Eosinophils and Food Allergy

Richard L. Wasserman, MD, PhD
Medical Director of Pediatric Allergy and Immunology

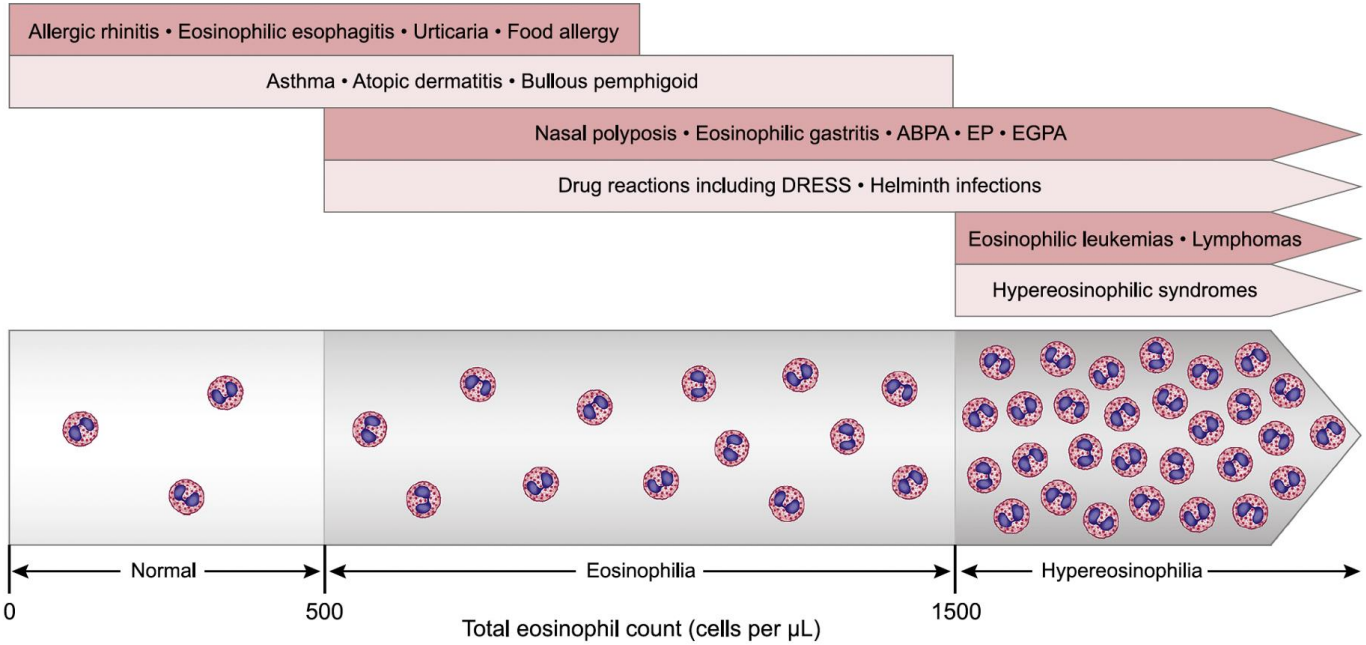
Medical City Children's Hospital℠

Learning Objectives

- Upon completion of this learning activity, participants should be able to:
  - Discuss eosinophil receptors and products
  - Explain the role of eosinophils in food-driven atopic diatheses
  - Counsel patients and families about treatments for food-driven allergic disorders

Medical City Children's Hospital

Disease-Associated Eosinophilia

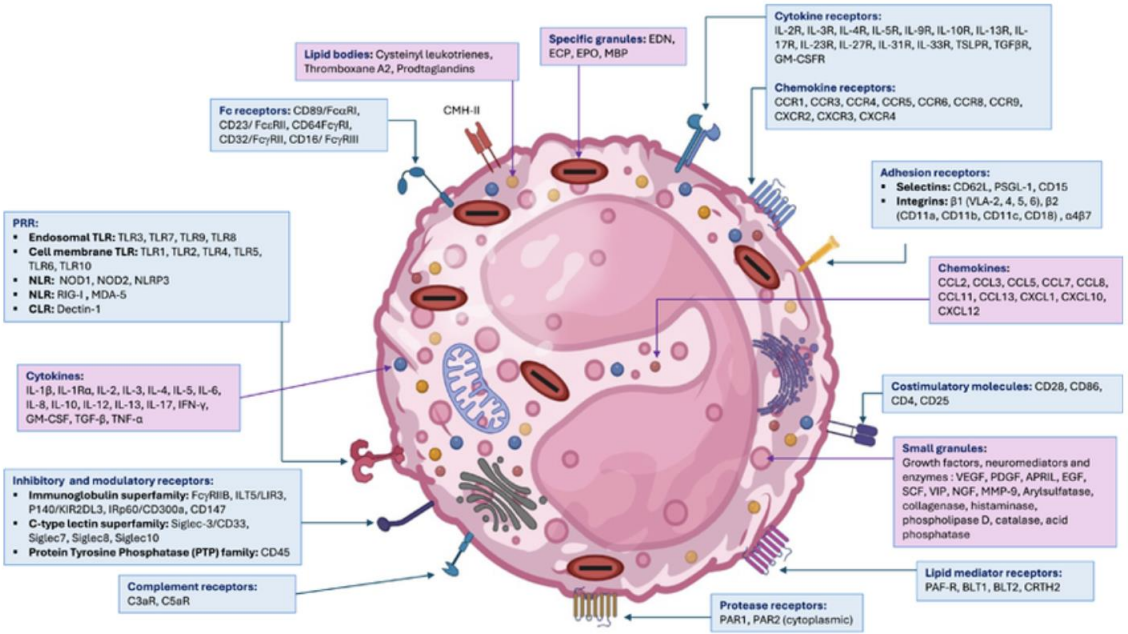


Typical level of blood eosinophils at presentation

Bochner BS, Ann Allergy Asthma Immunol 121:150-155

Medical City Children's Hospital

Eosinophil Ultrastructure



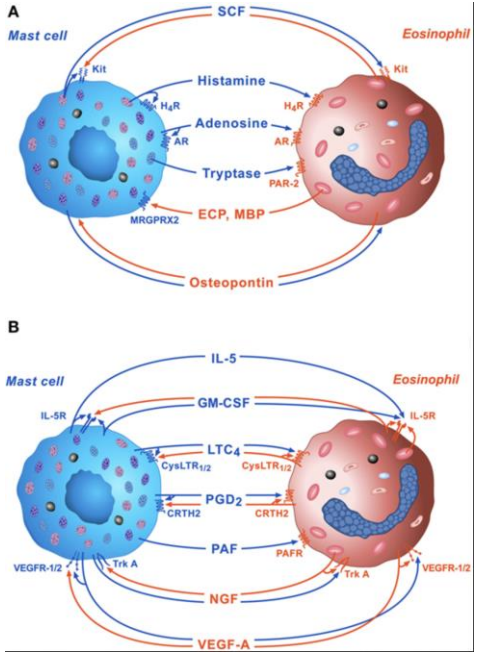
Receptor Families

- Adhesion
- Chemokine
- Complement
- Cytokine
- Growth factor
- Ig Fc
- Inhibitory and modulatory
- Lipid mediators
- Pattern recognition
- Protease

Sahli W, et al. Clinical and Translational Allergy. 2025;15.10.1002/clt2.70050.

Medical City Children's Hospital

Schematic Representation of Some of the Bidirectional Interactions Between Mast Cells and eosinophils



(A) Preformed MC mediators such as stem cell factor (SCF), histamine, adenosine, and tryptase can exert paracrine and/or autocrine functions through the engagement of Kit, H_4R, adenosine receptors, and protease-activated receptor 2 (PAR-2), respectively. **EO** cationic proteins [eosinophil cationic protein (ECP) and MBP], released by activated **EOs** modulate mast cell functions through the activation of MRGPRX2 on their surface. Osteopontin released by both activated **EOs** and **MCs** exert paracrine and autocrine effects.

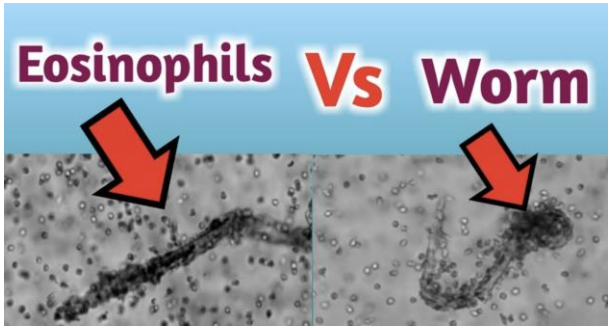
***(B) de novo* synthesized MC** mediators such as IL-5, granulocyte-macrophage colony-stimulating factor (GM-CSF), LTC_4, PGD_2, platelet-activating factor (PFA), nerve growth factor (NGF), and VEGF-A, released by activated MCs, can modulate eosinophil functions *via* the activation of IL-5R, $CysLTR_{1/2}$, CRTH2, platelet-activating factor receptor (PAFR), TrkA, and VEGF-R1/2, respectively, on their surface. IL-5, GM-CSF, LTC_4, PGD_2, NGF, and VEGF-A can also exert paracrine and/or autocrine effects.

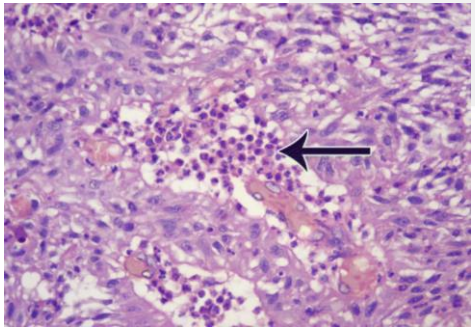
Galdiero, et al. https://doi.org/10.3389/fmed.2017.00103

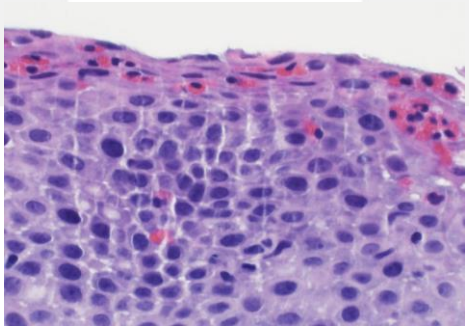
Medical City Children's Hospital

Eosinophil Functions

- Host defense
  - fighting parasitic infections, particularly helminth (worm) infections
- Tumor surveillance with the release of pro-inflammatory cytokines and lipid mediators
- Effector cells in atopic diatheses



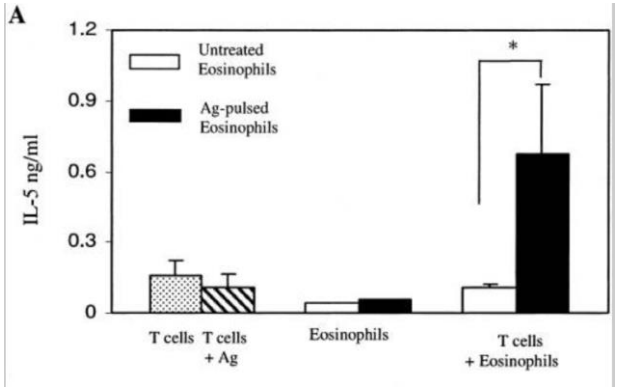


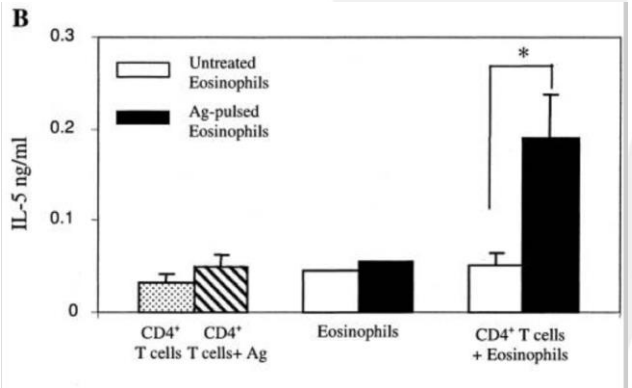


Eosinophil Functions

- Innate immune response
  - Eosinophils express pattern recognition receptors
  - Eosinohpils may be activated by large and small microbes as well as extracellular enzymes and small molecules
  - Effector cells
- Adaptive immune response
  - Antigen presentation
  - Th2 driven effector cell
  - Recruited by T cells
  - Recruits T cells
  - IgE receptors
- Inflammatory response
  - Upon activation, eosinophils release granule contents that can cause tissue damage
  - Maintain tissue homeostasis and repair
  - Fibrosis

Antigen Pulsed Eosinophils Support IL-5 Production by Primed T Cells and CD 4 T Cells

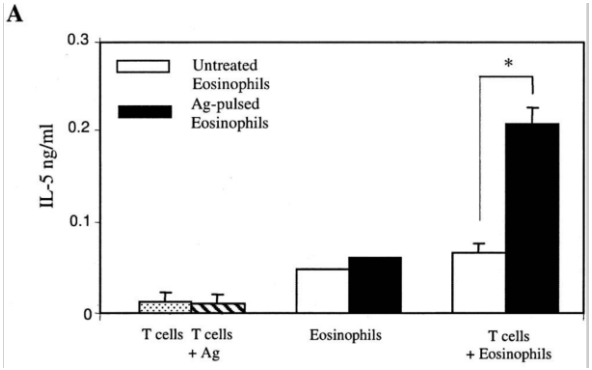


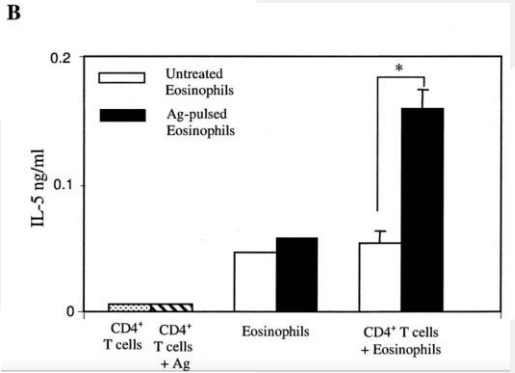


Padigel UM, et al Infect Immun. 2006 Jun;74(6):3232-8. doi: 10.1128/IAI.02067-05. PMID: 16714550.

Medical City Children's Hospital

Antigen Pulsed Eosinophils Support IL-5 Production by Antigen-Naive T Cells and CD 4 T Cells

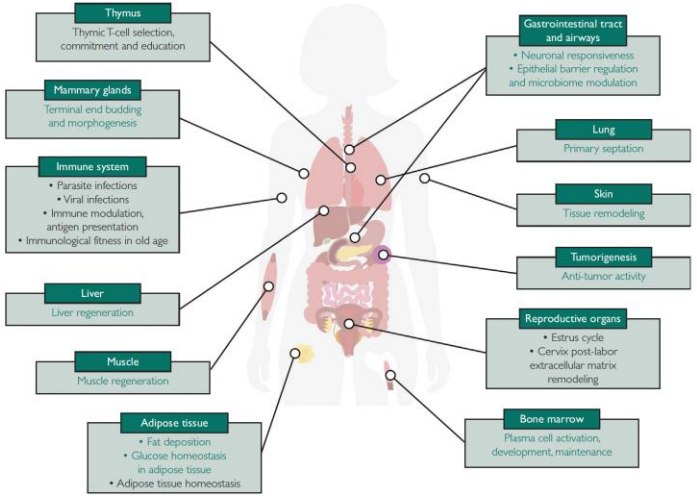




Padigel UM, et al Infect Immun. 2006 Jun;74(6):3232-8. doi: 10.1128/IAI.02067-05. PMID: 16714550

Medical City Children's Hospital

Eosinophils in Health and Disease



Resident In the gut but not esophagus - eosinophils reside in the lung, liver, kidney, skin, heart, spleen, lymph nodes, thymus, adipose tissue, mammary glands, digestive tract, and uterus

- Can function as antigen presenting cells
- Immunoregulatory capacity
  - Cross talk with CD4 T cells, mast cells
  - Autocrine and paracrine activitiy
  - Release proinflammatory cytokines
  - Promote Th2 – may precede lymphocytes and attract them
- Granules
  - Enzymatically active proteins that are defensive (helminths) and pathologic to tissues
  - Lipid mediators, leukotrienes
- Granule products are detectable in tissues when no eosinophils are seen

Weschler M, et al. Mayo Clin Proc. 2021;96:2694-2707 https://doi.org/10.1016/j.mayocp.2021.04.025

Activation and Recruitment

- Eosinophils are recruited to inflammatory sites by chemokines like CCL11 (eotaxin) and stimulated by cytokines such as IL-5, IL-25, and IL-33
- Activation triggers the release of granular contents (degranulation) and the secretion of additional mediators, which can amplify inflammation
- Eosinophils can be found in specific subsets, with different phenotypes potentially playing different roles in inflammation, as seen in allergic lung inflammation

Food Allergy Definition

- **An adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food**
- IgE mediated
  - Following sensitization, food-specific IgE antibodies mast cells
  - Encounter with the allergenic food triggers mast cell activation and degranulation
  - Clinical symptoms result from the action of released mast cell products
- Non-IgE mediated
  - Following T cell sensitization, tissue-resident, activated, food-specific T cells recruit effector T cells and other inflammatory cells
  - Food Protein-Induced Enterocolitis Syndrome (FPIES)
  - Food Protein-Induced Allergic Proctocolitis (FPIAP)
  - Eosinophilic gastrointestinal disorders (EGID)
- Mixed IgE and non-IgE mediated food allergy

Boyce JA, et al. J Allergy Clin Immunol 2010;126:S1–58

Eosinophils and IgE Mediated Food Allergy

- Antigen presenting cell or co-stimulator[1]
  - Depleting eosinophils in neonatal mice prior to peanut sensitization blocks anaphylaxis in reconstituted animals
  - Depleting eosinophils after peanut sensitization does not prevent anaphylaxis
- Neither anti-IL5 nor anti-IL5 receptor antibodies prevent food driven anaphylaxis[2]
- While anti-IL4 receptor antibody may diminish or prevent anaphylaxis in some individuals, the mechanism is uncertain[2]
- Eosinophils appear to be indirect targets of monoclonal antibody and small molecule treatments for IgE mediated food allergy

1. Gao H, et al. J Immunol. 2025;214:582-594. doi: 10.1093/jimmun/vkae044. PMID: 40073088
2. Chen M, et al. J Food Allergy. 2020;2:86-90. doi: 10.2500/jfa.2020.2.200004. PMID: 39022154

Noah, A 7-year-old with food allergies and comorbid asthma

Food Allergy History

- **Peanut** allergy since infancy (hives on first exposure; IgE positive)
- Strict avoidance of peanut; tolerates tree nuts
- Severe reaction to **sesame/tahini** 4 months ago → ED care with IM epinephrine, O_2, albuterol

Asthma History

- Onset age 4; **suboptimal control**
- ACT = **17**; albuterol ~3 × /week
- 2 prednisone bursts/year
- On budesonide/formoterol 80/4.5, 2 puffs BID

Atopic Comorbidities

- Chronic itchy/runny nose; partial control on loratadine + fluticasone
- Infantile eczema, mild recurrence

Medical City Children's Hospital

Noah, A 7-year-old with food allergies and comorbid asthma

Old Allergy Records (3 months ago)

- Total IgE: **1,000 IU/mL**
- Skin tests: >10 mm to **peanut**, **sesame**, HDM, cat, dog; negative to tree nuts
- Serum IgE: peanut **30 IU/mL**, sesame **20 IU/mL**
- Spirometry: normal
- FeNO: **45 ppb**
- Blood eosinophils: **600**
- C-ACT: **17**

Environment

- Lives with parents; dog + cat in home
- Bedroom HDM control; HEPA filter; pet restriction

Medical City Children's Hospital

Noah, A 7-year-old with food allergies and comorbid asthma

Medications

- Epinephrine autoinjector 0.15 mg
- Budesonide/formoterol BID
- Albuterol PRN
- Loratadine; fluticasone nasal spray

Exam

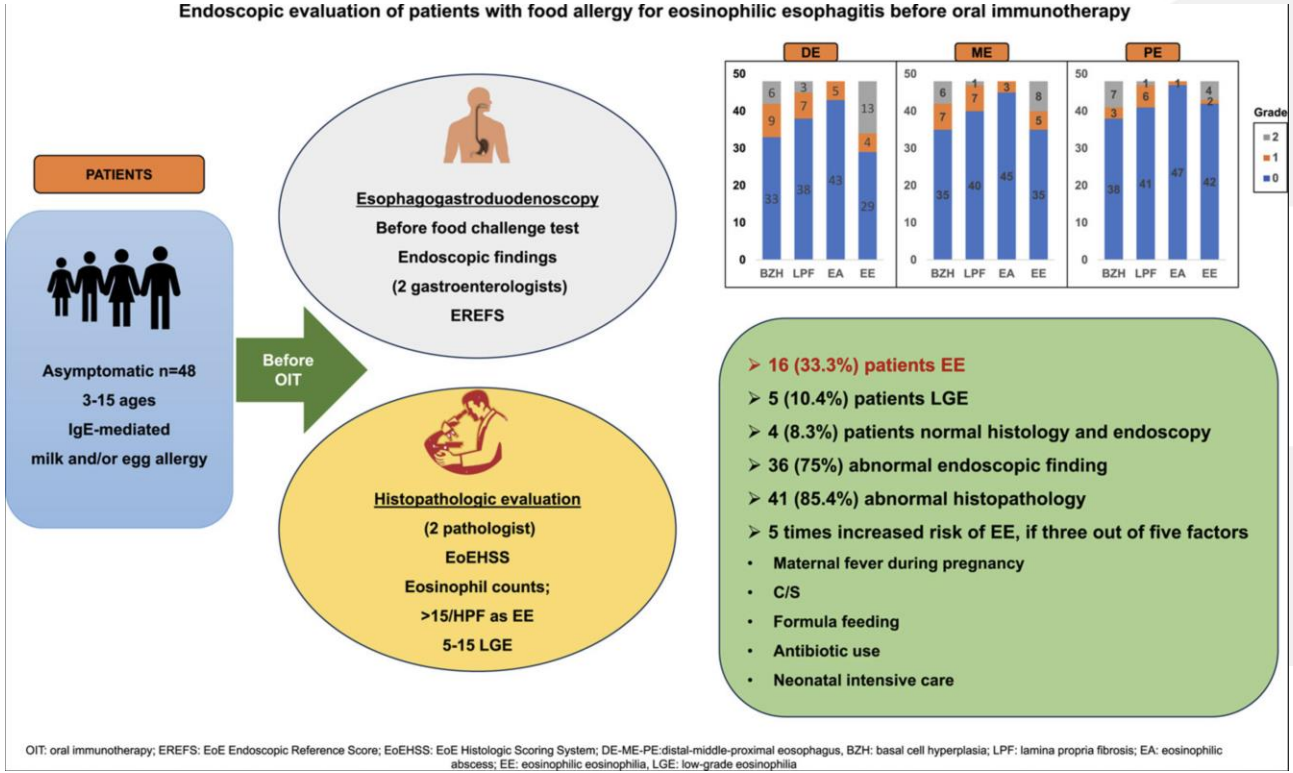
- Vitals normal; clear rhinorrhea; Dennie–Morgan lines; Flexural erythema; lungs clear

Testing Today

- Spirometry: normal
- FeNO: **45 ppb**
- ACT: **17**

Medical City Children's Hospital

Unrecognized EoE in Food Allergy



Senol DH, et al. J Allergy Clin Immunol Pract. 2025;13;3346-3354. doi: 10.1016/j.jaip.2025.08.029. Epub 2025 Sep 8.

Medical City Children's Hospital

Eosinophilic Esophagitis Diagnosis

- History suggestive of esophageal dysfunction
- Histopathologic confirmation of ≥15 eosinophils/high power field
- Exclusion of other causes of esophageal eosinophilia
  - Infection
  - Crohn's Disease
  - Drug hypersensitivity

Medical City Children's Hospital

Eosinophilic Esophagitis History

- **Infants and toddlers**
  - Failure to thrive may be the main manifestation
- **School-age children**
  - Vomiting
  - Abdominal pain
  - Slow eating
  - Food aversion are
- **Older children**
  - Dysphagia and regurgitation
  - By adolescence there may have been food impaction
- **Adults**
  - Dysphagia
  - Food impaction
  - Heartburn
- Older children, adolescents, and adults may develop **compensatory eating behaviors**
  - Overchewing food
  - Selectively avoiding foods

Gabryszewski SJ, et al. J Allergy Clin Immunol. 2024;153:1533-1535. doi: 10.1016/j.jaci.2024.03.015.

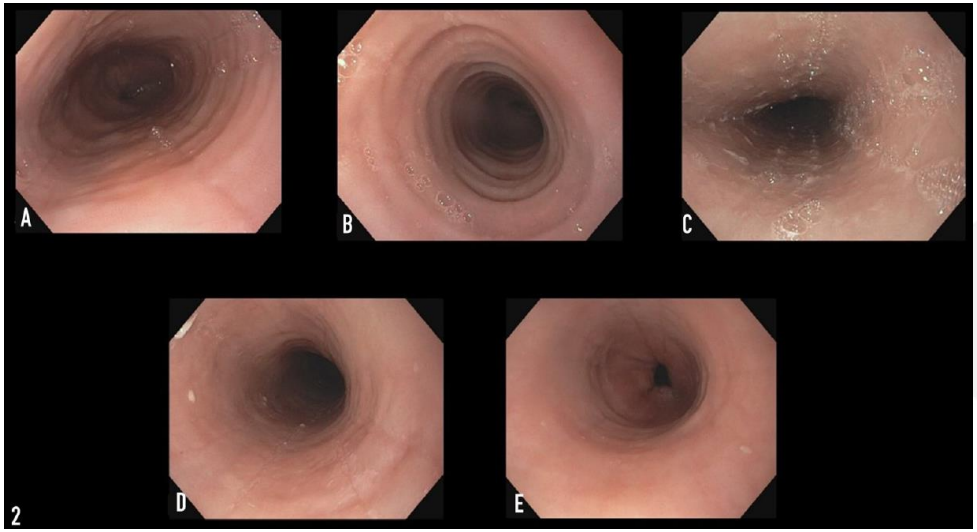
Medical City Children's Hospital

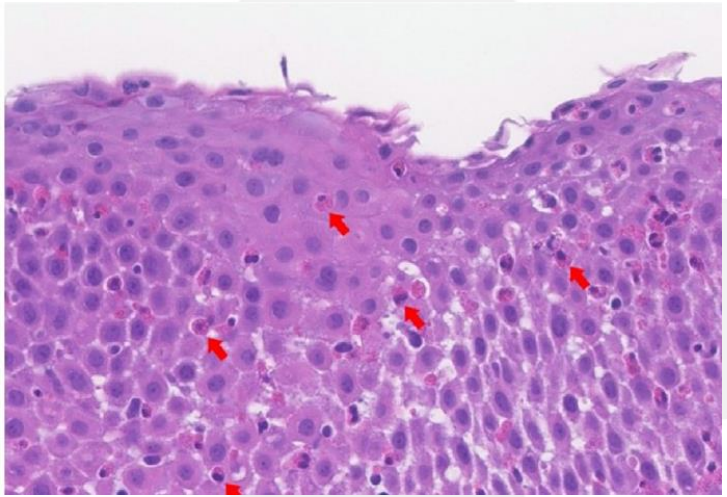
Laboratory Confirmation of Eosinophilic Esophagitis

- EGD with biopsies is the gold standard test
- Developing technologies
  - Less invasive sampling: cytosponge, eosphageal string test, transnasal endoscopy
  - Cellular blood-based biomarkers: eosinophil subsets, non-eosinophil circulating leukocytes
  - Non-cellular circulating biomarkers: eosinophil degranulation proteins, cytokines, chemokines
  - Oral cavity and saliva biomarkers: mRNA, microbiome
  - Advanced imaging: optical coherence tomography
  - Functional assessment: endoscopic functional lumen imaging probe (EndoFLIP), High-resolution manometry (HRM)
  - Genetic testing: EoE transcriptome
- AI-based multi-marker analysis

Noble SL, et al. Front Med (Lausanne). 2025;12:1607306. doi: 10.3389/fmed.2025.1607306.
Al Abdulqader AK. Eur J Med Res. 2025 Oct 1;30(1):924. doi: 10.1186/s40001-025-02989-3.

Endoscopic and Histologic Findings in EoE

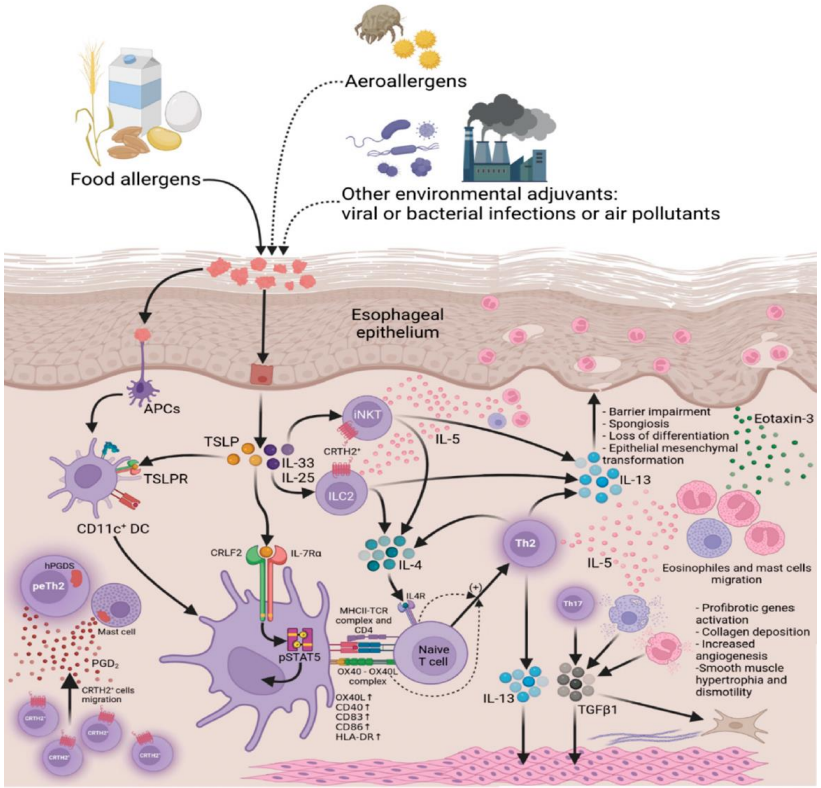




Goyat R, et al. Mayo Clin Proc. 2024; 99:640-648

Medical City Children's Hospital

Pathogenesis of Eosinophilic Esophagitis



- Eosinophils are not resident in the normal esophagus and, therefore do not initiate the allergic response to food
- Eosinophils are recruited as a homeostatic response to epithelial barrier disruption
- When type 2 inflammation persists, eosinophils promote inflammation
- Activated eosinophils increase angiogenesis, collagen deposition, and smooth muscle hypertrophy
- Fibrosis leading to stenosis

Zhernov YV, et al. Int. J. Mol. Sci. 2021, 22, 13183. https://doi.org/10.3390/ijms222413183
Doyle AD, et al. Front Immun 2020 doi:10.3389fimmun.2020.603295

Medical City Children's Hospital

Comparison of EoE in Adults and Children

Variable	Similarities	Differences
Medical history	● History of atopy ● Family history of disease	● Possible increased role for early-life environmental factors in children
Symptoms	—	● Include failure to thrive, vomiting, abdominal pain in young children ● Include dysphagia, food impaction in adolescents and adults
Diagnosis	● Histologic detection of ≥15 eosinophils/hpf	—
Response to therapy	● Dietary elimination, PPIs, swallowed steroids, dupilumab are comparable in terms of effectiveness	—
Endoscopic/ histologic phenotypes	● Mixed inflammatory-fibrostenotic phenotype can be seen in children and adults	● Inflammatory phenotype (exudates, furrows, edema) are more common in children ● Fibrostenotic phenotype (rings, strictures) are more common in adults
Molecular endotypes	● Same molecular endotypes can be seen in children and adults ● Aberrant allergic (type 1 and type 2) inflammation and epithelial barrier dysfunction	● *CAPN14* variants are more common in very-early-onset disease ● Possible age-specific differences (eg, increased T_H1 cell counts in adults vs in children)

Gabryszewski SJ, et al. J Allergy Clin Immunol. 2024;153:1533-1535. doi: 10.1016/j.jaci.2024.03.015.

Eosinophilic Esophagitis Treatment

- Empiric elimination diets
  - Elemental diet
  - 6-food elimination diet – milk, soy, egg, wheat, peanut/tree nuts, fish/shellfish
  - Single food elimination diet – milk
- Proton pump inhibitors
- Topical corticosteroids
  - Budesonide slurry
  - Fluticasone MDI
- Systemic corticosteroids
- Dupilumab

- Developing treatments
  - Benralizumab
  - Cendakimab
  - Tezepelumab
  - VOQUEZNA
- Therapeutic failures – histologic but not clinical improvement
  - Mepolizumab
  - Reslizumab
  - Lirentelimab

Medical City Children's Hospital

Review article

Triggers for eosinophilic esophagitis (EoE): The intersection of food allergy and EoE

Caitlin M. Burk, MD, and Wayne G. Shreffler, MD, PhD *Boston, Mass*

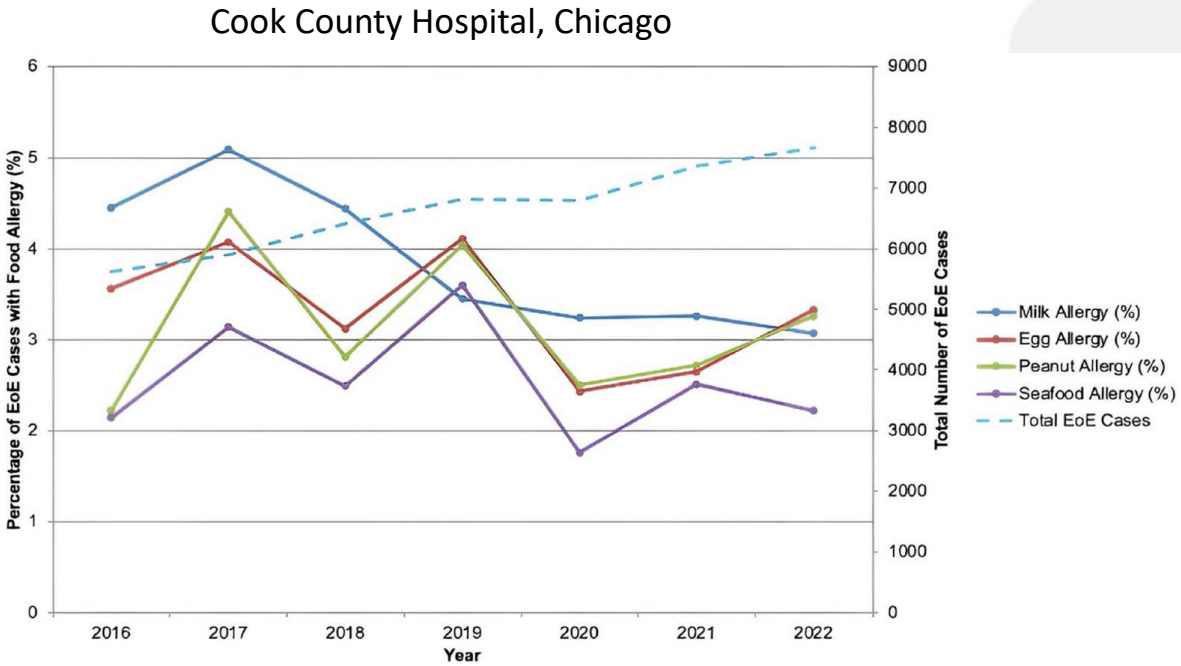
TABLE I. Overlap and differences between IgE-FA and EoE

Characteristic	IgE-FA	EoE
Immediate symptoms	Characteristic	Very uncommonly (FIRE)
Food exposure	Episodic	Chronic
Food trigger identification	Serum IgE, SPT, basophil activation test, food challenge	Empiric elimination
Most common food triggers	Similar	Similar
Monitoring food response	Serial tests as described above, food challenge to test outgrowth	Serial endoscopies to assess response to elimination
Food-related therapy	Avoidance or OIT	Avoidance only
Associated food-specific antibodies	IgE	IgG_4
Food-specific T-cell response	T_H2, Tfh13, T_H2-deviated Treg	T_H2, peT_H2

Tfh13, T follicular helper cell 13.

Burk C and Shreffler WG. JACI 2024; 153:1500-1509. https://doi.org/10.1016/j.jaci.2024.04.010

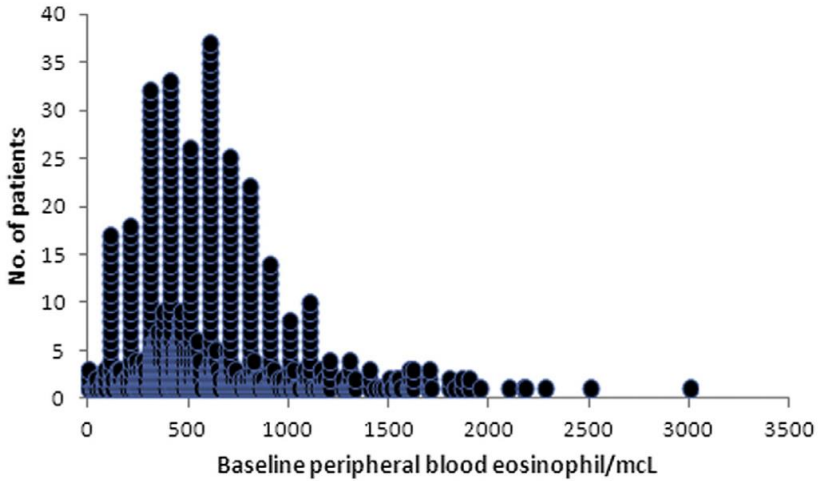
Trends in Food Allergy Prevalence Among EoE Cases (2016-2022)

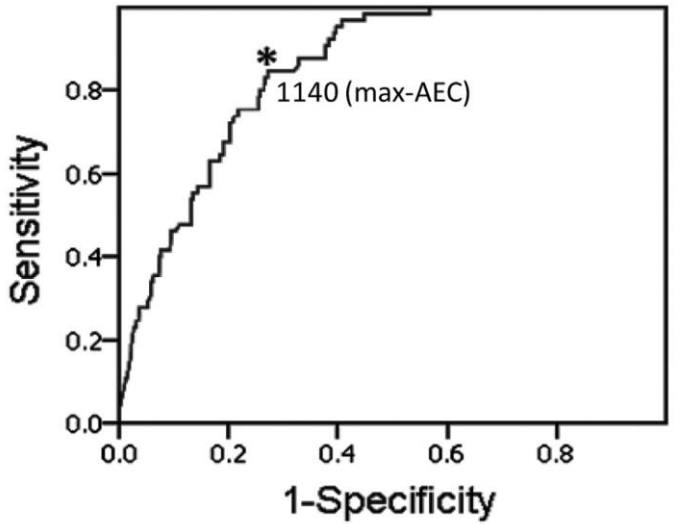


Shah M, et al. PLOS One 2025; https://doi.org/10.1371/journal.pone.00335078

Medical City Children's Hospital

Baseline AEC Predicts OITIGER* (ELORS**) During OIT





*OIT-induced gastrointestinal and eosinophilic responses
**Eosinophilic esophagitis-like OIT-related syndrome

Goldberg MR, et al. JACI 2017; 139:1388-1390

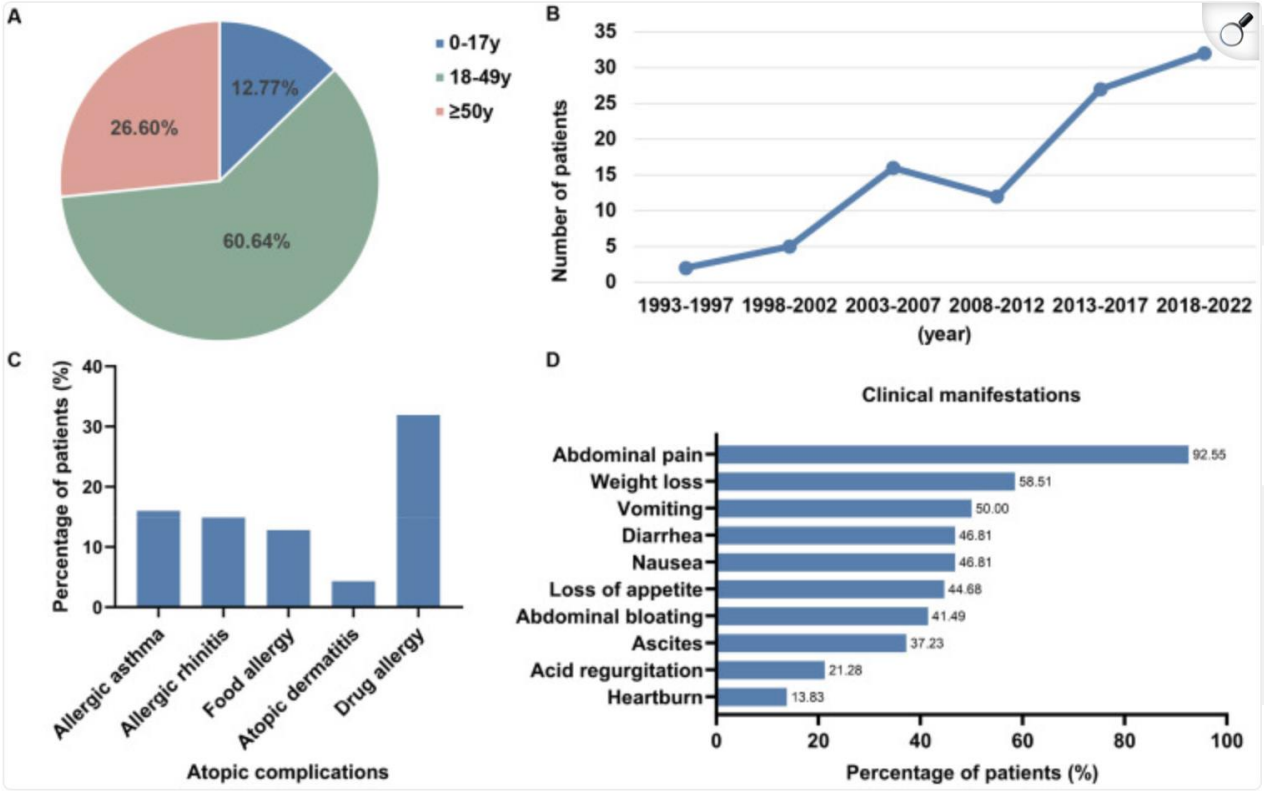
Medical City Children's Hospital

Non-Esophageal Eosinophilic Gastrointestinal Disease

	Eosinophilic Gastritis	Eosinophilic Gastroenteritis	Eosinophilic Colitis
Age of Prevalence	increases with age, 7th decade	less than 5 years	similar for all ages
Gender	Female > male	Female > male	Female > male
Symptoms	epigastric pain, dyspepsia, vomiting, early satiety, oral aversion, failure to gain weight	abdominal pain, dyspepsia, vomiting, hematemesis, bloating, diarrhea	abdominal pain, diarrhea and/or constipation, lower gastrointestinal bleeding, tenesmus
Mucosal eosinophilia	malabsorption weight loss, ulcerations,	malabsorption, anemia, protein-losing enteropathy	protein-losing enteropathy, bleeding
Muscularis mucosa eosinophilia	gastric outlet obstruction	intussusception, dysmotility	intussusception, dysmotility
Serosal eosinophilia	bloating	bloating, ascites	ascites, edema
Differential Diagnosis	peptic ulcer disease, infection, drug injury, toxins, neoplasm, vasculitis, hypereosinophilic syndrome, Langerhan cell histiocytosis		food protein-induced enterocolitis, allergic proctocolitis, inflammatory bowel disease

Medical City Children's Hospital

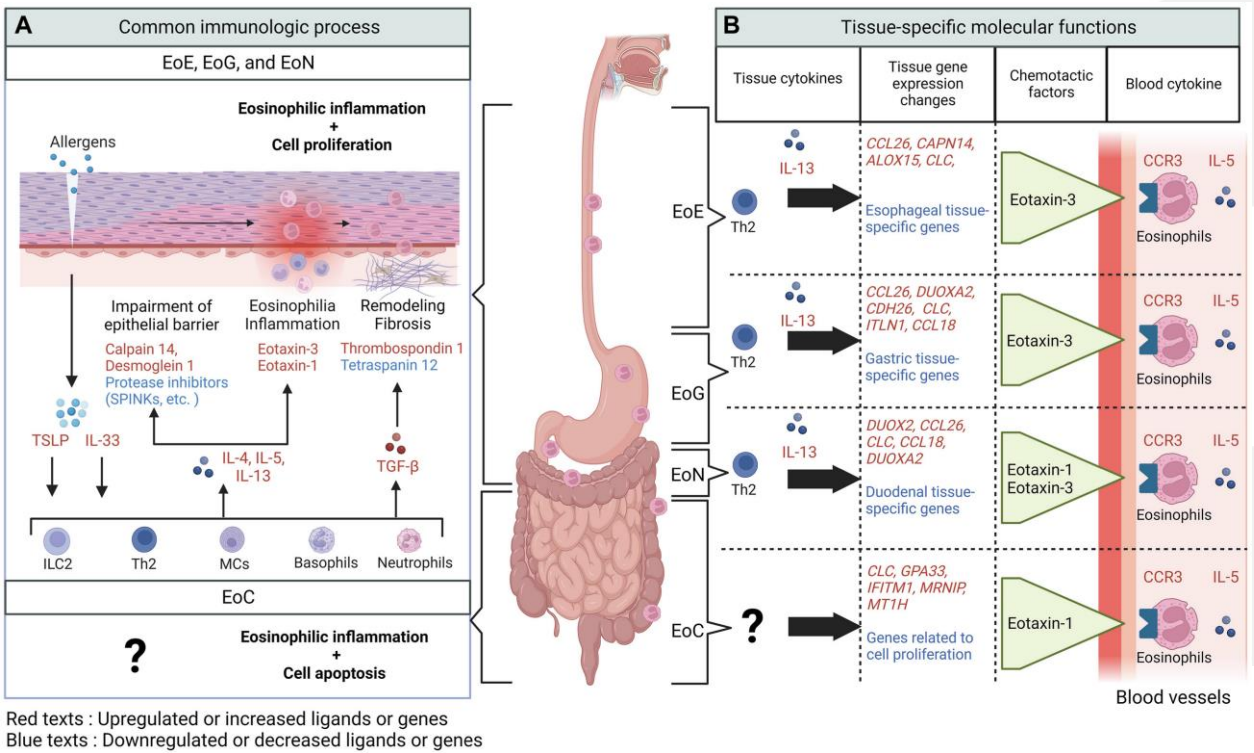
Non-Esophageal Eosinophilic Gastrointestinal Disease (Peking)



Du Z, et al. J Asthma Allergy. 2025;18:757-768. doi: 10.2147/JAA.S510375.

Medical City Children's Hospital

Common and Disparate Features Among EGIDs



Red texts : Upregulated or increased ligands or genes
Blue texts : Downregulated or decreased ligands or genes

Shoda T, et al. J Allergy Clin Immunol. 2024;153:1472-1484. doi: 10.1016/j.jaci.2024.03.013.

Medical City Children's Hospital

Non-Esophageal Eosinophilic Gastrointestinal Disease Treatment

- Low prevalence (<10 per patient year) limits treatment study opportunities
- Food avoidance
  - SPT, sIgE, and patch testing are not informative
  - 6-food elimination diet versus animal milk elimination
  - Elemental diet
- Corticosteroids
  - Systemic
  - Proximal EGIDs – budesonide capsules opened +/- crushed
  - Distal EGIDs – enteric coated budesonide capsules
- Biologics
  - Anti-IL-5 monoclonals induce histologic but not symptomatic remission
  - Dupilumab may induce symptomatic remission in some patients (studies ongoing)

Shoda T, et al. J Allergy Clin Immunol. 2024;153:1472-1484. doi: 10.1016/j.jaci.2024.03.013.

Food Protein-Induced Allergic Proctocolitis

- Clinical Presentation
  - Days of birth to 6 months of age (median ~ 2 months)
  - Cardinal symptom - Blood in stool
  - Additional symptoms - Mucus in stools, diarrhea, painful flatus, anal excoriation
- Implicated food proteins
  - Breast-fed infants: CM, soy, egg, corn and wheat, meat, fish, apple, carrot, nuts, and sesame
  - Formula-fed infants: CM and soy
- Work-up/Investigations are generally not required
  - If the diagnosis is unclear, consider fecal occult blood test, WBC
  - Allergy testing is not recommended; endoscopy and biopsy generally not indicated
- Laboratory abnormalities
  - Mild anemia, hypalbuminemia (rare), eosinophilia
  - Histology - Mild, focal colitis, **eosinophilic infiltration**, lymphonodular hyperplasia

Cook VE. Allergy Asthma Clin Immunol 2024;20 (S3), 70. https://doi.org/10.1186/s13223-024-00933-4

Food Protein-Induced Allergic Proctocolitis Management

- Avoidance of trigger food (from maternal diet if breast-feeding)
- Trial of extensively hydrolyzed or amino acid-based formula in either breastfed or formula-fed infants
- Natural history is resolution of symptoms by age 1 year

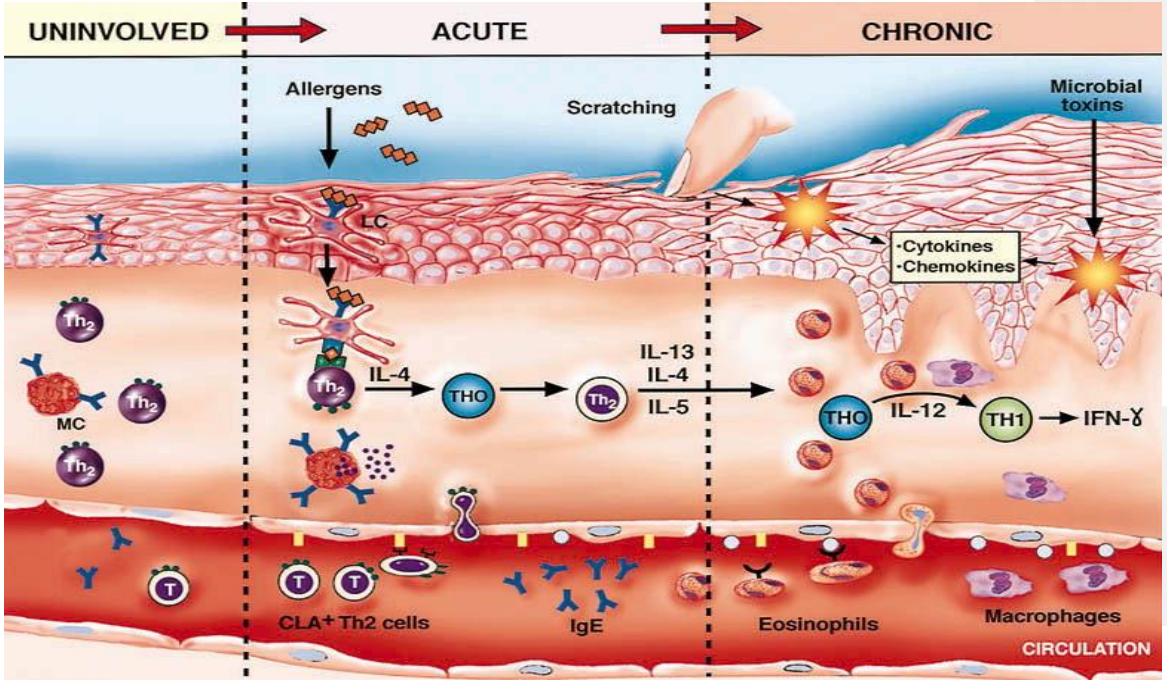
Cook VE. Allergy Asthma Clin Immunol 20 (Suppl 3), 70 (2024). https://doi.org/10.1186/s13223-024-00933-4

Medical City Children's Hospital

Atopic Dermatitis, Eosinophils, and Food Allergy

- Eosinophils are residents of normal skin
- Eosinophils are increased in the lesional skin of atopic dermatitis patients
- Eosinophils may play a role as antigen presenting cells in atopic dermatitis
- Eosinophil products recruit and activate other antigen presenting cells
- Eosinophil degranulation products are detectable when intact eosinophils are not
- For most patients with atopic dermatitis and food allergy, food allergy is a consequence, not a cause of atopic dermatitis

Cellular Pathogenesis of Atopic Dermatitis



Leung DYM. JACI. 2000,105:860 - 876

Medical City Children's Hospital

DBPCFC Results in 272 Children with Atopic Dermatitis

Reaction	Verum, No. (%)	Placebo, No. (%)	*P* value (McNemar test)
Immediate reactions (<2 hours after last dose)			
Exacerbation of AD only	2 (0.7)	1 (0.4)	
Only symptoms other than AD	110 (40.4)	25 (9.2)	<.01
Both exacerbation of AD and other symptoms	12 (4.4)	0	<.01
Intermediate reactions (2–6 hours after last dose)			
Exacerbation AD after immediate reaction	6 (2.2)	6 (2.2)	
Exacerbation AD without previous immediate reaction	2 (0.7)	3 (1.1)	
Late reactions (>6–48 hours after last dose)			
After immediate reaction	0 (0)	0	
No previous reaction	4 (1.5)	3 (1.1)	

Roerdink EM, et al. Ann Allergy Asthma Immunol. 2016;116:334-8. doi: 10.1016/j.anai.2016.01.022.

Eosinophilia Predicts Food Allergy in Atopic Dermatitis Patients

	High eosinophil count ≥5%	Normal eosinophil count <5%
Number of patients	136 (44.9%)	167 (55.1%)
Overall food allergy	70.8%	34.7%
IgE mediated (late eczematous)	20.0%	11.1%
Non-IgE mediated	70.8%	34.7%
Dust mite sensitization	37.5%	21.5%

Noh G, et al Allergy Asthma Proc. 2010; 31:e18-24. doi: 10.2500/aap.2010.31.3312.

Conclusions

- Eosinophil biology is complex and only partially understood
- Although eosinophils can function as antigen presenting cells, their primary role food allergy-related disorders is as an effector cell
- Eosinophils do not play a role in initiating the food allergy response that leads to eosinophilic esophagitis
- Targeted elimination of eosinophils treats neither IgE mediated food allergy nor eosinophilic esophagitis

Medical City Children's Hospital