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Practice Pattern Variation in Pediatric Eosinophilic Esophagitis in the Carolinas EoE Collaborative^A

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Abstract

Objectives—Differences in the initial management of pediatric eosinophilic esophagitis (EoE) by practice setting have not been well characterized. We aimed to characterize these differences for sites in the Carolinas EoE Collaborative (CEoEC), a multicenter network of academic and community practices.

Methods—We performed a retrospective cohort study of pediatric EoE patients at five CEoEC sites: University of North Carolina (UNC) Hospital, Charlotte Asthma and Allergy Specialists, Greenville Health Systems, Wake Forest Baptist Medical Center, and the Medical University of South Carolina Hospital. Cases of EoE were defined by consensus guidelines. Data were extracted from electronic medical records. We tested for differences among sites and used a multinomial

^AThe subtitle was deleted due to space constraints.

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Off-label/unapproved drugs or products: treatment of EoE with topical corticosteroids, which is not approved by the US Food and Drug Administration.

model (polytomous regression) to assess associations between treatment and site, adjusting on patient factors.

Results—We identified 464 children with EoE across the CEoEC sites. The median age was highest at Wake Forest (11.4 years), the median eosinophil count was highest at UNC (69 eos/hpf), and UNC had the most male patients (82%). UNC used topical steroids for initial treatment in 86% of cases, compared with <1% in Greenville ($P < 0.01$). Greenville used dietary elimination more frequently than UNC (81% vs 2%, $P < 0.01$). Differences in treatment approach held after adjusting for potential baseline confounders. There was no significant association between patient factors and initial treatment approach.

Conclusions—Significant differences in EoE patient factors and treatment approaches were identified across CEoEC sites and were not explained by patient or practice factors. This suggests that institutional or provider preferences drive initial treatment approaches, and that more data are needed to drive best practice decisions.

Keywords

children; dietary elimination; eosinophilic esophagitis; practice patterns; steroids

Eosinophilic esophagitis (EoE) is a chronic immune and antigen-mediated disorder that is characterized by eosinophilic infiltration of the esophageal epithelium that causes symptoms of esophageal dysfunction.^{1,2} In infants and children, symptoms may include poor growth, failure to thrive, food intolerance, vomiting, abdominal pain, heartburn, and regurgitation. In adolescents and adults, dysphagia and food impaction symptoms predominate.³ Because food allergens have been shown to mediate the disease in a large proportion of patients, one set of treatment strategies attempts to remove food triggers. In such cases, elimination diets can either be targeted, in which foods are removed based on allergy testing; empiric, in which the “top-six” food triggers in EoE (dairy, wheat, egg, soy, nuts, seafood) are removed; or based on a hypoallergenic elemental formula.^{4–6} An alternative approach is to use swallowed (or topical) corticosteroids, in which asthma preparations (fluticasone inhaler, budesonide respules) are swallowed rather than inhaled to provide an anti-inflammatory effect in the esophagus.^{7–10} Because dietary and pharmacologic treatments have been effective in inducing symptomatic and histological remission of EoE, they are both considered first-line therapies for the initial management of eosinophilic esophagitis in adults and children;² however, there are no comparative trials of these two approaches.¹¹ As a result, variations in the management of EoE could result from patient factors (eg, demographics, disease severity), provider factors, or patient or provider preferences. These variations have not been well characterized in pediatric populations with EoE, however.

The Carolinas EoE Collaborative (CEoEC) is a multisite referral and research network of academic and community practices in North and South Carolina with expertise in managing EoE. Because each site cares for patients independently, the CEoEC provides an opportunity to examine differences in practice patterns for pediatric EoE management.

The aim of this study was to characterize differences in patient factors and initial EoE treatment strategies among sites in the CEoEC and assess factors that may influence the

initial management of EoE. We hypothesized that there would be differences in treatment strategies by site that would be independent of patient factors.

Methods

Patient Population

We performed a retrospective cohort study of five sites in the CEoEC: University of North Carolina Hospitals (Chapel Hill, NC); Asthma and Allergy Specialists (Charlotte, NC); Division of Pediatric Gastroenterology, Greenville Health System (Greenville, SC); Wake Forest Baptist Medical Center (Winston-Salem, NC); and the Medical University of South Carolina Children's Hospital (Charleston, SC). Cases of EoE were defined clinically and per consensus guidelines,^{1,2} including clinical symptoms of esophageal dysphagia, esophageal tissue biopsies showing ≥ 15 eosinophils per high power field (eos/hpf) after a proton pump inhibitor trial, and exclusion of other causes of esophageal eosinophilia. We included patients aged 0 to 18 years who were newly diagnosed between 2005 and 2014 as having EoE and who had records indicating active management with pharmacologic or dietary interventions. This study was approved by the institutional review board from each of the participating sites.

Data Collection

Data were extracted using a standardized Web-based form created through the Qualtrics Research Suite (Provo, UT and Seattle, WA). Researchers at the various sites had expertise in EoE and received training in abstracting patient data from the electronic medical record. All of the sites were provided with a data dictionary. Patient factors included sex, race, ethnicity, and insurance status. Other baseline patient information included date of diagnosis, maximum tissue eosinophil count (eos/hpf) at initial diagnosis, and history of other atopic diseases such as asthma or allergic rhinitis. All of the data regarding initial treatment also were collected. Treatment changes at successive visits were not reflected in these data given the focus of this article on initial treatment decision making. Treatments were categorized into one of four categories: steroids only, dietary elimination (both top-six food and targeted), elemental diet only, and a combination of the above approaches.

Statistical Analysis

Descriptive statistics were used to summarize the data and examine distributions. The χ^2 and analysis of variance tests were performed to test for differences in patient factors between sites. The χ^2 tests were used for differences in frequencies and one-way analysis of variance tests were used for differences in means. The Fisher exact test was used in cases in which data were too sparse for χ^2 estimation. A multinomial model (polytomous regression) was used to assess the association between treatment and site, adjusting for patient factors (baseline tissue eosinophil count, age at diagnosis, date of diagnosis, atopic disease status, and insurance status) that could act as confounders.

Results

We identified 464 children with EoE from the 5 CEoEC sites. Across these sites, we observed differences in baseline patient characteristics, including age at diagnosis, maximum eosinophil counts, and distribution of sex (Table 1). The median age in years was highest in Winston-Salem (11.4 years). The median tissue eosinophil count was highest in patients at Chapel Hill (69 eos/hpf). Although all of the sites had a predominantly male patient population, Chapel Hill had the highest percentage of boys, at 82.2%. Charlotte had the greatest percentage of patients with a history of atopic disease (72%). Patients at all of the sites were predominantly white (79%–86%). No other significant differences in baseline characteristics were noted across the sites, including ethnicity or insurance status.

Initial treatment approach varied significantly across sites (Table 2). Chapel Hill used topical steroids for initial treatment in 86% of cases, whereas Greenville used topical steroids in initial treatment in <1% ($P < 0.01$). Topical steroid use was 50%, 49%, and 44% in Charlotte, Charleston, and Winston-Salem, respectively. In contrast, Greenville used dietary elimination as a first-line treatment in 81% of cases, whereas Chapel Hill used dietary elimination in only 2% ($P < 0.01$). At all of the sites, elemental diet was the least frequent method of initial treatment, used in 0% to 6% of cases.

After adjusting for potential confounders (baseline tissue eosinophil count, age, and insurance status), Greenville was significantly more likely than Chapel Hill to use dietary elimination compared with topical steroids (Table 3). There were few predictors of initial treatment choice with this modeling strategy. Although the odds of undergoing dietary elimination or the combination approach as compared with steroid treatment as an initial treatment was reduced as age increased (adjusted odds ratio 0.87 and 95% confidence interval 0.80–0.95 for dietary elimination; adjusted odds ratio 0.79 and 95% confidence interval 0.71–0.88 for combination approach), atopic disease, insurance status, date of diagnosis, and tissue eosinophil count were not associated with the initial treatment approach (data not shown). We also examined three time periods that corresponded to the publication of EoE consensus guidelines (before 2007, 2007–2011, and after 2011) and found that practice patterns remained consistent over time. Data on elemental diets were too sparse to be included in multinomial analysis.

Discussion

Treatment for EoE in children consists of several effective first-line options with no direct comparative data that would support one pharmacologic or dietary approach over the other.³ Given the lack of evidence-based guidance for an initial treatment approach to EoE, we suspected that substantial practice variability would exist among EoE providers based on provider preference or patient demographics. The CEoEC, made up of both community and academic centers of varying sizes in North and South Carolina, provides a uniquely ideal framework with which to explore this variation.

We observed significant differences in EoE patient factors and treatment approaches across the five CEoEC sites. Chapel Hill heavily favored steroids as an initial treatment approach,

whereas Greenville heavily favored dietary elimination. Notably, differences in baseline patient factors did not explain the differences in treatment approaches; treatment differences persisted even after multinomial analysis. Moreover, despite the strong treatment preferences of Chapel Hill and Greenville, both sites are academic/referral centers. More important, practice styles are influenced by resources available to the provider and patient, and the support of a dedicated dietitian to guide providers and patients through the dietary approaches is critical to using this approach; however, trained dietitians familiar with EoE were present at all of the CEoEC sites. As such, neither patient factors nor practice setting adequately explained the variability of treatment approaches across study sites. Most likely, differences were based on institutional preferences.

The degree of variability in the practice patterns in our data sample is not surprising in the context of continually evolving guidelines and the current literature on EoE practice patterns. Prior surveys of gastroenterology providers regarding preferred treatment approaches demonstrated wide variability in practice preferences.^{12–15} Peery et al reported that 54% of surveyed GI providers used steroids as first-line therapy, and within this group, 26% used some form of dietary therapy as second-line therapy.¹³ Spergel et al demonstrated similar variation in EoE treatment, with 44% of surveyed gastroenterology providers using steroids with proton pump inhibitors and 39% using dietary elimination.¹⁴ Furthermore, Lucendo and colleagues reported that 62% of patients received steroid therapy and 52% received some form of dietary therapy (and some received both), with patients at academic centers being more likely to receive steroids than patients at nonacademic centers.¹² Although in general these articles demonstrated a greater use of steroids over dietary elimination approaches, these differences seem to be driven more by institutional preferences than by patient factors. This would be consistent with our findings, but the underlying reason for the institutional preference has yet to be examined. This would be an important future direction for study. In addition, our multicenter collaborative of academic and community settings is unique in the EoE literature

Several limitations in our study deserve mention. Although the study includes both academic and community practices, the majority was large academic centers, which may have biased the data. The main practice variation found in this study was between two similar academic centers, thereby minimizing the possible effect of this bias. Data on practice variations among providers within the same CEoEC site were not collected, limiting our ability to attribute variations to provider preference. All of the providers, however, had at least 5 years of EoE experience at the time of the study and all were gastroenterologists, with the exception of one allergy/immunology provider at the Charlotte site. These similarities at the provider level suggest that the demonstrated institutional preferences also may reflect provider preferences. Because this was a retrospective study in which multiple sites entered data independently, the study also is limited by potentially incomplete data or errors in data entry; however, standardized data forms, training, and a data dictionary were used to reduce this possibility.

Despite these potential limitations, our study also had several strengths, including that it was a multicenter study that recruited a large number of patients from both academic and community practices. Limiting sites to the states of North and South Carolina also reduced

the likelihood that regional variation was a confounding factor in our analysis. Similarly, the focus on the pediatric population is a strength, because choice of treatment related to the adult or pediatric patient is not an issue, and there are few data about practice variation in children.

Conclusions

In this study of five practice sites in the CEEC, we identified several differences in the characteristics of children among sites and substantial practice variability among sites. Patient and disease factors did not explain the practice variations related to choice of initial treatment modality in EoE. Further work needs to be done to determine whether there are other factors beyond institutional preference that contribute to the practice patterns elucidated in this study, how practitioners decide which treatment to use, and whether the variability of treatment approach across sites leads to differences in patient outcomes. Moreover, the study highlights the need for data regarding best practices to drive treatment decisions in children with EoE to optimize outcomes.

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Key Points

- Baseline data from a cohort of 464 children from 5 practice sites in the Carolinas eosinophilic esophagitis collaborative were assessed for an initial treatment approach.
- There were substantial differences in initial treatment approach selected, with one center almost exclusively using dietary elimination and another center primarily choosing topical corticosteroid administration.
- The practice variations related to choice of initial treatment were not explained by patient or diseases factors.

Table 1

Baseline characteristics by CEoEC site

	Chapel Hill, NC (n = 135)	Charlotte, NC (n = 115)	Greenville, SC (n = 127)	Charleston, SC (n = 55)	Winston-Salem, NC (n = 32)	P
Age at diagnosis, y (range)	6.9 (2.8–12.5)	8.3 (2.9–10.9)	6.7 (3.3–11.3)	6.7 (3.0–12.6)	11.4 (6.6–15.2)	0.01
Eosinophil count (max eos/hpf)	69 (40–100)	40 (30–50)	40 (22–65)	35 (25–55)	47 (25–60)	<0.01
Male (n, %)	111 (82)	86 (75)	82 (65)	35 (64)	23 (72)	0.01
White (n, %)	95 (79)	83 (84)	103 (86)	46 (84)	24 (80)	0.04
Non-Hispanic (n, %)	124 (96)	97 (94)	121 (95)	54 (98)	31 (97)	0.8
Private insurance (n, %)	93 (69)	75 (65)	84 (66)	35 (64)	15 (47)	0.43
Medicaid (n, %)	38 (28)	38 (33)	41 (32)	20 (36)	16 (50)	
Atopic disease (n, %)	77 (57)	83 (72)	74 (59)	24 (44)	19 (59)	<0.01

CEoEC, Carolinas EoE Collaborative; EoE, eosinophilic esophagitis; eos, eosinophils; hpf, high power field.

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Table 2

Initial treatment frequencies across CEoEC sites

Treatment approach (n, %)	Chapel Hill, NC (n = 135)	Charlotte, NC (n = 115)	Greenville, SC (n = 127)	Charleston, SC (n = 55)	Winston-Salem, NC (n = 32)	P
Steroids	116 (86)	57 (50)	1 (1)	27 (49)	14 (44)	<0.01
Dietary elimination	3 (2)	39 (34)	103 (81)	4 (7)	4 (13)	<0.01
Elemental diet	2 (1)	3 (3)	7 (6)	1 (2)	0 (0)	0.36
Combination	14 (10)	16 (14)	16 (13)	23 (42)	14 (44)	<0.01

CEoEC, Carolinas EoE Collaborative; EoE, eosinophilic esophagitis.

Table 3

Associations between CEoEC sites and initial treatment

Treatment approach	OR	aOR ^a
Dietary elimination		
Chapel Hill, NC	Referent	Referent
Charlotte, NC	26.456 (7.839–89.285)	7.201 (1.796–28.877)
Greenville, SC	>999.999 (407.898 to >999.999)	>999.999 (272.363 to >999.999)
Charleston, SC	5.728 (1.210–27.109)	2.651 (0.503–13.984)
Winston-Salem, NC	11.048 (2.239–54.520)	2.776 (0.430–17.908)
Combination		
Chapel Hill, NC	Referent	Referent
Charlotte, NC	2.326 (1.062–5.095)	0.902 (0.326–2.494)
Greenville, SC	115.988 (14.160–950.108)	106.882 (12.003–951.726)
Charleston, SC	7.058 (3.218–15.480)	4.926 (1.900–12.769)
Winston-Salem, NC	8.286 (3.284–20.903)	3.900 (1.100–13.829)

aOR is the adjusted odds of treatment as compared with the referent treatment (topical steroids), for a given site as compared with the referent site (Chapel Hill), adjusting on baseline patient factors. aOR, adjusted odds ratio; CEoEC, Carolinas EoE Collaborative; EoE, eosinophilic esophagitis; eos, eosinophils; hpf, hpf, high power field; OR, odds ratio.

^a Adjusted for insurance, atopic disease, date of diagnosis, and maximum eos/hpf at baseline.

^{**} Multinomial model assessing study site in relation to baseline treatment approach. A