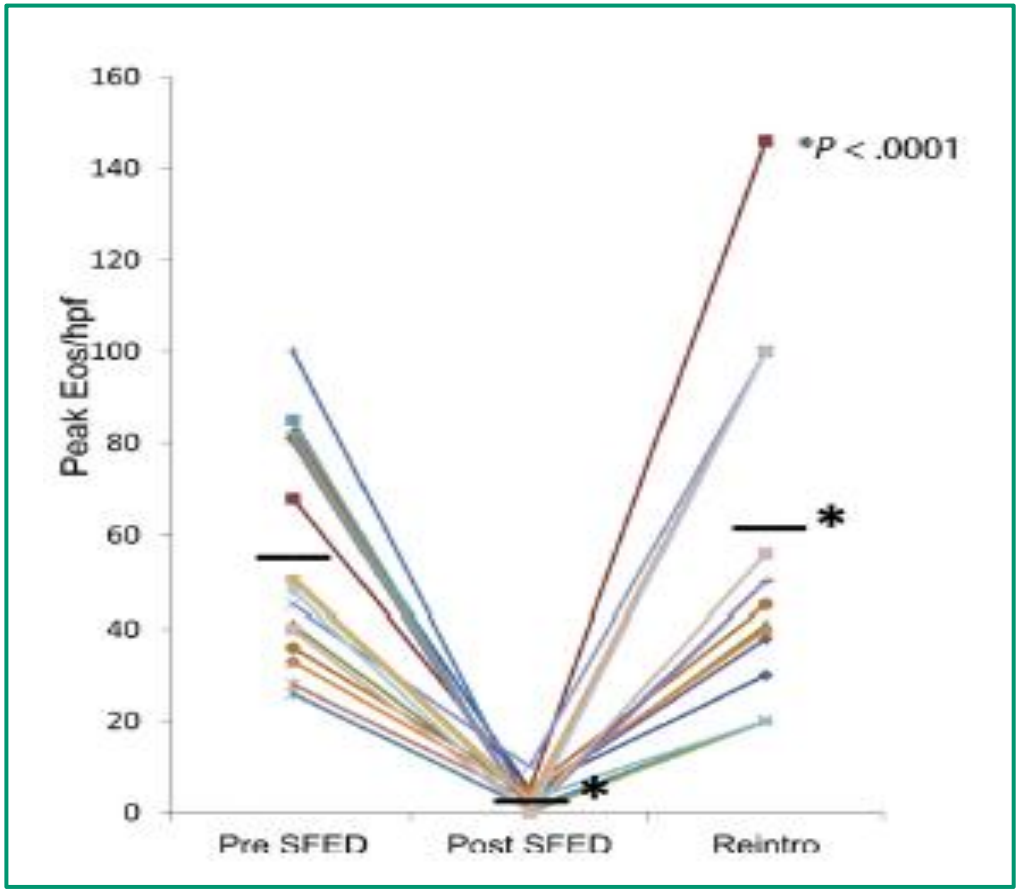
78% → greater than a 50% reduction in PEC

70% → 10 eos/hpf

64% → 5 eos/hpf

Dysphagia symptom scores improved

The systematic reintroduction of food in patients who achieved an initial complete response to the diet identified causative dietary agent(s) in all patients



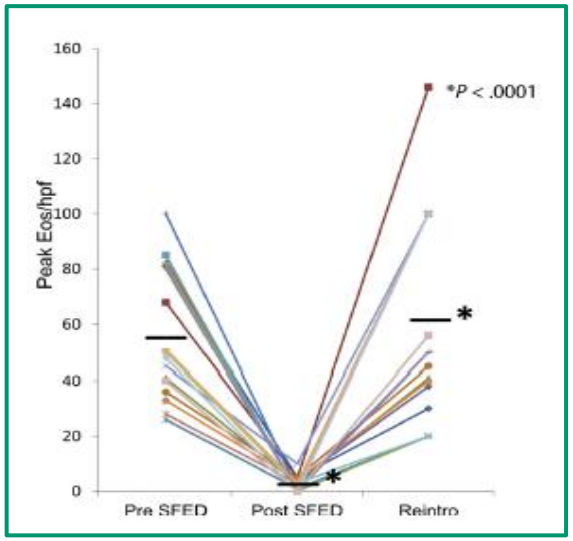
Gonsalves N. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. Gastroenterology. 2012;142:1451-9

Six Food Elimination Diet (SFED) Adults

Most common food triggers:

- wheat (60%)
- milk (50%)
- soy (10%)
- nuts (10%)
- egg (5%)
- seafood (0)

Three patients had more than one food trigger



SPT accurately predicted only 13% of causal agents

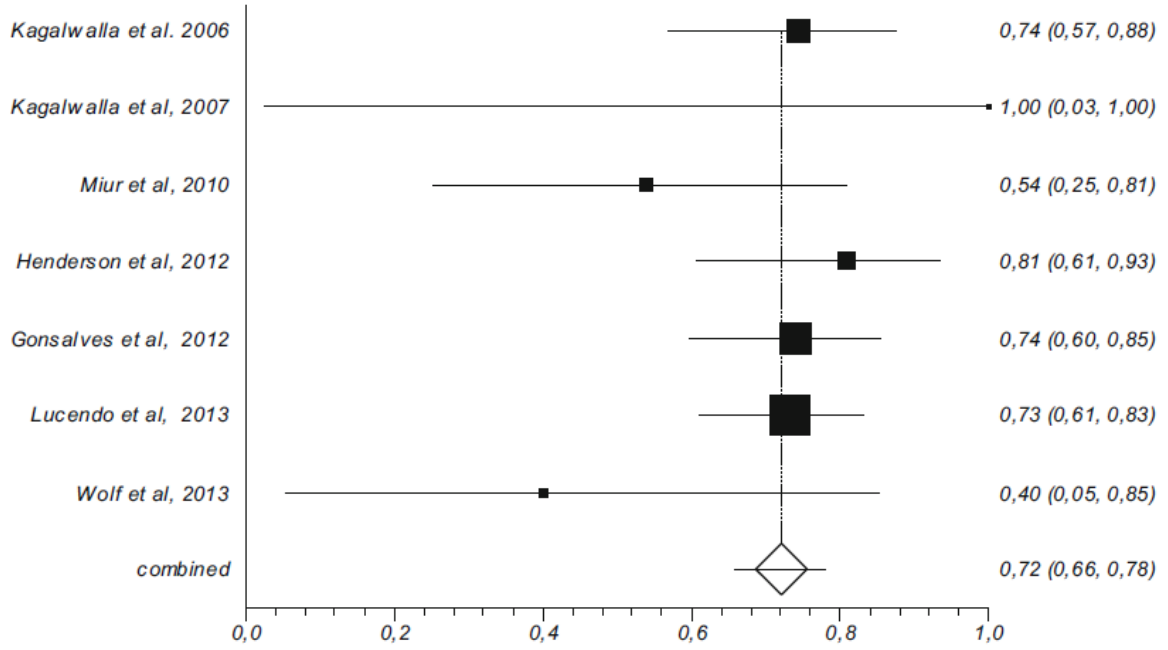
67% of patients who had a food trigger identified by the reintroduction process had a negative SPT to all foods

Common food allergens on skin prick test[a]	
Nuts	26/50(52%)
Wheat	10/50 (20%)
Soy	10/50 (20%)
Seafood	6/50 (12%)
Egg	6/50 (12%)
Milk	3/50 (6%)

Gonsalves N. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. Gastroenterology. 2012;142:1451-9

SFED and EoE: a metanalysis

- Studies extremely homogeneous
- Combined efficacy rate of 72.1%
- A major role as causative food allergens for cow's milk, wheat, eggs, and soy/legumes
- a minor role for nuts and fish/seafood



4-food elimination diet?

Arias A. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. Gastroenterology 2014;146:1639–1648

Four Food Elimination Diet - Adults

- A prospective trial
- 52 adults patients
- Elimination of milk, egg, legumes and wheat.
  - cow's and goat's milk
  - all gluten containing grains
  - peas, beans, lentils and peanuts.

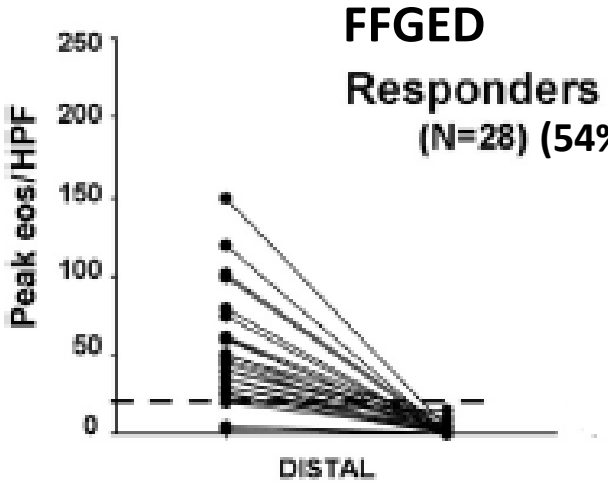
[this is more a four food group elimination not four individual foods - much harder for a patient to do]

54% patients responded to FFED

75% patients after further reduction to SFED

Molina-InfanteJ. Four-food group elimination diet for adult eosinophilic esophagitis: A prospective multicenter study. J Allergy Clin Immunol 2014;134:1093-9

Four Food Elimination Diet - Adults



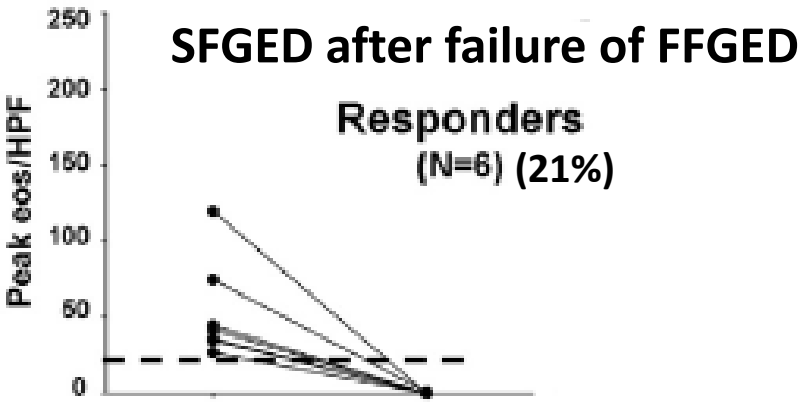


TABLE II. Food triggers identified by sequential food challenge (n = 22) after response to the FFGED

A single causative food group	10/22	45%
Milk	6/22	27%
Wheat	3/22	13%
Egg	1/22	4%
Two causative food groups	10/22	45%
Milk and egg	2/22	9%
Milk and legumes	2/22	9%
Milk and wheat	1/22	4%
Wheat and egg	3/22	13%
Egg and legumes	2/22	9%
Three or more causative food groups	0	0
No causative food group	2/22	9%

Molina-InfanteJ. Four-food group elimination diet for adult eosinophilic esophagitis: A prospective multicenter study. J Allergy Clin Immunol 2014;134:1093-9

One Food Elimination Diet (Milk); children

65% patients in a retrospective study responded to milk only elimination in a population of 17 patients

Kagalwalla AF. Cow's milk elimination: a novel dietary approach to treat eosinophilic esophagitis. Journal of Pediatric Gastroenterology and Nutrition 2012;55:711

In > 1000 patients, only 30% response rate to milk elimination

Spergel JM. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. J Allergy Clin Immunol 2012;130:461-7

A large multi-center study will be done through Consortium for Eosinophilic Gastrointestinal Researchers (CEGIR) and PCORI grants to identified the rate of single food allergy in both pediatric and adult population.

S

One Food Elimination Diet (Milk) vs. Fluticasone; children

- A prospective, comparative effectiveness trial
- newly diagnosed EoE patients (ages 2-18 years)
- swallowed fluticasone (n = 24) vs. elimination of cow's milk (n = 20).
- repeat esophageal biopsy (6-8 weeks)
- Pediatric Quality of Life Inventor (PedsQL)

PedsQL EoE Module total scores (69 vs. 82; $P < 0.005$)

Total Symptoms scores (58 vs. 75; $P = 0.001$)

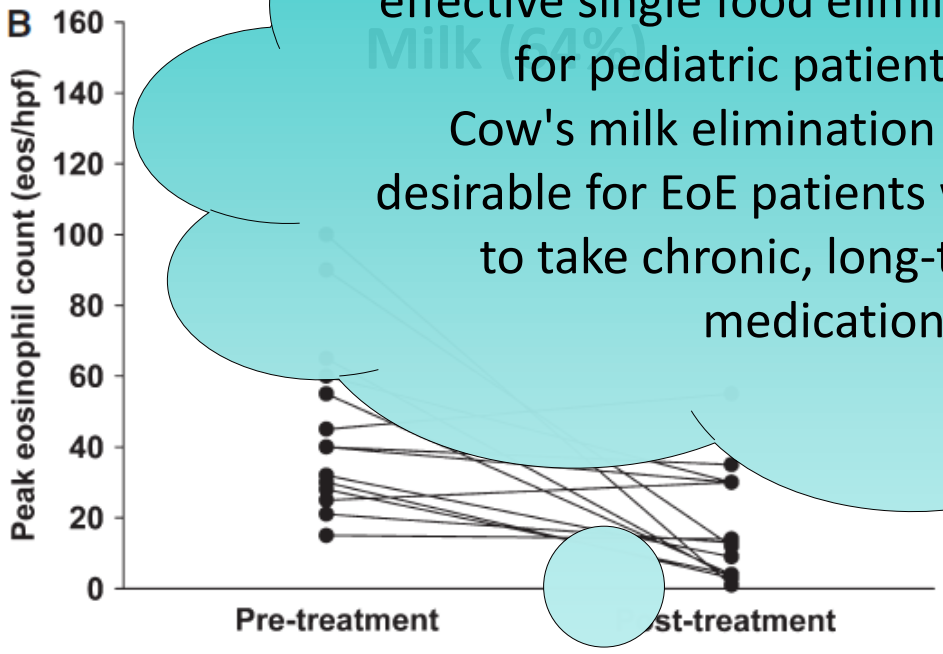
PedsQL EoE Module total scores (64 vs. 75; $P < 0.05$)

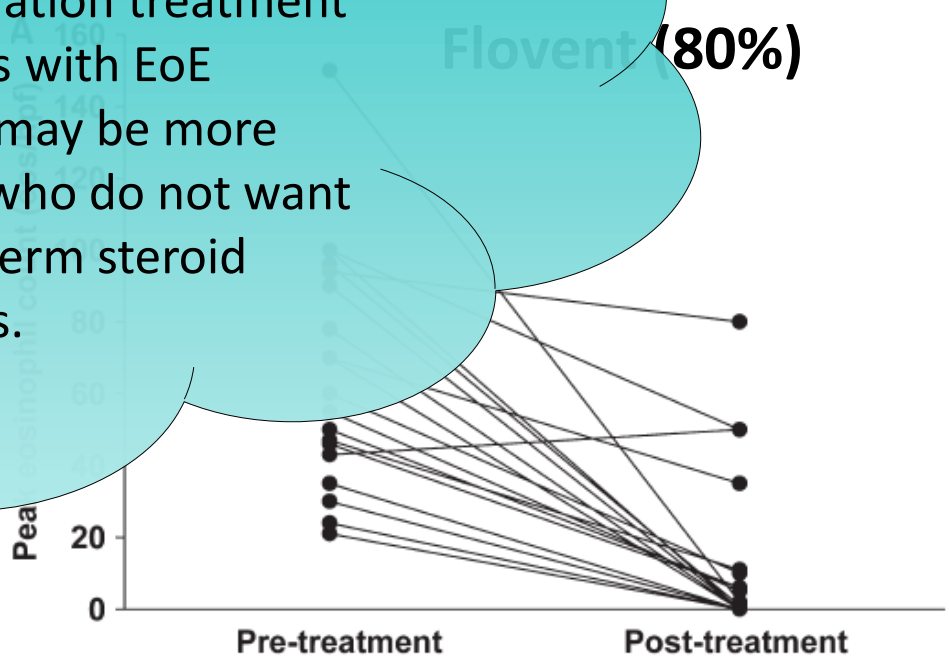
Total Symptoms scores (58 vs. 69; $P < 0.01$) significantly improved after 6-8 weeks of therapy.

Kruszewski PG. Prospective, comparative effectiveness trial of cow's milk elimination and swallowed fluticasone for pediatric eosinophilic esophagitis. Dis Esophagus. 2015 Feb 26. doi: 10.1111/dote.12339

One Food Elimination Diet (Milk) vs. Fluticasone; children

Removal of cow's milk from the diet is an effective single food elimination treatment for pediatric patients with EoE
Cow's milk elimination may be more desirable for EoE patients who do not want to take chronic, long-term steroid medications.





Kruszewski PG. Prospective, comparative effectiveness trial of cow's milk elimination and swallowed fluticasone for pediatric eosinophilic esophagitis. Dis Esophagus. 2015 Feb 26. doi: 10.1111/dote.12339

Allergy Testing Directed Diets

SPT, sIgE, APT: accuracy

- examined extensively for classic IgE mediated reactions (hives, anaphylaxis…),
- less so for non-IgE mediated food reactions like EGIDs
- the predictive values vary (food, age, clinical history, setting, incidence...)

SPT, sIgE, APT: reproducibility good, but not perfect

- location of skin test (arm vs back),
- season of the testing
- device used for skin testing
- APT not as standardized as skin testing or specific IgE
- sIgE whole vs. CRD

Spergel JM. An allergist's perspective to the evaluation of Eosinophilic Esophagitis. Best Pract Res Clin Gastroenterol. 2015;29:771-81

Allergy Testing Directed Diets

Only 13% of the foods that caused EoE based on biopsy changes had corresponding positive specific IgE

Gonsalves N. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. Gastroenterology. 2012;142:1451-9

SPT vs. sIgE vs. APT in a pediatric EoE population.

sIgE more sensitive for identifying sensitization to foods
no evaluation of the specificity of the tests

Erwin EA. Serum IgE measurement and detection of food allergy in pediatric patients with eosinophilic esophagitis. Ann Allergy Asthma Immunol 2010;104:496e502.

S

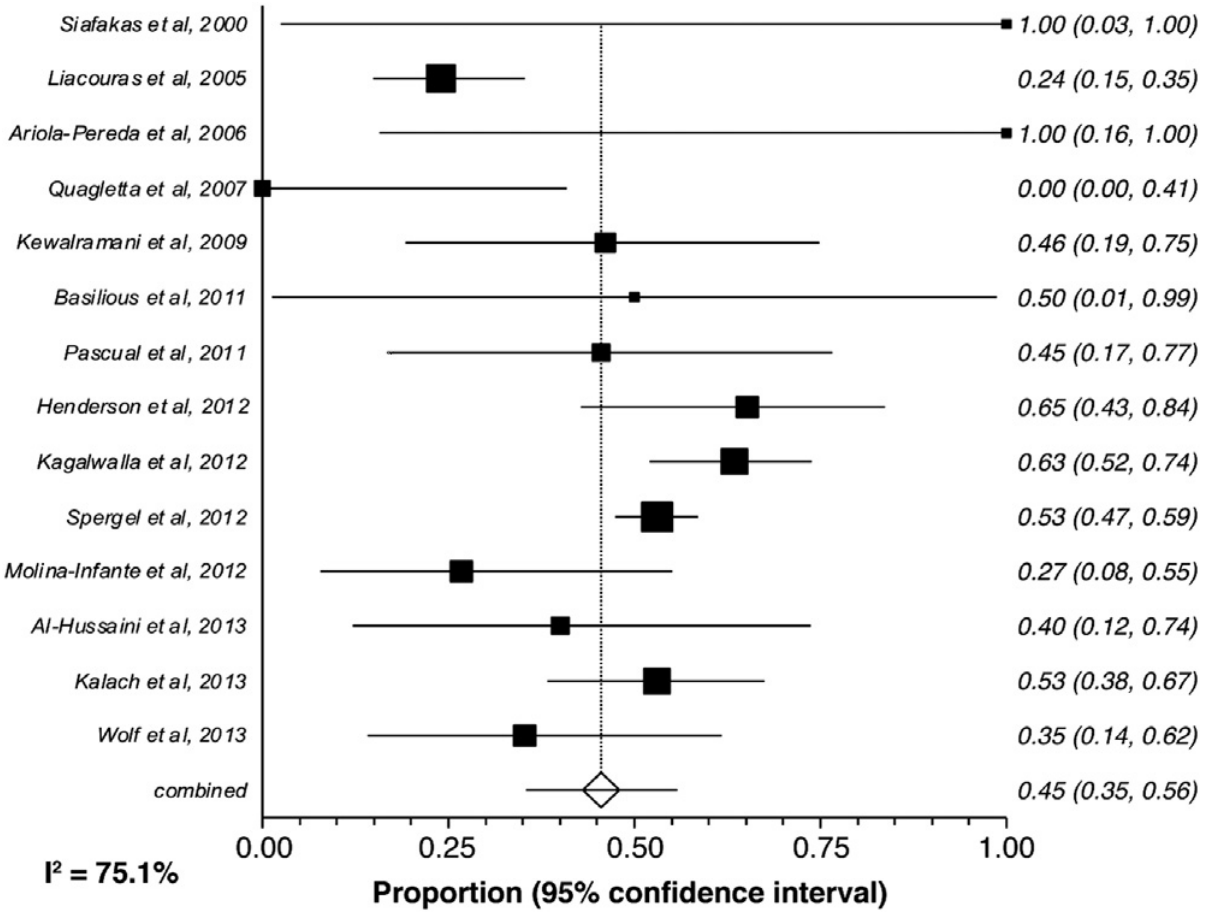
APT-Directed Diets?

Food	Combined SPT and APT			
	PPV	NPV	Specificity	Sensitivity
Milk (n = 46)	**92.0%**	**40.9%**	63.9%	81.8%
Egg (n = 39)	**84.8%**	**87.5%**	86.7%	85.7%
Soy (n = 28)	**73.7%**	**92.9%**	87.5%	83.9%
Wheat (n = 26)	**76.5%**	**90.0%**	81.3%	87.1%
Corn (n = 26)	**63.4%**	**92.5%**	86.7%	76.6%
Beef (n = 23)	**85.2%**	**92.5%**	82.1%	93.9%
Chicken (n = 15)	**62.5%**	**98.6%**	93.8%	88.5%
Apple (n=15)	**57.1%**	**97.7%**	66.7%	96.6%
Rice (n = 14)	**60.9%**	**100.0%**	100.0%	88.8%
Potato (n = 11)	**61.1%**	**97.4%**	84.6%	91.4%

Spergel JM. Eosinophilic esophagitis in adults and children: evidence for a food allergy component in many patients. Curr Opin Allergy Clin Immunol 2007; 7: 274-8.

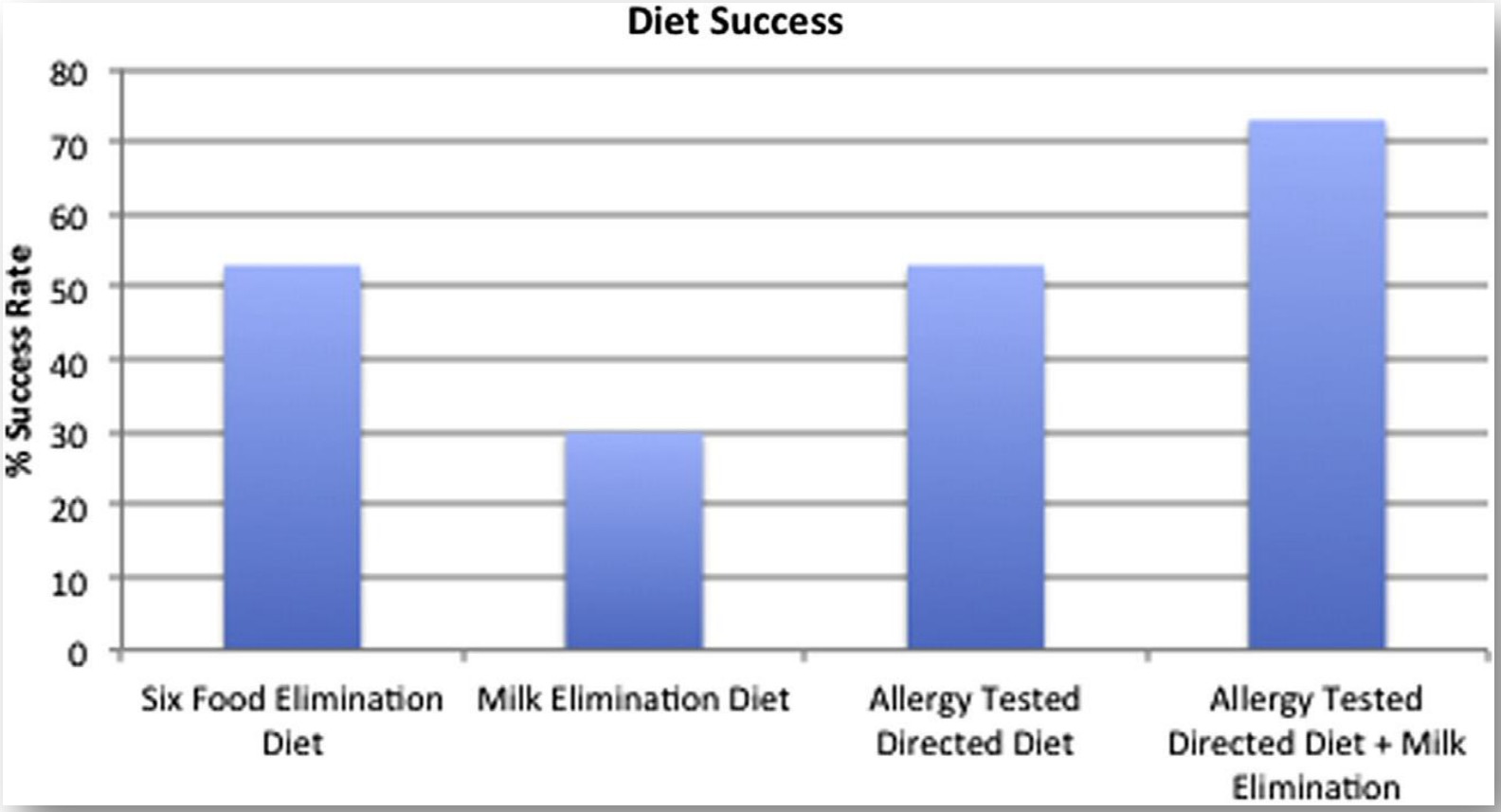
Allergy testing–directed food elimination and EoE

High efficacy rates reported by Spergel and colleagues using a combination of SPTs and atopy patch tests not universally reproduced by other authors.



Arias A. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. Gastroenterology 2014;146:1639–1648

Success rate of various diet therapies in patients with EoE



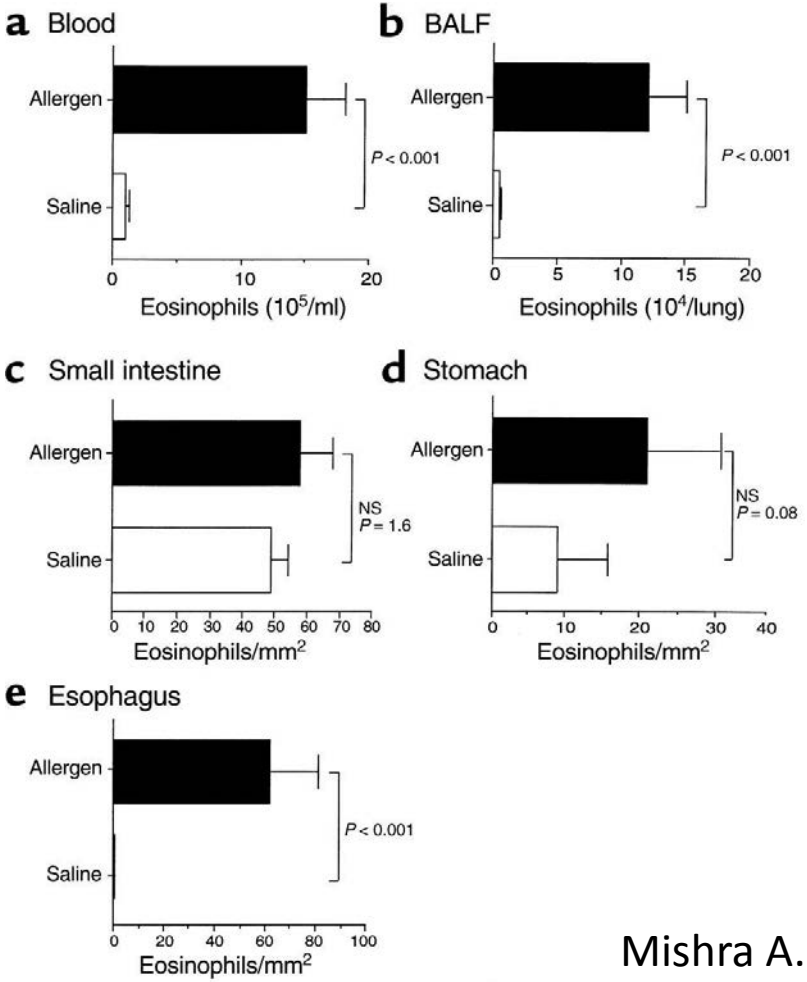
Spergel JM. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. J Allergy Clin Immunol 2012;130. 461e7 e5.

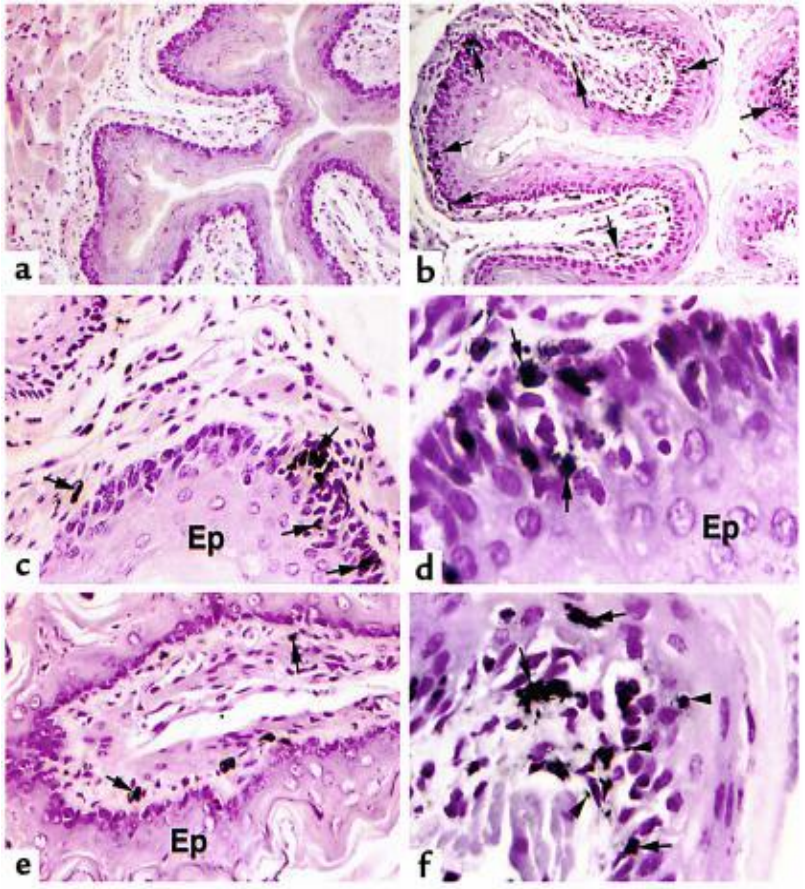
1. Allergie gastrointestinali ed EGID
2. Meccanismi delle EGID
3. Sintomi delle EGID
4. EGID, perché è una malattia allergica
5. EGID, quando è un'allergia alimentare
6. EGID ed allergia ambientale
7. Conclusioni

EoE is an atopic disease.

Aeroallergens

1. Esophageal eosinophilia develops in mice following intranasal exposure to Aspergillus fumigatus





Mishra A. An etiological role for aeroallergens and eosinophils in experimental esophagitis. J Clin Invest 2001;107:83-90

EoE is an atopic disease.

Aeroallergens

1. Esophageal eosinophilia develops in mice following intranasal exposure to Aspergillus fumigatus
2. 26% of patients with allergic rhinitis without GERD had esophageal eosinophilia when biopsied during a time of active allergy symptoms
3. Seasonality of EoE symptoms
4. Decreased EoE diagnosis in the winter and increased diagnosis in the spring, summer, and fall.
5. EoE after starting SLIT for pollen and grass allergies
6. Resolution of esophageal eosinophilia after 2 year SCIT to dust mite

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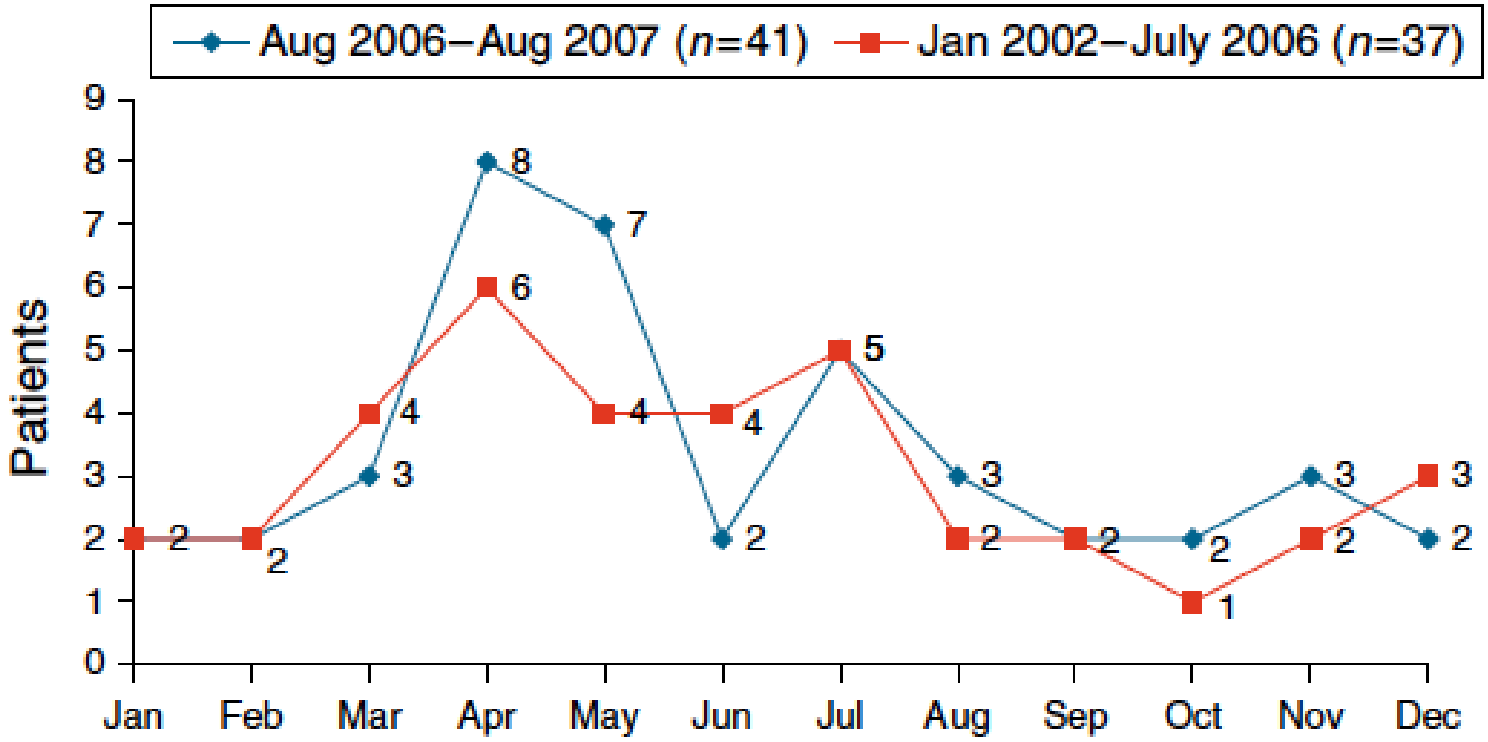
EoE is an atopic disease.

Seasonality



Almansa C. Seasonal distribution in newly diagnosed cases of eosinophilic esophagitis in adults. Am J Gastroenterol 2009;104:828-33.

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7. Conclusioni

Diets & EGID: conclusions

- Food allergy is there
- EoE is not totally food-driven
- Poor success rate of diet based completely on IgE testing
- IgE-depleted mice may develop food bolus impactions EoE
- anti-IgE therapy has no effect on esophageal eosinophilia
- Oral desensitization to foods is not effective for EoE
- Patients on OIT may develop EoE once the food is reintroduced in the diet

→ IgE is not important in the pathogenesis of EoE
→ IgE mediated food allergy and EoE have a different mechanism
→ IgE testing (SPT or sIgE testing) is not able to identify EoE specific food allergies.

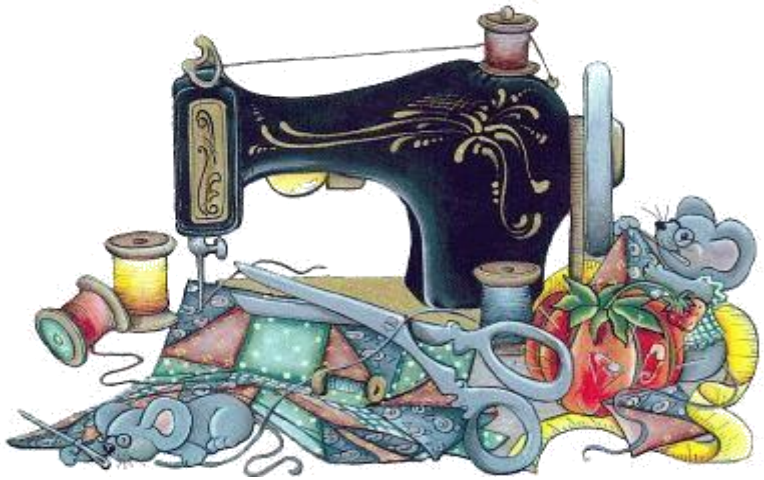
Spergel JM. An allergist's perspective to the evaluation of Eosinophilic Esophagitis. Best Pract Res Clin Gastroenterol 2015;29:771-81

The best strategy in 2015:

MULTIDISCIPLINARY APPROACH

QUALITY OF LIFE

"TAILORED TREATMENT"



Combined treatments

APLV@OPBG.NET