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Incidence of Pediatric Eosinophilic Esophagitis and Characterization of the Stricturing Phenotype in Alberta, Canada

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ABSTRACT

Introduction: Limited work has been done to characterize the stricturing pediatric eosinophilic esophagitis (EoE) phenotype. We aimed to determine, in pediatric EoE: the local incidence, the frequency of esophageal stricturing, and the safety of mechanical dilations.

Methods: We retrospectively identified all new cases of EoE at our center from 2015 to 2018 using esophageal biopsy reports, EoE clinic lists, and a local OR database of esophageal dilatations. Electronic medical records (EMRs) were reviewed to confirm EoE diagnosis. Clinical data were captured from the outpatient EMR and gastroscopy/pathology reports. Scope adverse event data were captured from multiple sources. The 2016 census data were used to calculate incidence rates.

Results: One hundred eighty-five new cases of EoE were diagnosed during the study period. For patients <15 years old living in Edmonton, the incidence over the 4 years was 11.1 cases per 100,000 person years. Eight of 185 (4%) patients had endoscopically confirmed esophageal strictures, 4 of which required mechanical dilation. Eleven of 185 (5.9%) patients had more subtle signs of esophageal narrowing, but no focal strictures. No perforations or episodes of significant bleeding were reported. Pain was reported after 15% of all scopes, including 50% of the 28 scopes with focal strictures. No unexpected admissions or emergency department visits occurred within 72 hours of a gastroscope with esophageal narrowing.

Conclusions: Edmonton zone has one of the highest incidences of pediatric EoE reported. In this cohort, 4% had focal esophageal strictures, and 6% had more subtle narrowing. Mechanical dilation of esophageal strictures was associated with no significant adverse events.

Key Words: eosinophilic esophagitis, stricture, dilation, incidence

What Is Known

- The incidence of pediatric eosinophilic esophagitis (EoE) has not been well studied in Canada, with no incidence data available using new 2018 diagnostic criteria.
- Esophageal narrowing is an uncommon but poorly understood complication of pediatric EoE.

What Is New

- Edmonton and Northern Alberta have some of the highest incidence rates reported for pediatric EoE.
- Esophageal narrowing is not uncommon in pediatric EoE, with a focal stricturing rate at diagnosis of 4%.
- Pain is more common in scopes with narrowing, but no significant adverse events were seen in our cohort.

INTRODUCTION

Although our scientific understanding of the natural history of eosinophilic esophagitis (EoE) remains in an early stage, EoE is increasingly recognized as a common cause of dysphagia in older children and adults. Younger children often present with a more nonspecific clinical picture, with picky eating, vomiting, and abdominal pain. EoE symptomatology relates to esophageal dysfunction due to chronic, antigen immune-mediated, eosinophil-predominant inflammation of the esophagus. The reported incidence is increasing, with most recent pediatric estimates between 0.7 and 10 cases per 100,000 person-years (1). The only study to date which reported Canada pediatric EoE incidence data relied on listed indication for esophagogastroduodenosocopy (EGD) on endoscopy reports as evidence of esophageal dysfunction (2).

The most severe manifestation of EoE is an esophageal stricture, associated with a high risk of esophageal food impaction (3). EoE-related esophageal strictures are commonly reported in adult studies, with rates as high as 70% when EoE has been diagnosed after significant delay (4). The reported rate of stricturing in pediatric EoE is generally closer to 8% (5), but the rates in the literature vary considerably from 0.2 to 28% (6,7). When strictures are identified on endoscopy, they often require mechanical dilation to prevent food bolus impaction. To date, the studies describing EoE stricture dilation in pediatrics have been limited to small single-center reports (8–10).

We aimed to review all newly diagnosed pediatric EoE cases in our center over a 4-year span, with the aim of reporting the first Canadian pediatric EoE incidence data to use both pathology and clinical data to meet the 2018 AGREE diagnostic criteria (11). We also hoped to further examine the stricturing-EoE phenotype by assessing the frequency of this disease subtype, and determining its associated clinical and endoscopic features. Finally, we aimed to assess the safety of endoscopy in this patient population, including the safety of mechanical dilation of esophageal strictures.

MATERIALS AND METHODS

Study Design and Population

We performed a retrospective chart review of all new cases of EoE diagnosed at the Stollery Children's Hospital (Edmonton, Alberta, Canada) from 2015 to 2018. The Stollery Children's

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Hospital is the only children's hospital in Northern Alberta, with the Alberta Children's Hospital (Calgary, Alberta) receiving referrals from the southern half of the province.

All EoE cases met the 2018 AGREE conference diagnostic criteria (11). Possible EoE cases were identified through one of 3 means: esophageal biopsy reports for the province of Alberta (CoPath database) were searched for key terms ("eosinophilic esophagitis" or "esophagitis with eosinophils"); outpatient EoE clinic lists; and esophageal dilatations performed at our center were identified in the Stollery OR Manager database. For all possible EoE cases, EoE diagnosis was confirmed after assessing esophageal pathology reports to confirm ≥15 eosinophils per high-powered field, and electronic medical records (EMRs) to confirm symptoms of esophageal dysfunction. Patients were included in cohort if <16 years old at diagnosis.

The study was approved by the University of Alberta Health Research Ethics Board (Study ID Pro00089709).

Incidence

The most recent Statistics Canada federal census data (2016) were used to calculate incidence rates. Incidence rates were calculated as the number of new EoE cases divided by the number of years each individual in the selected population was at risk for the disease (total person-years), presented as cases per 100,000 person-years.

To ensure all cases of EoE within our catchment area (Northern Alberta) were captured, only patients <15 years old were included in incidence calculations. Policies in *adult* endoscopy units in Northern Alberta do not permit scoping children under this age, so all diagnostic EGDs in this age cohort would be done in our center.

For the purposes of our incidence calculations, patients' places of residence were based on the postal code listed in our EMR at the time of data collection (fall 2019). Northern Alberta was defined as any location north of Red Deer, a city mid-way between Edmonton and Calgary which can send referrals to either center. Rural was defined as any town with a population of <10,000 individuals, based on most recent available federal or provincial census data.

Clinical, Endoscopic, and Pathology Data

Clinical information from the initial clinic visit was gathered from the outpatient EMR. Data were also captured from EGD procedure and pathology reports from the diagnostic scope and any follow-up endoscopies until the end of our data collection period (April 30, 2019). When standardized EoE endoscopic reference score (EREFS system) was not prospectively used, the EREFS components were extracted from the descriptive endoscopy report text.

The Alberta Ambulatory Care Reporting System and Alberta Health Services Admissions, Discharge, Transfer databases were searched for all patients to find unexpected emergency department visits and hospital admissions within 72 hours of EGD. An additional in-depth peri-endoscopy chart review was performed on a subset of patients (n = 75) to capture scope adverse events during/immediately after endoscopy. This subset included *all* patients with signs of esophageal narrowing (n = 19), as well as the first 56 patients without narrowing to be identified in our search (to serve as controls). A peri-endoscopy chart review could not be completed on the remaining 110 patients without esophageal narrowing due to the prohibitive time required for such a review.

No statistically significant differences were found in the reviewed and non-reviewed patients for gender (64% versus 72% male), median age at diagnosis (9.3 years old, 95% confidence interval [CI], 5.2–12.7 versus 9.7 years old, 95% CI, 5.8–13.3), and median duration of symptoms (12 months, 95% CI, 7–24 versus 12 months, 95% CI, 6–48).

Data Analysis

Incidence rates are presented as cases per 100,000 person-years. Medians are presented with interquartile ranges (IQRs).

RESULTS

One hundred eighty-five new EoE diagnoses were identified during our study period. These patients underwent a combined 506 EGDs, including 17 esophageal dilations. All dilations were performed by pediatric gastroenterologists in our center.

Incidence of pediatric EoE was calculated for all patients in Northern Alberta, and for the subsets of this population within Edmonton, from rural locations, and from urban locations (Table 1). The incidence for 0- to 14-year-old children was 11.1 and 9.1 per 100,000 person years in Edmonton and Northern Alberta, respectively. Incidence was highest in the 10- to 14-year-old age group in all jurisdictions, and incidence was notably lower in the rural compared to urban setting.

Review of endoscopy reports prompted categorization of patients into a few distinct subgroups (Table 2). The majority (166; 90%) of the 185 patients included in the study never had any endoscopic evidence of esophageal narrowing during the follow-up period. Eight patients (4.3%) had focal strictures identified on endoscopy, with 4 of these patients (2.1%) requiring mechanical stricture dilation at some point during the follow-up period. A further 11 patients (5.9%) had more subtle signs of esophageal narrowing, but no definitive focal area of stricture. Such "subtle" signs of narrowing included creation of rent with scope passage (6), diffuse esophageal narrowing (1), or a segment of possible narrowing noted but no resistance to passage of a standard gastroscope (3).

The median age at diagnosis was notably higher in patients with focal strictures, although with wide IQRs (Table 2). The median duration of symptoms at diagnosis was higher in the stricturing subset and much higher in the subtle narrowing group, although again with wide IQRs. The majority of patients were atopic, and the majority were male (70.3%). As expected, food impaction and dysphagia were more common in patients with esophageal narrowing, while other symptoms were less discriminating.

Patients with focal strictures, and particularly those requiring dilations, underwent more EGDs during the follow-up period (Table 2). At diagnosis, linear furrowing and loss of vascular pattern were overrepresented in the subtle narrowing subgroup, and trachealization was notably reduced in the nonnarrowing group.

Seven of the 8 children with focal strictures had strictures on their diagnostic scope; one had their low-grade stricture noted on follow-up scope within a few months of initial endoscopy that was assumed to have been missed at diagnostic scope.

Strictures were identified in proximal (5), mid (3), or distal (2) esophagus, with only 1 child having 2 focal strictures in separate esophageal segments. Of the 4 children with focal strictures who did *not* require dilation, the strictures of 2 resolved with topical steroids, 1 resolved with proton pump inhibitor (PPI), and 1 had not had a follow-up EGD during the data-collection period. Of the 4 children with focal strictures that *were* dilated, 2 had a persistence of stricture despite a trial of PPI, and 2 had persistence of stricture

TABLE 1. Incidence of EoE in patients less than 15 years old

	Incidence per 100,000 person-year (cases)			
Age (years)	**Edmonton**	**Northern Alberta**	**Rural**	**Urban**
0–4	8.7 (21)	6.4 (33)	0.9 (1)	8.0 (32)
5–9	7.6 (17)	9.4 (47)	6.0 (7)	10.4 (40)
10–14	18.1 (35)	12.1 (54)	5.5 (6)	14.2 (48)
0–14	11.1 (73)	9.1 (134)	4.1 (14)	10.6 (120)

Northern Alberta includes locations north of Red Deer, Alberta. Rural is defined as towns with populations <10,000.

TABLE 2. Clinical characteristics, endoscopic findings, and endoscopic adverse events, categorized by disease phenotype

	Strictures	Strictures req. dilation	Subtle signs narrowing	No narrowing	Overall
Number of patients	**8 (4.3)**	**4 (2.1)**	**11 (5.9)**	**166 (89.7)**	**185**
Clinical characteristics					
Atopic (%)	75.0%	100.0%	54.5%	72.3%	71.0%
Median age at diagnosis (years; IQR)	13.1 (9.6–14.0)	13.3 (11.0–14.0)	9 (5.4–13.9)	9.5 (5.6–12.8)	9.7 (5.7–13.3)
Median duration symptoms at diagnosis (months; IQR)	15 (12–84)	18 (12–84)	36 (24–60)	12 (6–36)	12 (6–36)
Median number of EGD during follow-up period (IQR)	3.5 (3–5)	5 (4.5–7)	2 (2–3)	2 (2–3)	2 (2–3)
Symptoms at diagnosis (%)					
Food impaction	87.5	75.0	54.5	20.5	25.3
Dysphagia	87.5	100.0	63.6	54.8	56.5
Nausea/emesis	25.0	25.0	18.2	44.0	41.4
GER	25.0	0.0	9.1	21.1	20.4
Heartburn/chest pain	25.0	25.0	18.2	17.5	17.7
Abdo pain	0.0	0.0	18.2	38.0	34.9
Weight loss/FTT	0.0	0.0	0.0	21.1	18.8
Findings on diagnostic EGD (%)					
Linear furrowing	50.0	25.0	90.9	77.1	78.5
LOVP	62.5	50.0	81.8	54.2	57.5
Trachealization	62.5	50.0	27.3	7.2	11.0
White exudates	37.5	25.0	54.5	54.8	55.2
Narrowing	87.5	100.0	54.5	0.0	7.7
Immediate post-EGD complications					
Number of patients' charts assessed (n)	8	4	11	56	75
EGD charts assessed (n)	28	16	14	171	239
Pain (%)	50	63	29	8	15
Analgesic use (%)	21	20	75	27	35

The "Strictures req. dilation" is a subset of the "Strictures" patients. Strictures req. (requiring) dilation. IQR (interquartile range). Healthcare utilization data were searched for all 185 patients in the study cohort. Chart review to collect immediate post-EGD complication was performed for all patients with narrowing (of any kind), and a number of patients with no narrowing. In each case, all available EGD records for a patient were reviewed. EGD = esophogastroduodenosocopy; FTT = failure to thrive; IQR = interquartile range; LOVP = loss of vascular pattern.

despite treatment with topical steroids. The children with focal stricture underwent a cumulative total of 15 dilations, with a median of 4 dilations each, and with repeat dilation spaced a median of 65 days apart. Two dilations were performed with a Savory dilator (bougie) with guidewire, but the remainder were performed with transendoscopic balloon dilatation. The median increase from lowest to highest dilation diameter in a single session was 2.0 mm. A single patient in the subtle signs of narrowing group was empirically dilated on 2 occasions due to ongoing symptoms of severe dysphagia, which were having debilitating effects on their quality of life.

No unexpected hospital admission within 72 hours of EGD was reported for any of the 185 patients included in the study.

One unexpected emergency department visit post-EGD was recorded for a patient in the nonnarrowing group; this patient presented with chest pain but was sent home on PPI after normal chest radiograph and normal esophageal contrast study. No perforations or significant bleeding events occurred in any of the 239 EGDs assessed, including 28 scopes with focal strictures and 16 that involved esophageal dilations. Pain was more common following endoscopies when narrowing was observed, particularly in patients when dilation was performed (Table 2).

A post-hoc analysis was performed on the data to assess the relative efficacy of the three most common EoE treatment modalities: PPI, dietary elimination (of any form), and topical steroids (such as oral viscous budesonide). PPI was overrepresented as a treatment modality, as it was required as part of the diagnostic criteria through much of the study period. PPI had the lowest rate of induced histologic remission (peak eosinophil count reduced to <15 Eo/HPF) or endoscopic remission (resolution of endoscopic EoE findings) and the lowest median reduction in peak eosinophil count (Table 3). Topical corticosteroids were more efficacious than dietary elimination in inducing histologic remission and in median reduction in peak eosinophil count.

DISCUSSION

We have described the first Canadian pediatric incidence for EoE that uses the 2018 AGREE diagnostic criteria (Table 1). A previous report from Calgary, Alberta, found approximately 4–7 EoE cases per 100,000 person-years among 0–19 year olds (2).

However, this study used indication for EGD (as listed on the endoscopy report) as a marker for esophageal symptoms, a method that has not been validated. Our incidence rates are higher than most studies listed in a previous systematic review (1) and are similar to what has been described for Canadian pediatric inflammatory bowel disease (12). Given the strength of our case-finding methodology and the access to free universal healthcare in our province, we are confident that our reported incidence rates are accurate for symptomatic EoE in our population. The notably increased incidence in the 10- to 14-year age group is consistent with previous studies, which show

TABLE 3. EoE treatment modalities and their relative efficacy

	PPI	Dietary elimination	Topical steroids
Patients started on selected treatment	82 (44%)	55 (30%)	50 (27%)
On the next EGD after initiating the selected treatment			
Median reduction in peak Eo/HPF (median; IQR)	0.0 (−21.5 to 19.5)	20.0 (0.5−47.0)	31.0 (12.0−60.0)
Peak Eo/HPF reduced to < 15 Eo/HPF (n; %)	14 (17%)	24 (44%)	32 (64%)
Normalization of macroscopic EoE findings (n; %)	7 (8%)	17 (30%)	14 (27%)

Eo/HPF = eosinophil per high powered field; IQR = interquartile range; PPI = proton pump inhibitor.

the incidence of EoE increasing to a peak in the third through fifth decades of life (2).

Our overrepresentation of patients living in an urban versus a rural setting (incidence 10.6 versus 4.1 per 100,000 person-years) has been described previously (13) and is also consistent with trends from other atopic diseases (14,15). However, other studies have demonstrated conflicting evidence of a higher prevalence of EoE in *rural* settings (16). One possible reason for this discrepancy is our study's inclusion of *only* pediatric patients and the Hygiene hypothesis' emphasis on childhood exposures. Adults are more likely to have moved from their place of birth/childhood, and their current location may therefore no longer be reflective of childhood exposures.

We describe 4.3% of patients with a focal stricture and 5.9% of patients having other subtle signs of narrowing, for a total 10.3% esophageal narrowing rate (Table 2). Widely disparate stricturing rates are reported previously. An early single-center retrospective report from Philadelphia described 381 new pediatric cases of EoE, but with only 1 focal stricture (0.2%) was noted on endoscopy. In contrast, multiple studies from Saudi Arabia have noted focal esophageal strictures in as many as 22%–28% of new pediatric EoE diagnoses (6,8). A 2012 meta-analysis reported a pediatric EoE stricturing rate of 8% (5), but this analysis included studies of specific subsets of patients (such as those with severe dysphagia), so this is not likely representative of the overall pediatric EoE population. Perhaps, the most robust data to date come from a retrospective multicenter Dutch study, which included 117 pediatric EoE cases and reported an esophageal stricturing rate of 14% (3). Given our larger pediatric sample size, our stricturing data are an important addition to the field.

We show a higher median age at diagnosis for patients with focal esophageal stricture and a longer duration of symptoms prediagnosis in those with narrowing of any kind (Table 2). Although our sample size limits our ability to comment on the statistical significance of these results, these trends are consistent with data from the adult literature, showing a clear association between the duration of symptoms and probability of stricture formation (4).

A low rate of trachealization on diagnostic endoscopy of patients without narrowing (7.2%) was observed compared with those with narrowing (42.1%), and particularly compared to those with a focal stricture at diagnosis (62.5%; Table 2). This trend is consistent with the proposed association of fibrosis with this endoscopic finding. The dramatic overrepresentation of linear furrowing and loss of vascular pattern in the subtle signs of narrowing group are more challenging to explain, as these endoscopic findings are more commonly associated with an inflammatory picture (4). One possible explanation is that in contrast to adults, a larger proportion of the esophageal narrowing seen in pediatric EoE may be driven by inflammation rather than fibrosis (further discussed below).

No perforations or significant bleeding events were reported among 239 EGDs reviewed, including 16 EGDs with dilation. This safety profile was not surprising, given the rarity of these severe outcomes in a larger pediatric case series (9). Although our rate of chest pain/odynophagia postdilation (63%; Table 2) was higher than a previous pediatric dilation study (15%), this larger study relied on various adverse event reporting systems to collect these data, instead of direct individualized chart review (9). Our postdilation pain rate is more consistent with the rates found in an adult EoE dilation study (74%), which assessed pain via a post-EGD survey (17). Unfortunately, this will likely remain a challenging area of study in pediatrics, as there will always be difficulty in accurately identifying post-procedural pain in young children who have undergone a general anesthetic.

In a post-hoc analysis of treatment efficacy in our population, PPI was notably less efficacious than either dietary restriction or topical steroids and was less effective than what has been described in the literature. In particular, only 17% of EGDs performed after adding PPI had a reduction in peak eosinophil count to below the 15 Eo/HPF in the diagnostic criteria, notably <50% rate seen in a recent meta-analysis (18). The effect of topical steroids on reduction in peak eosinophil count was striking and was similar to other reports (19). Unfortunately, it is difficult to definitively compare results from our dietary elimination cohort to the literature, as our data do not distinguish between the range of restrictions within this treatment paradigm (eg, 6 versus 4 versus 2 food elimination diets, allergy test-driven elimination diets).

Our study has a few limitations. As a single center study capturing only 4 years of new diagnoses, the number of stricturing cases is quite limited, limiting our ability to statistically analyze our data. Further, all endoscopic findings are inherently subjective, and an accurate chart review relies on thorough documentation of these findings. Similarly, capturing adverse event data from chart review relies on accurate physician/nursing assessments, and thorough documentation. Although the 2018 AGREE diagnostic criteria were used in the case definition for our study, there may have been differences in patient care after the first endoscopy if patients were classified according to ongoing clinical use of the previous diagnostic criteria (which required a trial of PPI prior to diagnosis of EoE). Additionally, cases of PPI-responsive EoE who were already being effectively treated with PPI at time of endoscopy may have normal esophageal biopsies and would therefore be missing from our incidence data. This issue is reflective of limitations of current clinical practices and, therefore, cannot be ascribed to a retrospective trial. Additionally, the treatment efficacy data must be interpreted with caution, as should any post-hoc analysis of a noncontrolled, nonrandomized, retrospectively collected clinical cohort. In particular, these treatment results are reflective of therapies started prior to an EGD, but we have been unable to control for therapies that may have been *stopped* since a patient's last EGD. Additionally, no effort was made to quantify adherence to prescribed treatment among our patients.

In conclusion, we show that pediatric EoE is very common in our population, with a notably lower incidence rate in rural areas. We found a 10% esophageal narrowing rate, including 4% focal esophageal strictures. Although pain was more commonly reported in EGD

with esophageal dilations, no major adverse events were reported. We continue to work on collecting multicenter data on pediatric esophageal strictures in Canada, with the hopes of clarifying key clinical/endoscopic features associated with stricturing. Moving forward, we would encourage more effort to understand the pathophysiology of esophageal narrowing in pediatric EoE. Although strictures of pediatric EoE are assumed to relate to the high levels of fibrosis associated with this disease in adults (20), the descriptions here and elsewhere in the pediatric literature of strictures resolving with *medical* therapy would seem to contradict this assumption.

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