

Pediatric Patients with Eosinophilic Esophagitis and Celiac Disease Treatment and Response Differences

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PI: Dr. Norelle Rizkalla Reilly, MD

Scientific Abstract

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Eosinophilic esophagitis (EoE) is a disorder involving eosinophilic infiltration of the esophagus that responds to dietary eliminations and not acid blockade. Celiac disease (CD) is an autoimmune enteropathy related to sensitivity to gluten, usually diagnosed via biopsy. Studies have shown an association between these two conditions, as individuals with CD appear to have a greater frequency of EoE than other individuals. The mainstay of treatment for both EoE and CD involves dietary restrictions. -When EoE and CD occur concurrently, gluten elimination is a part of the management of both conditions, though it is not clear whether EoE is more likely to respond to wheat elimination in the setting of CD, and whether those with EoE and CD require steroids less frequently for management of esophagitis than children without CD.

While serology is available to monitor progress of children CD after treatment, EoE must be followed with repeat biopsies to assess the impact of dietary elimination. Patients with EoE and CD who will require repeat endoscopies to monitor EoE may offer additional insight into rates of small bowel healing with respect to CD pathology, as routine follow-up small bowel biopsy for children with CD alone is controversial and not supported by current evidence. Patients will often undergo duodenal biopsy to assess the status of CD while undergoing routine biopsy for EoE. Our aims in this study are: 1) to evaluate differences in management and responses

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to treatment in EoE, specifically the frequency of remission of EoE following wheat exclusion for CD vs in those without CD, -as well as frequency of steroid use for EoE in those with and without CD; -and 2) to determine the frequency of small bowel healing in CD, focusing on those without serologic evidence of ongoing CD, using those undergoing endoscopy as a part of routine EoE management. With medications differs in patients with and without CD by looking at onset of treatment and uses of medications. We will look at biopsies of EoE and CD patients to assess disease response to treatment; specifically in CD patients who do not routinely get repeat biopsies.

Comment [RB1]: Are we comparing symptoms in CD to biopsy or serology to biopsy or both?

Lay Abstract:

Brief Background:

Celiac disease (CD) is an autoimmune enteropathy caused by sensitivity to gluten. Presenting symptoms that lead to testing often include diarrhea, failure to thrive, abdominal pain, and abdominal distension¹. The gold standard for diagnosis of CD is a duodenal biopsy. According to the CD clinical guidelines, the prevalence of CD in children aged 2.5 to 15 years of age is .33 to 1.25%¹. Another study reports an incidence of CD in the American population is estimated to be around 1:1000 or 0.1%¹. Initial treatment of CD is elimination of gluten. Repeat biopsies are rarely performed in CD patients generally performed only when patients are refractory to gluten elimination diet.

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Eosinophilic Esophagitis is a disease where eosinophilic white blood cells infiltrate the esophagus in response to allergens, typically food-related, that responds to dietary elimination³. Presenting symptoms of EoE vary by age of onset, but usually consist of feeding refusal, dysphagia, regurgitation, emesis, and abdominal pain⁴. A meta-analysis found the prevalence of Eosinophilic Esophagitis (EoE) in the United States in children less than 18 years of age ranges from 0.2 to 43 per 100 000 or

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0.0002 to 0.043%⁵. Diagnosis is made with esophageal biopsy showing a minimum of 15 eosinophils/hpf⁶. Recommendation for treatment of EoE is initially dietary elimination. Topical steroids are also recommended in initial and maintenance therapy; however; use is based on disease severity. In severe EoE, systemic steroids are also used.

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There are several studies that show a significantly higher prevalence of EoE in patients with Celiac Disease (CD). A study by Lucendo *et. al* showed the prevalence of EoE in patients with CD ranged from 0% to 10.7%⁷. A study by Pellicano *et al* showed the prevalence of EoE in subjects with CD is close to 10-times that of the general population. Many studies have tried to find a connection between the pathologies, without a strong conclusive link. Because treatment for CD can overlap with treatment of EoE, there are several studies looking at eliminating gluten in EoE patients with CD. Lucendo *et. al* discuss 15 studies that look at gluten elimination in EoE patients with CD. The end point evaluated amongst the studies was histological resolution or improvement of EoE on biopsy. The results vary from no improvement to significant improvement⁷. While there is some research looking at dietary changes in patients with EoE and CD without a consistent result, there are no studies looking at if management of CD in patients with EoE alters medical therapy or other treatments in managing EoE.

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We hypothesize that: (1) Patients with EoE and CD will have no difference in response to gluten elimination as EoE patients alone. (2) Patients with EoE and CD receive steroids less frequently than patients with EoE alone. (3) Repeat duodenal biopsies in patients with EoE and CD will correlate with symptoms.

We will test these hypotheses and achieve the following aims:

1. Response to gluten (including wheat) exclusion will be coded as a categorical variable and will be compared among those with and without celiac disease.
Likewise, use of corticosteroids (swallowed flovent and/or budesonide) for

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management of EoE will also be similarly coded and compared between children with and without celiac disease. A multivariate analysis, incorporating age of the patient, patient sex, and year of diagnosis will be performed to control for these potential confounders.

2. Histologic remission of celiac disease will be determined from small bowel biopsies collected at the time of celiac disease diagnosis (baseline) and through treatment for EoE insofar as repeat small intestinal biopsies are repeatedly collected in these patients. Remission will be scored according to the pathologists grading system (Marsh 1, 2, 3). We will examine the frequency of active celiac disease (Marsh 1 and above) and compare this frequency between individuals with positive celiac specific serologies and those with negative serologic markers, controlling for use of corticosteroids for treatment of EoE.

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1. Hill ID, Dirks, M. H., Liptak, G. S., Colletti, R. B., Fasano, A., Guandalini, S., Hoffenberg, E.J., Horvath, K., Murray, J.A., Pivor, M., Seidman, E. G. . Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *Journal of pediatric gastroenterology and nutrition* 2005; **40**(1): 1-19.
2. Rostom A, Murray JA, Kagnoff MF. American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of celiac disease. *Gastroenterology* 2006; **131**(6): 1981-2002.
3. Markowitz JE, Spergel JM, Ruchelli E, Liacouras CA. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. *The American journal of gastroenterology* 2003; **98**(4): 777-82.
4. Furuta GT, Liacouras CA, Collins MH, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007; **133**(4): 1342-63.
5. Soon IS, Butzner JD, Kaplan GG, deBruyn JC. Incidence and prevalence of eosinophilic esophagitis in children. *Journal of pediatric gastroenterology and nutrition* 2013; **57**(1): 72-80.

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6. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *The Journal of allergy and clinical immunology* 2011; **128**(1): 3-20 e6; quiz 1-2.
7. Lucendo AJ, Arias A, Tenias JM. Systematic review: the association between eosinophilic oesophagitis and coeliac disease. *Alimentary pharmacology & therapeutics* 2014; **40**(5): 422-34.

Design and Statistics:

Design:

This is a retrospective analysis of patient records. We will submit a Columbia University Discovery request to access a list of patients with:

1. Celiac Disease and Eosinophilic Esophagitis and
2. Eosinophilic Esophagitis alone

Data Source:

Using the resulting patient list, we will access patient medical records to collect the following data: patient age, patient sex, year of endoscopy, pathology results (Marsh score of celiac disease, eosinophil count from esophageal biopsies, number of biopsies submitted to pathology), gross endoscopic findings, diagnosis, serologies including allergen testing and celiac serology results, and records of treatment.

Inclusion criteria:

All patients age 0-18, diagnosis of EoE and CD made via biopsy, diagnosis of EoE alone made via biopsy, biopsy results available, records of treatment available for review

Exclusion Criteria:

Patients age >18 years at time of diagnosis or treatment, patients diagnosis with EoE or CD without biopsy, patients lost to follow-up after diagnosis

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Statistical Considerations:

The hypotheses being tested are that: (1) Patients with EoE and CD receive less steroids than patients with EoE alone. (2) Repeat celiac biopsies in patients with EoE and CD will correlate with symptoms.

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Study Design: This is a retrospective analysis of patient records. We will submit a Columbia University Discovery request to access a list of patients with Celiac Disease and Eosinophilic Esophagitis and 2 Eosinophilic Esophagitis alone

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Using the resulting patient list, we will access patient medical records to collect the following data: patient age, patient sex, year of endoscopy, pathology results (Marsh score of celiac disease, eosinophil count from esophageal biopsies, number of biopsies submitted to pathology), gross endoscopic findings, diagnosis, serologies including allergen testing and celiac serology results, and records of treatment.

Inclusion criteria: All patients age 0-18, diagnosis of EoE and CD made via biopsy, diagnosis of EoE alone made via biopsy, biopsy results available, records of treatment available for review

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Exclusion Criteria: Patients age >18 years at time of diagnosis or treatment, patients diagnosis with EoE or CD without biopsy, patients lost to follow-up after diagnosis

Statistical Considerations: The hypotheses being tested are that: (1) Patients with EoE and CD receive less steroids than patients with EoE alone. (2) Repeat celiac biopsies in patients with EoE and CD will correlate with symptoms.

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Statistical Procedures: Chi square analysis to compare differences between groups. A multivariate analysis, incorporating age of the patient, patient sex, and year of diagnosis will be performed to control for these potential confounders.

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Aim 1: Response to gluten (including wheat) exclusion will be coded as a categorical variable and will be compared among those with and without celiac disease. Likewise, use of corticosteroids (swallowed flovent and/or budesonide) for management of EoE will also be similarly coded and compared between children with and without celiac disease. A multivariate analysis, incorporating age of the patient, patient sex, and year of diagnosis will be performed to control for these potential confounders.

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Aim 2: Histologic remission of celiac disease will be determined from small bowel biopsies collected at the time of celiac disease diagnosis (baseline) and through treatment for EoE insofar as repeat small intestinal biopsies are repeatedly collected in these patients. Remission will be scored according to the pathologists grading system (Marsh 1, 2, 3). We will examine the frequency of active celiac disease (Marsh 1 and above) and compare this frequency between individuals with positive celiac specific serologies and those with negative serologic markers, controlling for use of corticosteroids for treatment of EoE.

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