

Evaluation of Growth Outcomes in Children with Eosinophilic Esophagitis

Introduction

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease characterized by eosinophilic infiltration of esophageal epithelium. Adult patients typically present with food impaction and dysphagia, whereas children present with vomiting, feeding dysfunction, and failure to thrive.¹ EoE is thought to be an allergic disease with the underlying pathogenesis related to exposure to food allergens.² Accordingly, dietary elimination is an effective initial therapy for EoE. Strategies for dietary treatment include selective elimination diets, in which potential food allergens are removed from the diet, and elemental formulas, in which hypoallergenic liquid formulations are administered as the sole source of nutrition.

Growth and development is a major concern for pediatric EoE patients, as feeding dysfunction and restrictive diets can prevent patients with EoE from receiving sufficient nutrient intake. Moreover, elimination diets can lead to poor growth and development if nutritional replacements for the eliminated food are not provided.³ Milk and wheat, the two most common allergic triggers of EoE,¹ are highly important parts of a child's diet, and replacement sources are necessary to ensure normal growth and development.³ Use of elemental formulas can circumvent these disadvantages because they provide a complete source of nutrients. Thus, elemental formulas may help children with EoE achieve normal growth by providing a more complete source of nutrients compared to restrictive diets. However, despite the importance of nutrition and growth in children with EoE, outcomes related to growth and EoE-specific treatments have never been examined, and this is a major gap in knowledge. The proposed study seeks to investigate the growth rates for pediatric EoE patients using elemental formulas as compared to elimination diets and pharmacological therapies. We will analyze patient data from the Carolinas EoE Collaborative (CEoEC), a multi-center network that includes UNC (Chapel Hill, NC), Asthma and Allergy Specialists Clinic (Charlotte, NC), and Greenville Health System Children's Hospital Pediatric Gastroenterology Clinic (Greenville, SC).

Specific Aims and Hypotheses

Aim 1: To determine the growth rates of children with EoE who were treated initially with elemental formula therapy as compared to those who were initially administered topical steroids and dietary elimination therapies.

Hypothesis for Aim 1: Growth rates will be higher in pediatric EoE patients on an elemental formula therapy than those not on an elemental formula therapy.

Aim 2: Evaluate the growth of children with refractory EoE (no response to pharmacological or diet elimination therapies) who were placed on elemental formula as compared with the growth of children with refractory EoE who were placed on other second-line treatments.

Hypothesis for Aim 2: Children with refractory EoE will have an improved growth rate after starting an elemental formula diet.

Background

Eosinophilic Esophagitis: Symptoms and Diagnosis

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease that is characterized by eosinophilic infiltration of esophageal epithelium. Adult patients typically present with food impaction and dysphagia, whereas children typically present with vomiting, abdominal pain, feeding dysfunction, and failure to thrive.¹ Diagnosis of EoE is based on these clinical symptoms and histological evidence of eosinophilic infiltration of the esophageal epithelium.¹ Treatments for EoE currently include topical steroids (fluticasone, budesonide), dietary therapies, and endoscopic dilation.¹

EoE is linked to food allergies

EoE is currently thought to be an allergic disease based on epidemiological data, pathophysiological evidence, and clinical response to trigger food elimination. Like other atopic conditions such as asthma and allergic rhinitis, incidence and prevalence of EoE has grown markedly in the past two decades.⁴⁻⁸ Cohort studies have shown that the majority of EoE patients have concomitant asthma, allergic rhinitis, or atopic dermatitis.⁷ At the cellular level, EoE is largely a T_H2 mediated response, with IL-5 and IL-13 cytokines being critically involved in EoE pathogenesis.^{7,9-11} Histological remission and symptom improvement in EoE patients undergoing elimination diets provides clinical evidence supporting the link between EoE and food allergies.²

Dietary therapies are effective as treatment of EoE patients

Both elemental diets and elimination diets are effective in managing EoE in children.³ Elemental diets involve replacing all intact protein in the diet with a liquid formulation of amino acids.¹⁶ Elemental diets have been shown to be more effective at inducing remission than any other therapy including topical steroids,¹⁶ and are much more likely to achieve mucosal healing and result in lower residual eosinophil counts.³ However, the high cost of elemental formulas, poor oral tolerability, and need for a feeding tube for certain patients are disadvantages of this approach.¹ Because of this, elimination diets based on either allergy test results (“targeted elimination diets”) or with the six most common allergens eliminated (“six-food elimination diets”; SFED) have been developed. Response rates for these approaches range from 60-75%, a level that is comparable to pharmacologic therapy.¹⁷

Growth is an important but poorly described consideration in pediatric EoE patients

Children with EoE who present with feeding dysfunction can develop maladaptive feeding behaviors.¹³ Moreover, dietary therapies used to address such symptoms can often lead to impairments in nutritional intake, which can affect growth.³ When compared to healthy controls and expected values based on age, children with food allergies in general, and allergy to cow’s milk in particular, show decreased growth.^{14,15} While monitoring nutritional intake is important when children are placed on long-term elimination diets,² outcomes related to this for EoE are poorly described in the current literature. In particular, there is a surprising and unacceptable lack of data concerning growth outcomes based on treatment type. Further research is needed to better understand how dietary management of EoE in children impacts growth rates.

Present Study

To date, elemental diets, elimination diets, and other EoE treatments have only been compared for their effectiveness in producing clinical and histological remissions. Growth, which is especially important in children with EoE, has not been extensively assessed as a specific outcome, and the various treatment modalities have not been compared with respect to growth outcomes. Analyzing these differences could help pediatric gastroenterologists and nutritionists guide the treatment of pediatric EoE patients and select optimal treatment and nutritional approaches. Therefore, the overall goal of this study is to assess growth outcomes by treatment types in children with EoE, and the central hypothesis is that those who take elemental formula will have better growth outcomes. To do this, we will analyze data from children with EoE from three centers in the Carolinas EoE Collaborative (CEoEC), a consortium of EoE centers in North and South Carolina co-founded and co-directed by the faculty advisor on this project.

Research Design and Methods

Study Population

Our study population will include all children (<18) diagnosed with EoE at University of North Carolina Hospitals (Chapel Hill, NC), Asthma and Allergy Specialists Clinic (Charlotte, NC), and Greenville Health System Children’s Hospital Pediatric Gastroenterology Clinic (Greenville, SC), three of the centers in the CEoEC. We will review records from 2005 - 2014. To assess growth, we will include patients who have at least 3 visits.

Study Design and Data

This will be a retrospective cohort study. Data on age, demographic, clinical symptoms, endoscopic features, histological findings, anthropometric measures (height, weight, growth velocity), treatment approaches and adherence, and frequency of encounters with the physician and nutritionist will be extracted using a standardized case report form. The same form will be utilized at all sites.

Student's Role

The student's role in this study will be to assist in the study's design, medical record data abstraction, data analysis, and write up of the results of the study for presentation and publication.

Data Analysis

Statistical analysis

Demographic, clinical, endoscopic, histologic, and treatment-related data for the study population will be summarized using descriptive statistics. Baseline characteristics of EoE patients will be compared by treatment type (steroids vs dietary elimination vs elemental formula) and by the presence or absence of elemental formula supplementation. The primary outcome of interest will be growth. We will use metrics standardized to a normative population, and will specifically calculate both the change in the BMI Z-score and the change in height Z-score pre- and post-therapy. To test the hypotheses stated above, these changes will be compared between initial treatment types (Aim 1) and for refractory treatment types (Aim 2). A longitudinal modeling approach will accommodate adjustment for potential confounders (ie presence of other atopic conditions, EoE disease duration, age, gender, etc), use of multiple data points over time, with variable numbers of data points per subject. We will explore whether a linear mixed effects model may be appropriate to assess change over time, introducing a random effect for intercept (baseline BMI Z-score).

Sample Size

We have already established that, between 2005 and 2014, approximately 700 pediatric patients have been treated for EoE at the above three centers in the CEoEC.

Aim 1: Assuming 80% of patients have a minimum of 3 visits on record, we anticipate a study sample of 560 patients.

Aim 2: Of these 560 patients, assuming 40% are refractory to first line elimination diet or pharmacological treatments, we anticipate a study sample of 224 patients.

Expected Outcome / Alternative Approaches

We predict that EoE patients receiving elemental formulas will have favorable growth rates than EoE patients not on elemental formulas. We also predict that EoE patients refractory to other treatments will regain or experience improved growth following the initiation of elemental diet therapy. It is possible that a number of subjects may have incomplete follow-up data. If that is the case, we will first then compare those with and without incomplete records or missing data to assess for systematic biases. If this does not resolve this issue, we can modify our IRB applications to contact the pediatricians of the patients with incomplete records to acquire the necessary growth data.

Candidates Statement

The CMSRP program was designed to provide students like me with a meaningful exposure to medical research. My undergraduate and medical studies have peaked my interest in research and the generation of new knowledge, and thus, I believe I would be a perfect fit for this program. This experience will not only be invaluable to my development as a physician-scientist, but will also help me explore the possibilities of pursuing an academic career in medical research in the future. During the course of this research study, I will gain experience working on all aspects of this project, including study design, data collection, analysis, and reporting of results. I am very much looking forward to the process of gaining these skills and working with Dr. Dellon on this project during the upcoming summer.

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