Questions from Families and Patients of the Cincinnati Center for Eosinophilic Disorders

Here at the Cincinnati Center for Eosinophilic Disorders (CCED) at Cincinnati Children’s Hospital Medical Center, we hear many great questions about eosinophilic disorders from patients and families. Herein, we have compiled answers to many of the questions that we have received. We have arranged them in the following categories for your convenience:

- How to Explain
- Eosinophilic Gastrointestinal Disorders
- Eosinophilic Esophagitis
- Eosinophilic Colitis
- Eosinophilic Gastritis
- Eosinophilic Disorders
- Risk
How to Explain

How can I explain eosinophilic gastrointestinal disorders to my child? How can I explain why we are eliminating things from his diet in a way that he understands?

A child-friendly explanation is that his body is overacting and attacking something that he is eating or breathing in because his body thinks that it is dangerous. As his body fights that something, there is sometimes pain. We want to find out what his body considers dangerous so that he can avoid it so that his body will stop fighting it and he will feel better. Since we do not know what his body is fighting, we have to take some or all foods away, calm his body down and then check those foods one by one to see which ones his body fights and which ones it does not.
Eosinophilic Gastrointestinal Disorders

**Does someone with an eosinophilic gastrointestinal disorder (EGID) always have elevated eosinophils?**
The eosinophils are sometimes elevated in the blood of individuals with eosinophilic gastrointestinal disorders (EGIDs) (in less than half of patients), and the blood eosinophil levels generally correlate with the severity of tissue disease. Eosinophil levels are always elevated in the gastrointestinal tract for diagnosis; this is the definition of the disease. When the EGID is active, the gastrointestinal eosinophil levels are elevated. When the EGID is in remission, the gastrointestinal eosinophil levels are not elevated.

**What is the difference between multiple food allergies and eosinophilic gastrointestinal disorders (EGIDs)? Are EGIDs a consequence of multiple food allergies?**
The current research shows that eosinophilic gastrointestinal disorders (EGIDs) [i.e. eosinophilic esophagitis (EoE), eosinophilic gastritis (EG), eosinophilic colitis (EC), and eosinophilic gastroenteritis (EGE)] are associated with food allergies. However, EGIDs and food allergies are not the same. EGIDs are defined by the presence of eosinophils in the gastrointestinal tract as measured by endoscopy. It is common for people with EGIDs to have single or multiple food allergies. However, those with single or multiple food allergies do not always develop EGIDs.

**Are eosinophilic gastrointestinal disorders (EGIDs) specific to particular foods?**
A variety of foods can be associated with eosinophilic gastrointestinal disorders (EGIDs). Unlike classic anaphylaxis, there appears to be a broader range of foods identified as triggers. This is an active area of research.

**Do you believe that the "types" of eosinophilic gastrointestinal disorders (EGIDs) will ever be more separate?**
The common theme with these diseases is the presence of eosinophils; however, specific knowledge of eosinophilic colitis (EC) and eosinophilic gastritis (EG) is limited because they are so rare and there are not standardized diagnostic criteria for EG or EC. With the support of patients, families, organizations and others, research will continue. It is our hope that with further research more will be known about the specifics of mechanisms involved in each of these disorders, which will open up new possibilities for development of diagnostic criteria and treatments. ([2014 EG characterization publication](http://example.com))
**Eosinophilic Gastrointestinal Disorders (continued)**

*Could you share your views on whether helminth therapy would help eosinophilic gastrointestinal disorders (EGIDs)?*
Helminth therapy can certainly modulate immunity; however, it may be expected to exacerbate eosinophilic esophagitis (EoE)–like diseases. As eosinophils normally increase in response to parasites, this would likely not be an effective therapy for eosinophilic gastrointestinal disorders (EGIDs).

*Are you finding environmental allergens to be a factor in eosinophilic disorders such as eosinophilic esophagitis (EoE) or only food allergens?*
Environmental allergens, such as aeroallergens, may be a factor in eosinophilic disorders. In our experimental mouse models, intranasal administration of allergens can induce eosinophilic esophagitis (EoE). Additionally, some of our prior investigations have shown that indoor insect allergens can induce EoE in mice (Rayapudi et al. J Leukoc Biol. 2010). Thus, the oral/gastrointestinal exposure of an individual to food allergens may not be the only route/allergens to consider.

*Is the lifespan of someone with an eosinophilic gastrointestinal disorder (EGID) shortened?*
The long-term consequences of eosinophilic gastrointestinal disorders (EGIDs) are currently being studied. However, most patients with EGID do not have a life-threatening disease and can live a long life.

*Is it typical for an eosinophilic gastrointestinal disorder (EGID) to present very suddenly? Could it have been virally induced? Could it also leave suddenly or could my child grow out of it?*
Eosinophilic gastrointestinal disorders (EGIDs) can present acutely in association with a viral illness. Though the start of EGID symptoms may be sudden, it is likely that the EGID intestinal inflammation was present well before the onset of symptoms. The new insult (i.e., the viral illness) may promote the severity of the EGID symptoms because of the underlying problem. However, it is important to note that EGID is a chronic disorder that waxes and wanes. However, it does respond rather rapidly to effective treatment. Effective treatment involve altering the diet or medications. A true remission is only determined by repeat endoscopy and biopsy. An experienced physician should carefully scrutinize the biopsy slides; one must be sure that the problem is truly EGID and not another process.
Eosinophilic Esophagitis

My child was diagnosed with eosinophilic esophagitis (EoE), but his/her allergy tests were all negative. What does that mean?
This is one of the more frustrating situations encountered by families and physicians. About 25% of those with confirmed eosinophilic esophagitis (EoE) diagnosis do not test positive to foods. This does not necessarily mean that there is not an issue with a food(s). Allergy testing is not perfect. We have found that many of the children who tested negative to food(s) still respond when certain foods were removed from their diet. Figuring this out often takes patience. Medication therapy is one of the first approaches in cases like this; however, dietary changes can still be used. As always, you need to consult with your medical team to work through this. Treatment for eosinophilic disorders is not a "one glove fits all" approach.

Is it possible that eosinophilic esophagitis (EoE) is related to asthma? I have come to think that my child's EoE is more environmental than food allergy.
Environmental allergens, such as aeroallergens, may indeed be a factor in eosinophilic disorders. In our experimental mouse models, intranasal administration of allergens can induce eosinophilic esophagitis (EoE). Additionally, some of our prior investigations have shown that indoor insect allergens can induce EoE in mice (Rayapudi et al. J Leukoc Biol. 2010). Thus, the oral/gastrointestinal exposure of an individual to food allergens may not be the only route/allergens to consider.

Can eosinophilic esophagitis (EoE) be seasonal?
Eosinophilic esophagitis (EoE) does have seasonal variation in some patients, typically with worse symptoms in the spring and summer.

Is IgG4 delayed sensitivity food testing helpful for EoE patients?
There is currently no proven value in IgG4 measurements in EoE, although this is an active area of research.
Eosinophilic Esophagitis (continued)

Can I have your opinion on whether oral immunotherapy (OIT) may cause eosinophilic esophagitis (EoE)?
One of the possible side effects of oral immunotherapy (OIT) is the development of an eosinophilic gastrointestinal disorder (EGID), such as eosinophilic esophagitis (EoE). This highlights the intimate connections between allergic responses that cause anaphylaxis and those involved in EGIDs. When anaphylaxis is blocked with OIT, the immune system can continue to be allergic but manifest this continued allergy via a different response (e.g., an EGID). Indeed, patients with EGID generally have IgE against specific foods but do not have concurrent anaphylaxis, further highlighting the connection. Research concerning both disorders provides novel insight on each that may not have become apparent from researching these disorders individually, emphasizing why we strongly advocate for broad research inquiry rather than a strictly focused approach and why we aim to encourage food allergy research organizations/foundations to support EGID research. To more specifically answer your question, we do not have a formal recommendation about OIT but wish to point out that most patients on OIT have not been reported to develop EGID but that EoE is a current contraindication to OIT.

Why do we use Splenda with the slurry?
Splenda is used because it is thought to be inert, tasty and generally a safe mixture for individuals with food allergies or eosinophilic disorders. Additionally, mixing the liquid medication with Splenda provides the viscosity, or thickness, needed for the solution to coat the esophagus. A thinner solution may "rush" past the esophagus on its descent through the gastrointestinal tract.

Do you notice a difference in oral thrush infections with kids that use Splenda versus honey with their swallowed Pulmicort? Would the honey increase the risk of getting thrush because of the sugar?
It is unknown whether thrush would be worsened by the use of honey; however, there could be a concern regarding the use of honey simply as an added food agent.

Where can I find information about the long-term use of Flovent for the purpose of treating eosinophilic esophagitis (EoE)?
Inhaled Flovent has been used for long-term treatment of asthma in children. It is generally considered safe, although it can have effects on the rate of stature growth. The long-term effects of swallowing topical steroids for eosinophilic esophagitis (EoE) is not known, but it is generally thought to be even safer than taking the medicine for asthma as the swallowed form is generally not absorbed and the amount absorbed is degraded by the liver.
Eosinophilic Esophagitis (continued)

*My child has eosinophilic esophagitis (EoE) and his/her doctor believes that it is aeroallergen-induced EoE. My child also has asthma. Could his/her asthma be a result of eosinophils in his airways? If so, is narrowing of airways as he grows older a concern?*

Asthma is an allergic disease of the airways associated with eosinophilic lung inflammation, and it is generally believed that eosinophils are causing part of the lung problems and symptoms in this disease. In fact, the first class of new asthma medicines in over a decade were approved in late 2015 and early 2016, and the two drugs (Nucala and Cinqair) work by blocking eosinophils.

*I know someone who had a nasal smear done because of repeated sinus infections. They found a high number of eosinophils, and when they repeated the smear while she was doing a dairy trial, the eosinophils increased. How are nasal eosinophils related to EoE?*

Nasal eosinophils are not directly related to eosinophilic esophagitis (EoE); however, EoE is associated with allergic disorders, including upper respiratory allergies such as allergic rhinitis and nasal polyps. Both allergic rhinitis and nasal polyps are associated with nasal eosinophilia.

*With so many organizations and people doing fundraisers, can you tell me how much money it will actually take for research to find a cure for eosinophilic esophagitis (EoE)?*

We wish that we had that answer. We wish that we could accurately predict what the cure will be, how long it will take to find, and how much money it would take to do so. Unfortunately, the name of the process, "research", is very fitting in that we search over and over again ("re"). Research is the process of learning, discovery, and testing. We make headway with our hypotheses, learning from all research done, even (or perhaps "especially") that which overturns our theories on what may be happening. Every day we hope that one of our "Ah-ha!" moments will become the cure for eosinophilic gastrointestinal disorders (EGIDs). We can say with confidence that our research is already greatly influencing the way people think and treat EGIDs around the world.
Eosinophilic Colitis

Does treatment of eosinophilic colitis (EC) differ from that of eosinophilic esophagitis (EoE)?

Eosinophilic colitis (EC) is also part of the broader category of eosinophilic conditions called eosinophilic gastrointestinal disorders (EGIDs), along with eosinophilic esophagitis (EoE) and eosinophilic gastritis (EG). Treatments do vary depending on the location of the disorder. Sometimes diets / elemental formulas will be used, as well as systemic medications such as steroids. We do know through experience that medications used for EoE, such as Flovent and Pulmicort, do not help in the treatment of EC. An accurate diagnosis is important in understanding which treatment to take.

Is having some eosinophils in the colon is normal? Is there a cutoff number for diagnosing eosinophilic colitis (EC)? Does it differ depending on which side of the colon? If so, why?

We have examined the amount and location of eosinphils in the colon in a limited set of healthy normal patients (Debroesse et al. Pediatr Dev Pathol. 2006) and found that the average number of eosinophils in the ascending and transverse colon were not significantly different. The peak eosinophil count was 50 eosinophils/high-power field in the ascending colon and 42 eosinophils/high-power field in the transverse colon. However, an exact cut-off of eosinophil levels for a diagnosis for eosinophilic colitis (EC) is not yet agreed upon.

What about the eosinophil number for the cecum and the ileum in eosinophilic colitis (EC)? These areas are very exact. I cannot get an average number for these areas from any doctor but did read a published report online that states that eosinophils over 30 in the cecum is a high indicator of EC.

We have examined the amount and location of eosinophils in the colon in a limited set of patients (Debroesse et al. Pediatr Dev Pathol. 2006). The peak counts were obtained from samples containing biopsies from both the cecum (i.e., first part of the colon) and the ascending colon (50 eosinophils/high-power field) and from samples containing biopsies from both the transverse and descending colon (42 eosinophils/high-power field). The peak count for samples containing biopsies from the ileum (i.e., the last part of the small intestine) was only 28 eosinophils/high-power field. Still, there is not consensus for an exact cut-off number for any of those sites; all biopsy findings must be correlated with clinical findings.
Eosinophilic Colitis (continued)

*Is it common for patients with eosinophilic colitis (EC) to have a positive antinuclear antibody (ANA) test result?*

It is not common for patients with eosinophilic colitis (EC) to have a positive antinuclear antibody (ANA) test result but points to the fact that eosinophilic colitis (EC) may be more related to autoimmunity in many patients, whereas eosinophilic gastrointestinal disorders (EGIDs) are classically related to food allergy. More specifically, EC does not typically respond to dietary changes (food allergy–based treatment) but more frequently requires immunosuppressive therapy (autoimmunity–based treatment). [Marc E. Rothenberg, MD, PhD](mailto:Marc.E.Rothenberg@childrenshospital.org) authored a [review of EGIDs](https://www.childrenshospital.org) several years ago that you may find helpful.
Eosinophilic Gastritis

Are there any new findings or studies related to eosinophilic gastritis (EG)? So much of the research is based on eosinophilic esophagitis (EoE), which seems so different.
The diagnostic criteria for eosinophilic gastritis (EG) are not well defined, and the exact cause of EG is not known. To address these problems, we are examining genetic differences between the stomach tissue of patients with EG and without EG. By discovering genes with altered structure or expression, we can identify molecular pathways that are dysregulated in the stomach of EG patients, which will allow further understanding of the cause of EG. The pathways identified may also serve as targets for treatment of EG. One of the molecules that was highly increased in the stomach of EG patients was a cell adhesion molecule, cadherin-like 26 (CDH26). Cadherins can be thought of as intracellular Velcro, with each cadherin protein acting like a hook that snags cadherin on other cells, thus attaching cells to each other. CDH26 was also increased in the esophagus of patients with eosinophilic esophagitis (EoE), so it may have a common function in different types of eosinophilic gastrointestinal disorders (EGIDs). We have produced recombinant CDH26 in a form that is stable and in a format that is amenable to being used as a drug. We are hoping that this and related molecules will open up new diagnostic and treatment possibilities for EG and other EGIDs. We published a characterization of EG in 2014 and about CDH26 in 2017. The Consortium for Eosinophilic Gastrointestinal Disease Researchers (CEGIR) is conducting a pilot study for EG in which dietary therapies are being tested.

Can someone have both eosinophilic esophagitis (EoE) and eosinophilic gastritis (EG)? Is this unusual? Are they related?
The term “eosinophilic gastroenteritis” (EGE) is used to describe when someone has a confirmed eosinophilic disorder in more than one region of the gastrointestinal tract (esophagus, stomach, colon). Therefore, having both eosinophilic esophagitis (EoE) and eosinophilic gastritis (EG) would be EGE. Here at our center, a portion of our patients do have EGE with both EoE and EG. In fact, most patients with EG also have EoE, but most patients with EoE do not have EG. Are EoE and EG related? We are working to find this out. The common theme with these diseases is the presence of eosinophils; however, specific knowledge of eosinophilic disorders beyond the esophagus is limited. One reason for this lack of knowledge for EG or eosinophilic colitis (EC) is that these diseases are very rare and there is not a standardized diagnostic criteria set for EG or EC. We did publish a characterization of EG in 2014.
Eosinophilic Disorders

There is much debate over whether eosinophilic disorders are autoimmune. Please give us your insight.

Eosinophilic disorders are part of the broad category of inflammatory disorders and are not formally considered autoimmune. There are currently no substantial data to support an autoimmune cause for eosinophilic disorders, but research on this topic is actively ongoing. Patients with eosinophilic gastrointestinal disorders have a higher rate of autoimmune diseases and have a higher rate of autoimmune diseases such as systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), and Celiac disease in blood relatives.

Do research hypereosinophilic syndromes (HES)? Is research continuing for HES, as well as the other eosinophilic diseases?

The Rothenberg Research Laboratory, a collaborator of the Cincinnati Center for Eosinophilic Disorders, takes a multi-faceted research approach to understanding eosinophils and their involvement in a wide spectrum of eosinophilic disorders, including hypereosinophilic syndrome (HES). When Marc E. Rothenberg, MD, PhD was a PhD student, he was the first to publish that interleukin 5 (IL-5) was involved in HES. Subsequently, he confirmed this finding in pre-clinical models. He and his collaborators demonstrated that anti-IL-5 (humanized antibody against IL-5, also called "mepolizumab") is helpful for patients with HES, as reported in his landmark article in the New England Journal of Medicine in 2008. Drugs that block IL-5 (Nucala and Cinqair) are now FDA approved for patients with asthma with high eosinophil counts. Studies are now underway to use these and related medicines for other eosinophilic disorders.

My son was diagnosed with Mucosal Eosinophilia last week. For months, he has been dealing with nausea, vomiting, and mild to severe stomach pains. He also has increased gas, and he says that it burns when he uses the bathroom or passes gas.

“Mucosal eosinophilia” is a term used to describe modestly increased levels of eosinophils in a specific region of the gastrointestinal tract. It generally means that the eosinophil levels do not meet those typically seen in eosinophilic gastrointestinal disorders (EGID) and that the tissue itself does not appear to be pathological. It is important to point out that the diagnosis of EGID requires multiple biopsies; thus, the finding of mucosal eosinophilia has to be interpreted in the context of the findings of the other biopsies and the clinical setting. Furthermore, eosinophils normally reside in the gastrointestinal tract so simply finding them (even modest increases in their levels) is not indicative of a disease process.
Eosinophilic Disorders (continued)

Has any research been done that links eosinophilic disorders and depression?
There is no known direct link between eosinophilic disorders and depression. However, there can be higher rates of anxiety and depression in children with chronic illness in general.

Are any of you working with broad-spectrum chemokine inhibitors?
Marc E. Rothenberg, MD, PhD was the first to show a role for chemokines in eosinophilic esophagitis (EoE; see his original publication) and is actively pursuing this for the treatment of eosinophilic gastrointestinal disorders (EGIDs). Additional suggestions and/or leads about broad-spectrum chemokine inhibitors would be welcome.

Are there any studies being done on the use of Ketotifen at the Cincinnati Center for Eosinophilic Disorders (CCED)?
Ketotifen is not currently available in the U.S.A. in an oral formulation.
Risk

Is there an increased chance of having another child with eosinophilic esophagitis (EoE) if you already have one child with this condition?

Our research has shown that there is an approximately 2.5% chance of having another child with eosinophilic esophagitis (EoE) if you already have one child with this condition. This represents a large increase in risk compared with the general population, but it also means that there is a greater than 95% chance of not having another child with EoE. There is a short video (“Does eosinophilic disorders run in families?”) posted on our Facebook page by Marc E. Rothenberg, MD, PhD about this topic.

Is there genetic testing available that can help with family planning in regard to EoE?

Eosinophilic esophagitis (EoE) susceptibility involves a combination of genetic and environmental risk factors. Though there are inherited genetic variants that confer susceptibility, the increase in risk is generally less than 2-fold, which is not substantial enough to be used for genetic counseling. Consistent with this, genetically identical twins only have ~50% concordance of EoE, indicating a dominant role for the environment.