

RESEARCH ARTICLE

Pediatric Eosinophilic Gastrointestinal Disease: Perspectives and Pearls from the Allergy Clinic

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Abstract

Eosinophilic gastrointestinal diseases (EGID) are not common, and are often diagnosed and followed in specialty clinics. As more children are diagnosed, the burden for care will also fall to primary care providers. To provide a perspective for these diseases, the classic clinical presentation and less common features and treatment plans identified in specialty clinic care is provided. Eosinophilic Gastrointestinal Diseases (EGID) are uncommon to rare gastrointestinal eosinophilic infiltrated clinicopathological conditions, ranging from the esophagus to the sigmoid colon. Outside of the near immediate newborn period, associated with milk or soy protein colitis (Food protein-induced allergic proctocolitis)¹ the presence of exaggerated gastrointestinal eosinophilia is clinically relevant and has long-term concerns. In this review the separate clinical EGID conditions will be briefly reviewed, with added clinical pearls, based on an extensive Pediatric Allergy-Immunology experience to assist with the early recognition and/or their on-going care in primary care clinics.

Eosinophilic Esophagitis (EoE)

Eosinophilic esophagitis is the most common EGID, and has undergone a recent consensus update² and a concise and clinically relevant

review.³ With or without a proton pump inhibitor being utilized prior to histological confirmation of esophageal eosinophilia, an expanded differential diagnosis was recently proposed and is featured in Table 1.²

Table 1

Conditions associated with esophageal eosinophilia

- Eosinophilic esophagitis
- Eosinophilic gastritis, gastroenteritis, or colitis with esophageal involvement
- Gastroesophageal reflux disease
- Achalasia and other disorders of esophageal dysmotility
- Hypereosinophilic syndrome
- Crohn's disease with esophageal involvement
- Infections (fungal, viral)
- Connective tissue disorders
- Hypermobility syndromes
- Autoimmune disorders and vasculitides
- Dermatologic conditions with esophageal involvement (i.e. pemphigus)
- Drug hypersensitivity reactions
- Pill esophagitis
- Graft vs host disease
- Mendelian disorders (Marfan Syndrome Type II, Hyper-IgE Syndrome, PTEN Hamartoma Tumor Syndrome, Netherton's Syndrome, Severe Atopy Metabolic Wasting Syndrome)

Gastrointestinal complaints with these co-features should promptly alert concern and appropriate referral. Treatment opportunities have been recently reviewed.³

EoE Pearls

- Females rarely get food or foreign body impaction.
- Esophageal impaction in a boy should be considered EoE until proven otherwise

- In asthmatics, the dose of inhaled steroid has no impact on EoE histology
- The esophageal compartment must be directly treated by swallowed steroids and/or food avoidance
- Food avoidance decisions are virtually never aided by allergy testing
- EoE may actually have a relatively short time to onset

- Discontinuation of successful therapy virtually always results in an exaggeration of symptoms and/or a return of esophageal eosinophilia
- A mixture of swallowed inhaled steroids and selected food avoidance can be successful; milk and (or) wheat avoidance is generally the best benefit
- Food avoidance only as therapy can work but requires high patient/family diligence and multiple endoscopies
- Refractory EoE may eventually be a target of asthma-approved biological modifiers
- EoE and Celiac disease may co-exist
- Eosinophilic esophagitis in children has had exceedingly low incidence of requirement for dilatation

Eosinophilic Gastritis (EG)

Isolated EG is a rare pediatric disease, with a prevalence of less than 1:10,000.^{4, 5} The available data suggests the disease has a minimal genetic signature with eosinophilic esophagitis.^{6, 7} It's co-presence with other allergic disease provides a basis of concern when concomitant gastrointestinal symptoms are present. In children, the clinical presentation often overlaps with EoE; including pain and vomiting.⁸ Unlike EoE, a protein losing enteropathy can exist, and edema might be the presenting complaint.⁸ A failure to thrive with anemia and eosinophilia might also be present.⁸ A gastric biopsy at the time of an Esophagogastroduodenoscopy (EGD) will be revealing. The normal number of eosinophils in gastric biopsies are less than

10/HPF.⁹ There are two forms, nodular and hemorrhagic, although therapy doesn't differ.⁷ Mast cells are also increased in all EGID locations, including gastric, but the identification of this cell requires a specialty stain.

Treatment for EG requires diligence and an individualized approach.^{10, 11} Food avoidance with deposition of swallowed corticosteroids can work, although controlled studies are not available. A low serum albumin can be a marker, and followed for clinical benefit of therapy.

EG Pearls

- A newer approach to the treatment EG is the use of enteral budesonide, open and crushed and swallowed
- Swallowed budesonide (slurry) may have a supplemental or direct EG benefit
- All initial endoscopies for EoE type symptoms require gastric biopsies for elimination of EG as a concomitant disease
- EG could appear on subsequent gastric biopsies in EoE patients, especially when the EoE is refractory
- Successful EoE therapy may "protect" against the development of EG

Eosinophilic enteritis (small bowel)

The duodenum and proximal jejunum (beyond the ligament of Treitz) are accessible via standard or specialized upper endoscopies. Eosinophilic involvement in these areas is exceedingly rare, with

eosinophilic number/HPF of greater than 30-50 being a histological abnormality.⁹ Isolated small bowel eosinophilia is a concern for inflammatory bowel disease; but the concomitant presence of EoE (or EG) and small bowel eosinophilia is almost certainly a multi-site EGID.⁸

The clinical presentation depends on age; including, failure to thrive, abdominal pain, nausea; hypo-proteinemia and peripheral eosinophilia.⁸ A high index of suspicion might carry the decision to do an EGD, but chronic abdominal issues in any allergic child should push the potential to proceed. Exceedingly rare, sole muscular involvement (obstruction) or serosal (ascites) can be the only presentation.

The terminal ileum is accessible via a colonoscopy. Isolated EGID of the ileum is rare; but may be accompanied by other sites. Eosinophilia > 50/HPF is highly suspicious.⁹ Bowel obstruction has been reported. Therapy can utilize enteric budesonide using a swallowed capsule technique.¹¹ Selected food avoidance may accompany swallowed steroids, or be added for sub-optimal response.

- The natural history for isolated eosinophilic enteritis is not known.
- Protein losing enteropathy can accompany eosinophilic enteritis, and may serve as a laboratory marker of improvement
- Topical presentation of enteric budesonide appears to have the greatest therapeutic benefit
- Selective food avoidance may have additive or supplemental benefit

- Patients using tacrolimus, after organ transplant, appear to be at greater risk for eosinophilic enteritis
- Spontaneous resolution may occur
- Biologics may have a potential future role
- The esophagus and duodenum are more together involved than stomach alone or esophagus and stomach

Eosinophilic Colitis (EC)

A very rare eosinophilic condition, when compared to EoE, EC has mucosal based presentations, but even less commonly muscularis or serosal, or transmural pathology.¹² Symptoms can range from diarrhea and abdominal pain, to obstruction and/or ascites. Eosinophils in the range of > 75/HPF and higher are generally required.⁹ Children are usually allergic.^{8, 12}

Inflammatory bowel disease is always a consideration, with a greater presentation of bloody diarrhea.

There is a transcriptome difference between EoE and EG^{6,7}, and although untested, the other non-esophageal sites might also have specific diseases transcriptomes, including EC.

- Backwash eosinophilic infiltration into the cecum may occur; although isolated increased eosinophils in the cecum/appendix has been reported
- This condition is not the same clinical condition is as seen in infants, termed food protein-induced allergic proctocolitis¹

- EC may have proximal concomitant gastrointestinal tract eosinophilic disease
- Adolescent males seem to have a larger presence
- Spontaneous remission can occur
- IBD and EC may co-exist
- Deposition of enteric budesonide via swallowed capsule is beneficial
- The role of elective food avoidance is unclear, although cow's milk would be a reasonable avoidance
- Biologics directed against Interleukin-5 may have a future role

Summary

Persisting gastrointestinal symptoms in any allergic child should prompt a thorough gastrointestinal evaluation. The decision to proceed to an EGD alone or with a colonoscopy is based on the clinical situation. Proximal disease is much more prevalent, and limited studies have suggested a role of proximal eosinophilic disease with distal symptoms.^{13, 14} The natural history of non-esophageal eosinophilic disease remains a clinical challenge. Esophageal disease is exceedingly more common, and has extensive observations, with updated clinical guidelines.²

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