

Eosinophilic Esophagitis in Children Under the Age of 5 Years: Clinical Characteristics

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Objectives/Hypothesis: To delineate clinical characteristics and treatment outcomes of eosinophilic esophagitis (EoE) in the youngest of children.

Study Design: Retrospective chart review.

Methods: A 7-year retrospective chart review of children with clinicopathologic diagnosis of EoE was performed with specific analysis of patients under 5 years old. EoE was defined as the presence of symptoms of esophageal dysfunction with pathologically proven eosinophilic inflammation (≥ 15 eosinophils per high-power field [EOS/HPF]) unresponsive to reflux therapy. Patient parameters and clinical results were systematically reviewed.

Results: Of 558 children diagnosed with EoE, 127 (22.8%) were younger than 5 years old (mean age 2.5 years). This subgroup presented with reflux symptoms (90.1%), vomiting (86.2%), diarrhea (55.3%), liquid dysphagia (52.0%), and constipation (50.0%), whereas food impaction (1.6%) was rare. Liquid dysphagia was present at all ages but significantly more common in younger children ($P = .0101$). The most common food and environmental allergens were egg whites (39.7%), cow's milk (36.5%), peanuts (34.9%), animal dander (15.1%), and weed pollen (11.1%). Patients were managed with antireflux medication (100%), elimination diet (83.5%), and steroid medication (68.5%). After treatment, 86% of parents reported symptom improvement. Mean reduction of EOS in post-treatment biopsy was 33.5 EOS/HPF ($P < .0001$), and 67 patients showed histologic resolution of EoE (56.8%, $P < .0001$).

Conclusions: Approximately one-quarter of children with EoE present under 5 years of age with multiple esophageal symptoms, comorbidities, and allergen-sensitization profiles. These patients demonstrate substantial clinicohistologic improvement following therapy.

Key Words: Eosinophilic esophagitis, children, dysphagia, atopy, pediatric, reflux.

Level of Evidence: 4

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INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated disease of the esophagus that is characterized by esophageal dysfunction and the presence of eosinophil-rich inflammation.¹ First characterized as a distinct disorder 2 decades ago, EoE is now recognized as one of the fastest growing causes of chronic esophageal symptoms. In recent years, EoE has presented more

frequently in pediatric patients in North America.¹ In the United States alone, the incidence of eosinophilic esophagitis in children ages 0 to 4 years ranges from 3.28 to 15.92 per 100,000 per year.²

A combination of clinical, endoscopic, and histopathologic findings is used to confirm the diagnosis of EoE. Clinical presentation of EoE in children varies by age. It is suspected that younger children are more likely to present with nonspecific gastrointestinal issues such as feeding difficulties, vomiting, failure to thrive, and gagging, whereas more specific symptoms such as solid food dysphagia present in older children.^{2,3} Furthermore, EoE in children is often associated with food allergen sensitization and atopic diathesis such as asthma and eczema.¹ Endoscopic findings of esophageal furrowing and patchy infiltrates are common in early stages of the disease. Histopathologic diagnosis requires a minimum threshold of 15 eosinophils (EOS) per high-power field (HPF) through esophageal biopsy in at least one area of the esophagus. Patients are initially placed on proton pump inhibitors (PPIs) to exclude gastroesophageal reflux and PPI-responsive esophageal eosinophilia (PPI-REE).¹ Persistent disease suggests EoE, and patients are subsequently managed with swallowed corticosteroids, food elimination diets, or both. Fibrostenosis such

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as concentric rings, fixed strictures, and luminal narrowing are frequent late endoscopic findings in EoE patients with uncontrolled inflammation.

Several studies on steroid therapy have shown consistent histologic improvement in children, ranging from a 47.1% to 86.7% reduction in EOS/HPF.⁴⁻⁶ Dietary therapy, the identification and elimination of food-based antigenic stimuli that cause allergic sensitization, is equally effective.⁷⁻⁹ The three most common dietary interventions are the elemental diet, the six-food elimination diet (SFED), and allergen-specific dietary restrictions, with elimination diet being the most effective in improving clinical and histologic symptoms.⁷⁻⁹

Despite a pronounced increase in the amount of EoE research and publications over the past 20 years, there is little information about EoE in the youngest of children. Our aerodigestive center has recently seen a rise in toddlers diagnosed with EoE presenting with a disparate symptom profile than historically described for older patients. This retrospective study thus aimed to delineate the incidence, clinical characteristics, and treatment outcomes of EoE in children under 5 years old presenting to a primary tertiary referral center in a single state.

MATERIALS AND METHODS

All patients (0–19 years of age) with diagnoses of EoE from August 1, 2009 to October 1, 2016 were identified through the hospital electronic medical record database using the *International Classification of Diseases, Ninth Revision* diagnosis code 530.13 and *International Classification of Diseases, Tenth Revision* diagnosis code K20.0. This included patients evaluated at one or more of the following clinics: pediatric otolaryngology, allergy/immunology, aerodigestive, gastroenterology, and/or eosinophilic disorder clinics at Arkansas Children's Hospital (ACH) in Little Rock, Arkansas. Information regarding demographics, history of prematurity, medications, medical comorbidities, specialty clinic visits, clinical presentation, diagnosis, treatments, and response to therapy was retrieved from medical records. Specifically, sensitization to environmental allergens, food allergens, medications, and miscellaneous allergen profiles were collected and analyzed. Data collection was approved by the University of Arkansas for Medical Sciences Institutional Review Board.

Subjects were considered to have a diagnosis of EoE if they presented with a minimum of one symptom of esophageal dysfunction (food impaction, chest pain, reflux, nausea/emesis, failure to thrive, or dysphagia) as well as ≥ 15 EOS/HPF ($400\times$ magnification) by a board-certified pathologist in at least one esophageal biopsy during esophageal endoscopy. All subjects were required to have received at least 8 weeks of treatment with a PPI (0.5–1 mg/kg per dose twice daily) prior to the endoscopy. Lansoprazole and omeprazole were the two most prescribed PPIs. Repeat biopsies were analyzed after therapeutic treatments such as elimination of specific foods and the use of steroid medication. A reduction of peak eosinophils <15 EOS/HPF was considered as histologic resolution in this study.

Determination of serum-specific immunoglobulin (Ig)-E against allergens including cow's milk, egg, seafood (fish/shellfish), wheat, soybean, peanut/tree nuts, tree pollens (birch, elm, hickory, maple, oak, walnut), weed pollens (lamb's quarter, sheep sorrel, English plantain, pigweed), grass pollens (common bahia, Bermuda, fescue, Johnson, timothy), mites/arthropods,

mold (*Alternaria alternata*, *Aspergillus*, *Chaetomium globosum*, *Cladosporium herbarum*, *Curvularia*) and animal dandruff (cat, dog, horse, chicken feather) was performed using the ImmunoCAP enzyme immunoassay (Thermo Fisher Scientific/Phadia, Uppsala, Sweden). Specific IgE antibody results ≥ 0.35 IU/mL were considered positive.

Statistical Analysis

Variables measured in the nominal or ordinal scale were summarized as mean and standard deviation, and compared for treatment effect and across age groups using Kruskal-Wallis nonparametric analysis of variance. For variables measured in the nominal or ordinal scale, counts and percentages were presented. The Fisher exact test was used to compare treatment effect and across age groups. All tests were conducted at a significance level of $P < .05$. All statistical analyses were performed using Stata 14.2 (StataCorp LLC, College Station, TX).

RESULTS

Patient Demographics, Symptoms, and Medical Comorbidities

Five hundred fifty-eight patients with a diagnosis of EoE presented to ACH from August 1, 2009 to October 1, 2016 and were eligible for enrollment; 171 subjects (30.7%) were under the age of 5 years. Twenty-three patients were diagnosed with gastroesophageal reflux based on follow-up esophagogastroduodenoscopies (EGDs) and physician observation and were excluded from further analysis. Additionally, 17 patients did not receive any PPI therapy and were excluded from analysis. Four patients received PPI therapy, underwent subsequent biopsy examination, and no longer met the diagnostic criteria for EoE. Therefore, they were considered to have PPI-REE. This left 127 pediatric patients under the age of 5 years who had physician-confirmed diagnosis of EoE after an 8-week trial of PPI medication. These eligible subjects were retrospectively analyzed for demographics and medical history including date of diagnosis, presenting symptoms, history of atopic comorbidities, results of allergen profiling, and endoscopic/pathologic findings.

The average age at diagnosis was 2.5 years, with the majority being male (81.9%). Patient demographics (Table I) showed the largest category of patients was 1 to 2 years old ($n = 43$), and the smallest group was 0 to 1 year old ($n = 10$). Patients were mainly seen at ACH gastroenterology (92.9%) and eosinophilic disorder (69.3%) clinics. Otolaryngology visits occurred in 38.6% of patients.

The most common clinical symptoms (Fig. 1) were reflux (90.1%), nausea/emesis (86.2%), diarrhea (55.3%), liquid dysphagia (52.0%), and constipation (50.0%), whereas food impaction and chest pain ($<2\%$) were rare (Table I). Symptoms varied based on patient age; occurrence of bloating and nausea/emesis decreased with age. Liquid dysphagia was the most common presenting symptom in the youngest age group ($P = 0.0101$) (Fig. 2). Many patients had several comorbidities at initial presentation. Eczema (59.5%) and asthma (33.1%) were the most common conditions.

	Total, N = 127	0–1 Year Old, N = 10	1–2 Years Old, N = 43	2–3 Years Old, N = 23	3–4 Years Old, N = 33	4–5 Years Old, N = 18	P
Gender, no. (%)							.8174
Females	23 (18.1%)	2 (20.0%)	7 (16.3%)	4 (17.4%)	5 (15.2%)	5 (27.8%)	
Males	104 (81.9%)	8 (80.0%)	36 (83.7%)	19 (82.6%)	28 (84.8%)	13 (72.2%)	
Age at diagnosis, y, mean (SD)	2.5 (1.2)	0.8 (0.1)	1.5 (0.3)	2.5 (0.3)	3.5 (0.3)	4.3 (0.2)	<.0001
Symptoms, no. (%)							
Bloating	25 (21.0%)	3 (33.3%)	11 (28.9%)	2 (8.7%)	6 (18.8%)	3 (17.6%)	.3152
Chest pain	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)	0 (0.0%)	.6529
Constipation	61 (50.0%)	5 (50.0%)	22 (55.0%)	11 (47.8%)	15 (46.9%)	8 (47.1%)	.9632
Diarrhea	68 (55.3%)	8 (80.0%)	22 (55.0%)	11 (47.8%)	18 (54.5%)	9 (52.9%)	.5747
Dysphagia (aspiration)	64 (52.0%)	9 (90.0%)	25 (62.5%)	11 (50.0%)	14 (42.4%)	5 (27.8%)	.0101
Dysphagia (solid food)	16 (13.0%)	0 (0.0%)	5 (12.5%)	6 (27.3%)	4 (12.1%)	1 (5.6%)	.2542
Food impaction	2 (1.6%)	0 (0.0%)	1 (2.4%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	.8122
Nausea/emesis	106 (86.2%)	10 (100.0%)	37 (92.5%)	19 (82.6%)	29 (87.9%)	11 (64.7%)	.0624
Reflux	109 (90.1%)	8 (88.9%)	34 (87.2%)	21 (91.3%)	30 (90.9%)	16 (94.1%)	.9770
Medical comorbidities, no. (%)							
Asthma	41 (33.1%)	2 (20.0%)	13 (31.7%)	10 (43.5%)	8 (24.2%)	8 (47.1%)	.3474
Eczema	75 (59.5%)	6 (60.0%)	28 (66.7%)	14 (60.9%)	18 (54.5%)	9 (50.0%)	.7533
Failure to thrive	31 (25.0%)	5 (50.0%)	13 (31.0%)	5 (21.7%)	6 (18.8%)	2 (11.8%)	.1839
Premature	30 (23.6%)	3 (30.0%)	12 (27.9%)	5 (21.7%)	5 (15.2%)	5 (27.8%)	.6653
No. of clinic visits, no. (%)							
Allergy/ immunology	71 (55.9%)	5 (50.0%)	22 (51.2%)	12 (52.2%)	26 (78.8%)	6 (33.3%)	.0186
ENT	49 (38.6%)	8 (80.0%)	13 (30.2%)	7 (30.4%)	12 (36.4%)	9 (50.0%)	.0420
EOE	88 (69.3%)	6 (60.0%)	30 (69.8%)	20 (87.0%)	18 (54.5%)	14 (77.8%)	.0960
GI	118 (92.9%)	9 (90.0%)	42 (97.7%)	20 (87.0%)	30 (90.9%)	17 (94.4%)	.3793

ENT = ear, nose, and throat; EoE = eosinophilic esophagitis; GI = gastroenterology; SD = standard deviation.

Allergen Sensitization Profiles

ImmunoCAP analysis for food and environmental allergen sensitization was performed in 126 patients. Overall, over 75% of patients did not have sensitization to environmental allergens, whereas nearly half did not have sensitization to any foods. Evaluating six common environmental allergens (tree, grass, and weed pollen; animal dander; dust mite/arthropods; mold), 30 patients (23.8%) had sensitization to at least one allergen, with the average patient having sensitization to one environmental allergen (Table II). The most common environmental allergens identified across all age groups were animal dander (15.1%) and weed pollen (11.1%).

Assessing eight common food allergens (cow's milk, eggs, fish, shellfish, tree nuts, peanuts, wheat, soybean), 70 patients (55.6%) had a positive test to at least one food (Table II). The average patient was sensitized to at least two food allergens. There were no significant differences between infants (0–1 year) and older age groups

($P = .6291$). The most common food allergies identified across all age groups were egg (39.7%), cow's milk (36.5%), and peanuts (34.9%).

Treatments

Because there is variability in patient and physician perspective, treatment decisions were made based on patient and provider preference. More patients received dietary therapy ($n = 106$, 83.5%) (Table III) compared to topical steroids ($n = 76$, 59.8%). Eighty-six patients (70.1%) were placed on allergen-specific exclusion diets, whereas 24 (18.9%) received six-food elimination diets. Elemental diets were prescribed to six children (4.7%), all under the age of 3 years. Swallowed viscous budesonide ($n = 50$, 39.4%) and swallowed fluticasone ($n = 59$, 46.5%) were the topical steroid treatments of choice; some received both. A small number of patients also received systemic steroids ($n = 11$, 8.7%),

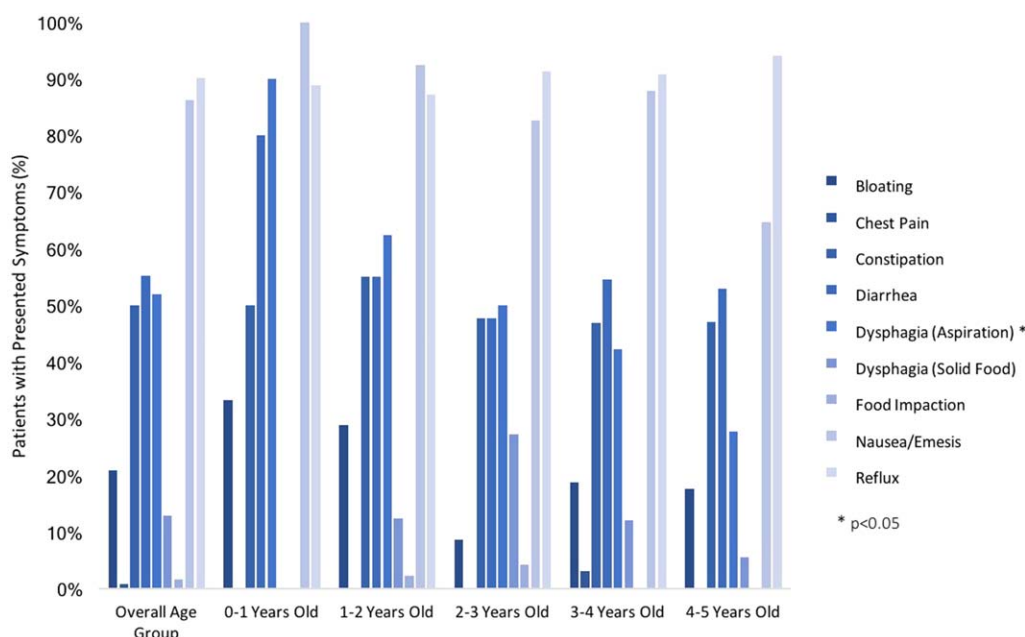


Fig. 1. Percentage of pediatric patients structured by age group with symptoms associated with eosinophilic esophagitis.

but none of those patients were in the 0 to 1-year age group.

Response to Treatment

Improvement in patients was judged on resolution of clinical symptoms and decrease in peak EOS count on follow-up esophageal endoscopy and biopsy (Table IV). Change in symptoms was determined from parent feedback and physician observation made in clinic. Overall, 105 patients (86.1%) showed improvement in clinical symptoms. Of the 122 patients who underwent follow-up EGD and biopsy, 96 patients (81.4%) showed histologic response in biopsy and had an average reduction of 33.5 EOS ($P < .0001$) from their initial biopsy (Fig. 3). Both improvement in symptoms and reduction in EOS count were consistent across all age groups. There were 88 study patients (83.8%) who had both histologic response and improvement of clinical symptoms. Of the 96 patients who showed improvement from initial biopsy,

67 (56.8%) had histologic resolution of EoE (<15 EOS/HPF). Those patients had an average reduction of 50.1 EOS/HPF ($P < .0001$) and approximately 90% ($P < .0001$) reduction in EOS.

DISCUSSION

EoE is a chronic, allergy-based disease characterized in children by clinical symptoms of feeding difficulties, reflux, and histologic evidence of esophageal eosinophilia. Previous investigations of this disorder have been focused on a broad distribution of patient ages. Herein, we provide an analysis of a single pediatric population of the youngest patients—less than 5 years of age—with confirmed diagnosis of EoE. This included nearly one-quarter of the total number of children with the *International Classification of Diseases* code for EoE treated for this condition at the primary referral center in the state. Demographically, this group was consistent with prior reports and reviews of older children presenting with EoE including male predominance, a significant history of allergies and atopy, and clinical symptoms associated with esophageal dysfunction and gastroesophageal reflux.^{1,7,10,11} However, this study demonstrates that when stratified by year, the youngest children have a varying symptom presentation, which emphasizes the need to better identify and understand the treatment of EoE in toddlers.

As expected, reflux (90.1%), along with nausea and regurgitation (86.2%), were the most common presenting symptoms in our very young cohort. Lower gastrointestinal symptoms such as diarrhea (55.3%), constipation (50.0%), and bloating (21.0%) were also present. Conversely, solid food dysphagia was rare (13.0%), and food impaction (1.6%) and its associated chest pain (0.8%), frequently seen in older children and adults with EoE,

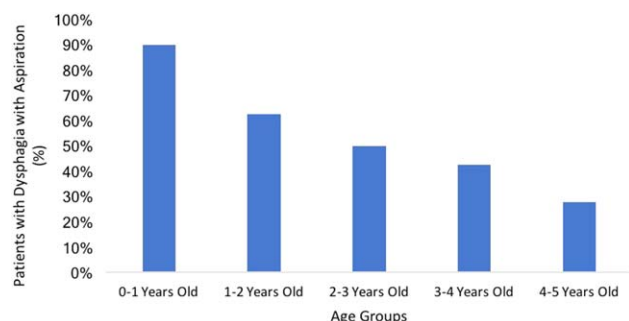


Fig. 2. Presentation of liquid dysphagia in pediatric patients structured by age ($P < .05$ for all groups). [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

TABLE II.
Environmental and Food Sensitization of Pediatric EoE Patients Under the Age of 5 Years

	Total, N = 127	0–1 Year Old, N = 10	1–2 Years Old, N = 43	2–3 Years Old, N = 23	3–4 Years Old, N = 33	4–5 Years Old, N = 18	P
Environmental allergens, no (%)							
Animal dander	19 (15.1%)	2 (20.0%)	9 (21.4%)	3 (13.0%)	4 (12.1%)	1 (5.6%)	.5694
Dust mite/arthropods	12 (9.5%)	1 (10.0%)	3 (7.1%)	4 (17.4%)	3 (9.1%)	1 (5.6%)	.7166
Grass	12 (9.5%)	1 (10.0%)	2 (4.8%)	3 (13.0%)	5 (15.2%)	1 (5.6%)	.5205
Mold	11 (8.7%)	0 (0.0%)	1 (2.4%)	4 (17.4%)	5 (15.2%)	1 (5.6%)	.1225
Trees	12 (9.5%)	0 (0.0%)	4 (9.5%)	3 (13.0%)	4 (12.1%)	1 (5.6%)	.8541
Weeds	14 (11.1%)	1 (10.0%)	5 (11.9%)	3 (13.0%)	4 (12.1%)	1 (5.6%)	.9721
No. of allergens, no (%)							.6960
0	96 (76.2%)	7 (70.0%)	32 (76.2%)	17 (73.9%)	24 (72.7%)	16 (88.9%)	
1	12 (9.5%)	2 (20.0%)	3 (7.1%)	2 (8.7%)	4 (12.1%)	1 (5.6%)	
2	4 (3.2%)	0 (0.0%)	2 (4.8%)	1 (4.3%)	1 (3.0%)	0 (0.0%)	
3	5 (4.0%)	1 (10.0%)	4 (9.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
4	2 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.1%)	0 (0.0%)	
5	5 (4.0%)	0 (0.0%)	1 (2.4%)	2 (8.7%)	1 (3.0%)	1 (5.6%)	
6	2 (1.6%)	0 (0.0%)	0 (0.0%)	1 (4.3%)	1 (3.0%)	0 (0.0%)	
Environmental allergen sensitization, mean (SD)	0.6 (1.4)	0.5 (1.0)	0.6 (1.2)	0.9 (1.8)	0.8 (1.6)	0.3 (1.2)	.7427
Food allergens, no (%)							
Eggs	50 (39.7%)	6 (60.0%)	20 (47.6%)	8 (34.8%)	10 (30.3%)	6 (33.3%)	.3479
Fish	16 (12.7%)	1 (10.0%)	7 (16.7%)	4 (17.4%)	2 (6.1%)	2 (11.1%)	.6416
Milk	46 (36.5%)	3 (30.0%)	20 (47.6%)	5 (21.7%)	13 (39.4%)	5 (27.8%)	.2704
Peanuts	44 (34.9%)	5 (50.0%)	16 (38.1%)	8 (34.8%)	9 (27.3%)	6 (33.3%)	.7198
Shellfish	15 (11.9%)	1 (10.0%)	6 (14.3%)	4 (17.4%)	2 (6.1%)	2 (11.1%)	.7100
Soybean	34 (27.0%)	2 (20.0%)	16 (38.1%)	6 (26.1%)	6 (18.2%)	4 (22.2%)	.3936
Tree nuts	36 (28.6%)	2 (20.0%)	13 (31.0%)	7 (30.4%)	8 (24.2%)	6 (33.3%)	.9192
Wheat	37 (29.4%)	3 (30.0%)	14 (33.3%)	6 (26.1%)	9 (27.3%)	5 (27.8%)	.9758
No. of allergens, no (%)							.7605
0	56 (44.4%)	4 (40.0%)	16 (38.1%)	10 (43.5%)	19 (57.6%)	7 (38.9%)	
1	17 (13.5%)	1 (10.0%)	6 (14.3%)	3 (13.0%)	3 (9.1%)	4 (22.2%)	
2	5 (4.0%)	1 (10.0%)	2 (4.8%)	2 (8.7%)	0 (0.0%)	0 (0.0%)	
3	15 (11.9%)	2 (20.0%)	4 (9.5%)	2 (8.7%)	3 (9.1%)	4 (22.2%)	
4	3 (2.4%)	0 (0.0%)	0 (0.0%)	2 (8.7%)	1 (3.0%)	0 (0.0%)	
5	7 (5.6%)	0 (0.0%)	3 (7.1%)	1 (4.3%)	3 (9.1%)	0 (0.0%)	
6	9 (7.1%)	1 (10.0%)	5 (11.9%)	0 (0.0%)	1 (3.0%)	2 (11.1%)	
7	7 (5.6%)	0 (0.0%)	3 (7.1%)	2 (8.7%)	2 (6.1%)	0 (0.0%)	
8	7 (5.6%)	1 (10.0%)	3 (7.1%)	1 (4.3%)	1 (3.0%)	1 (5.6%)	
Food allergen sensitization, mean (SD)	2.2 (2.7)	2.3 (2.8)	2.7 (2.9)	2.1 (2.6)	1.8 (2.6)	2.0 (2.5)	.6291

EoE = eosinophilic esophagitis; SD = standard deviation.

were practically nonexistent in our population of younger children.^{1,12} Similarly, 52% of our young cohort had dysphagia with aspiration of liquids, which is not currently known as a symptom of EoE in teenagers and adults. This, in particular, seemed to be age dependent, with a higher incidence at younger ages ($P = .0101$), and

suggests a variation in dysphagia type (solid vs. liquid) found by age in pediatric EoE patients. A recent review by Durvasula et al. describes a rising incidence of oropharyngeal dysphagia in younger infants and children that is similar to the liquid dysphagia we found in our youngest EoE children.¹³ Infants (<1 year of age) are

TABLE III.
Various Therapies Prescribed to Pediatric EoE Patients Under the Age of 5 Years

	Total, N = 127	0–1 Year Old, N = 10	1–2 Years Old, N = 43	2–3 Years Old, N = 23	3–4 Years Old, N = 33	4–5 Years Old, N = 18	P
Proton pump inhibitors							
Omeprazole	63 (49.6%)	6 (60.0%)	18 (41.9%)	14 (60.9%)	18 (54.5%)	7 (38.9%)	.4452
Lansoprazole	93 (73.2%)	7 (70.0%)	33 (76.7%)	17 (73.9%)	23 (69.7%)	13 (72.2%)	.9562
Steroids	87 (68.5%)	7 (70.0%)	26 (60.5%)	18 (78.3%)	24 (72.7%)	12 (66.7%)	.6472
Oral steroid							
Viscous budesonide	50 (39.4%)	4 (40.0%)	14 (32.6%)	13 (56.5%)	12 (36.4%)	7 (38.9%)	.4411
Fluticasone	59 (46.5%)	4 (40.0%)	18 (41.9%)	13 (56.5%)	14 (42.4%)	10 (55.6%)	.6925
Inhaled steroid, inhaled budesonide	4 (3.1%)	0 (0.0%)	1 (2.3%)	1 (4.3%)	2 (6.1%)	0 (0.0%)	.8249
Systemic steroid, prednisolone	11 (8.7%)	0 (0.0%)	4 (9.3%)	3 (13.0%)	2 (6.1%)	2 (11.1%)	.7930
Elimination diet	106 (83.5%)	9 (90.0%)	36 (83.7%)	20 (87.0%)	27 (81.8%)	14 (77.8%)	.9394
Allergen specific	89 (70.1%)	5 (50.0%)	32 (74.4%)	16 (69.6%)	23 (69.7%)	13 (72.2%)	.6868
Elemental diet	6 (4.7%)	2 (20.0%)	2 (4.7%)	2 (8.7%)	0 (0.0%)	0 (0.0%)	.0725
SFED	24 (18.9%)	2 (20.0%)	11 (25.6%)	3 (13.0%)	7 (21.2%)	1 (5.6%)	.4089

SFED = six-food elimination diet.

primarily on a liquid diet, and in our study, displayed the highest incidence of liquid dysphagia. However, patients > 1 year of age, who are also normally eating solid food at this age, present with high levels of liquid dysphagia in the setting of EoE. During the identification of pediatric EoE patients, liquid dysphagia should be taken into consideration.

Food allergies are thought to be associated with EoE, with milk (24%), eggs (13%), wheat (9%), and soy (9%) as the most common triggers in the general pediatric EoE population.^{14,15} In comparison, patients in our study had high sensitization to eggs (39.7%), milk (36.5%), and wheat (29.4%) along with peanuts (34.9%) (Table II). In contrast to results by Spergel et al.¹⁴ from a cohort of children ranging from 1 year to 18 years (mean age 6.4 years), we reported higher occurrences of food sensitization. Both Chadha et al. and Spergel et al. concluded that food sensitization decreases with age.^{11,14} Less evidence has been discovered on the role for environmental allergens in pediatric patients with EoE. However, common environmental allergens, including dust mites, cockroaches, and mold, have been shown to induce esophageal eosinophilia in vivo.^{16,17} A study of children aged 0 to 20 years by Chadha et al. found tree pollen (41%), grass pollen (39%), weed pollen (38%), and dust mite (36%) as the most common environmental allergens in kids, with 53% patients in the 0 to 4-year-old age group having sensitization to at least one environmental allergen.¹¹ In comparison, we report a lower overall (23.8%) and specific environmental allergen sensitization in the less than 5-year-old age group. Weed pollen (11.1%), tree pollen (9.5%), grass pollen (9.5%), and dust mite/arthropods (9.5%) were four of the most

common allergens in our study. Additionally, we found no significant difference in environmental allergen sensitization between infants and toddlers.

Corticosteroids are effective in treating pediatric EoE.^{4,5} Swallowed fluticasone (46.5%) and viscous swallowed budesonide (39.4%) were the most commonly used topical steroids in our population of children under the age of 5 years old, similar to results described by Krishna et al. on the general EoE population.¹⁸ Prednisolone, a systemic steroid, usage (8.7%) fell far below that of topical steroids (59.8%). Considering the possible adverse side effects of systemic steroids, including secondary adrenal insufficiency, bone mineral density abnormalities, glaucoma, and hyperglycemia,¹⁹ the limited use of this therapeutic tool was expected at our institution.

Elimination diets are efficacious in improving symptoms and reducing esophageal eosinophilia,^{7–9} with amino acid formula-based elemental diets as the most effective, with a response rate of 97% in pediatric patients (mean age 9.1 years).⁷ However, many patients find elemental formula unpalatable, explaining why only six of our study patients (4.7%), all under the age of 3 years, were on elemental diet compared to 24 patients (18.9%) and 89 patients (70.1%) on an SFED and allergen-specific restriction diet, respectively. The allergen-specific restriction diet was the most common diet prescribed by our physician teams. Prevalence of this diet increased by age, from 50.0% in the 0 to 1-year-old age group to 72.2% in the 4–5 year old age group. This increase capitulates the diet treatment timeline, a shift over time from broad elimination of foods to the restriction of one or few dietary elements.²⁰

	Total, N = 127	0–1 Year Old, N = 10	1–2 Years Old, N = 43	2–3 Years Old, N = 23	3–4 Years Old, N = 33	4–5 Years Old, N = 18	P
Change in symptoms, improvement in symptoms, no. of patients (%)	105 (86.1%)	9 (90.0%)	37 (88.1%)	20 (87.0%)	26 (81.3%)	13 (86.7%)	.9490
EOS/HPF							
Initial EOS/HPF, mean (SD)	59.7 (31.5)	40.2 (17.6)	61.8 (31.2)	62.6 (28.8)	53.4 (29.9)	73.8 (40.6)	.0510
Post-treatment EOS/HPF, mean (SD)	26.2 (34.6)	5.1 (11.3)	25.3 (33.5)	32.7 (37.7)	21.8 (29.8)	40.5 (44.8)	.1162
Change in EOS, (Δ EOS/HPF, mean (SD)	33.5 (39.1)	35.1 (18.5)	36.5 (39.7)	29.9 (46.5)	31.6 (30.2)	33.3 (52.9)	.9752
P value (Ho = null hypothesis: initial = post)	<.0001	.0005	<.0001	.008	<.0001	.0236	
Histologic response to treatment, improvement in biopsy, no. of patients (%)	96 (81.4%)	9 (100.0%)	33 (82.5%)	16 (72.7%)	27 (87.1%)	11 (68.8%)	.2541
Histologic resolution of EOE, <15 EOS/HPF							
No. of patients (%)	67 (56.8%)	8 (88.9%)	24 (60.0%)	10 (45.5%)	17 (54.8%)	8 (50.0%)	.2449
Change in EOS, Δ EOS/HPF, mean (SD)	50.1 (30.8)	37.6 (18.1)	53.0 (30.7)	64.5 (24.7)	38.2 (24.0)	61.1 (49.2)	.1385
P value, Ho: initial = post	<.0001	.0006	<.0001	<.0001	<.0001	<.0001	
% improvement in EOS, mean (SD)	0.9 (0.1)	1.0 (0.0)	0.9 (0.1)	1.0 (0.0)	0.9 (0.2)	0.9 (0.2)	.7934
P value, Ho: initial = post	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	

EOS = eosinophils; Δ EOS/HPF = EOS per HPF; HPF = high-power field; SD = standard deviation; Ho = null hypothesis.

Several limitations of this study were due to the methods of diagnosis and treatment. When reviewing samples, some pathologists listed the values of EOS/HPF in range of values. Therefore, the mean was used for calculation of statistics. Diagnosis of EoE was made by physicians in multiple departments. The standard for diagnosis and treatment varied between specialties. Seventeen of the 45 patients (37.8%) excluded from the study did not receive any PPI therapy before or after diagnosis of EoE. Considering the recurrent, chronic nature of EoE, patients might have received multiple medications or therapies over time. At the institution, treatment decisions are determined by provider and patient preference. Disease severity is not a particular variable in affecting treatment strategies. Currently, we have no standard protocol for treating EoE. However, we will consider moving to a standard approach when

discussing future multidisciplinary treatment of EoE. However, it should be noted that despite the treatment approach at this age, that improvement often occurs, regardless of strategy. Response to single-treatment modalities was not calculated. When patients were separated by response to only steroid or diet therapy, few or none were in the age categories. Loss of power restricted our ability to compare efficacies of different treatments. Although liquid dysphagia has a higher incidence in the younger patients of our study, it must be acknowledged that infants are primarily on a liquid diet. Other study limitations were due to its retrospective design. In some patient charts, it was difficult to determine the presence of symptoms and comorbidities. In determining environmental and food allergen sensitization, six groups of environmental allergens and eight groups of foods associated with SFED were considered. Other miscellaneous

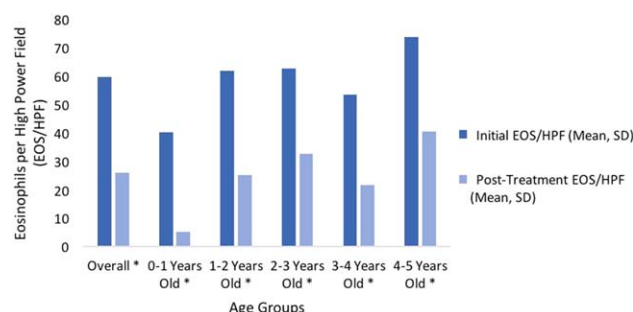


Fig. 3. Treatment response of pediatric patients by age group. All groups showed a significant difference between initial and post-treatment biopsies ($P < .05$). EOS = eosinophils; HPF = high-power field; SD standard deviation. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

allergies were recorded but excluded from analysis, as they were less than two standard deviations below the mean.

In summary, EoE has a diverse presentation in the pediatric population that needs to be clearly defined. Herein we provide clinical data of children presenting with EoE at very young ages. In fact, nearly 25% of our single institution's experience with EoE is surprisingly in the less than 5-years-old population. Moreover, evidence suggests substantial differences in disease presentation when stratified by patient age with younger children presenting with liquid dysphagia more commonly than the historic older patient. Treatment, however, remains successful, despite the approach of steroid versus food elimination. Differences in allergy presentation and esophageal dysfunction have been discussed but need to be further demarcated.

CONCLUSION

The aims of this retrospective clinical study were to provide insight into symptoms, comorbidities, and treatment outcomes unique to the pediatric EoE population under the age of 5 years. We confirmed previously published information regarding common symptoms of reflux and esophageal dysfunction, with new evidence supporting clear distinctions in disease characteristics by age. Dysphagia with aspiration was found in children with EoE and reported to be significantly greater at younger ages. Dysphagia with solid food was rare in our study population, and food impaction and chest pain were almost nonexistent. Additionally, higher levels of food allergen sensitization compared to the general

pediatric population lend evidence to the idea of food sensitization decreasing by age. Defining a distinct clinical profile of the youngest EoE patients will lead to more effective identification and treatments for the pediatric population as a whole.

BIBLIOGRAPHY

1. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol* 2011;128:3–20.
2. Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. *N Engl J Med* 2004;351:940–941.
3. Mukkada VA, Haas A, Maune NC, et al. Feeding dysfunction in children with eosinophilic gastrointestinal diseases. *Pediatrics* 2010;126:e672–e677.
4. Gupta SK, Vitanza JM, Collins MH. Efficacy and safety of oral budesonide suspension in pediatric patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2015;13:66–76.
5. Konikoff MR, Noel RJ, Blanchard C, et al. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. *Gastroenterology* 2006;131:1381–1391.
6. Konikoff MR, Noel RJ, Blanchard C, et al. Oral viscous budesonide is effective in children with eosinophilic esophagitis in a randomized, placebo-controlled trial. *Gastroenterology* 2010;139:418–429.
7. Liacouras CA, Spergel JM, Ruchelli E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastroenterol Hepatol* 2005;3:1198–1206.
8. Kagalwalla AF, Sentongo TA, Ritz S, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2006;4:1097–1102.
9. Spergel JM, Andrews T, Brown-Whitehorn TF, Beausoleil JL, Liacouras CA. Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. *Ann Allergy Asthma Immunol* 2005;95:336–343.
10. Assa'ad AH, Putnam PE, Collins MH, et al. Pediatric patients with eosinophilic esophagitis: an 8-year follow-up. *J Allergy Clin Immunol* 2007;119:731–738.
11. Chadha SN, Wang L, Correa H, Moulton D, Hummel DS. Pediatric eosinophilic esophagitis: the Vanderbilt experience. *Ann Allergy Asthma Immunol* 2014;113:445–451.
12. Nurko S, Rosen R. Esophageal dysmotility in patients with eosinophilic esophagitis. *Gastrointest Endosc Clin N Am* 2008;18:73–89; ix.
13. Durvasula VS, O'Neill AC, Richter GT. Oropharyngeal dysphagia in children: mechanism, source, and management. *Otolaryngol Clin North Am* 2014;47:691–720.
14. Spergel JM, Brown-Whitehorn TF, Cianferoni A, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J Allergy Clin Immunol* 2012;130:461–467.e5.
15. Kagalwalla AF, Shah A, Li BU, et al. Identification of specific foods responsible for inflammation in children with eosinophilic esophagitis successfully treated with empiric elimination diet. *J Pediatr Gastroenterol Nutr* 2011;53:145–149.
16. Mishra A, Hogan SP, Brandt EB, Rothenberg ME. An etiological role for aeroallergens and eosinophils in experimental esophagitis. *J Clin Invest* 2001;107:83–90.
17. Rayapudi M, Mavi P, Zhu X, et al. Indoor insect allergens are potent inducers of experimental eosinophilic esophagitis in mice. *J Leukoc Biol* 2010;88:337–346.
18. Krishna SG, Kakati BR, Olden KW, Brown DK. Treatment of eosinophilic esophagitis: is oral viscous budesonide superior to swallowed fluticasone spray? *Gastroenterol Hepatol (N Y)* 2011;7:55–59.
19. Dougherty T, Stephen S, Borum ML, Doman DB. Emerging therapeutic options for eosinophilic esophagitis? *Gastroenterol Hepatol (N Y)* 2014;10:106–116.
20. Sodikoff J, Hirano I. Therapeutic strategies in eosinophilic esophagitis: induction, maintenance and refractory disease? *Best Pract Res Clin Gastroenterol* 2015;29:829–839.