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Epidemiology of Eosinophilic Esophagitis in Patients with Cystic Fibrosis: A Population-Based 5-Year Study

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ABSTRACT

Purpose: The prevalence of eosinophilic esophagitis (EoE) has been on the rise since it was first described in the 1990s. Several diseases and exogenous factors have been associated with EoE. Our aim was to investigate the epidemiology of EoE in cystic fibrosis (CF) patients.
Methods: We identified individuals with CF from September 2014 to September 2019 within a database (IBM Explorys Solutions, Inc.). The prevalence of EoE in patients with CF was compared to the general population.
Results: The database included 36,111,860 patients during the 5-year study period: 12,950 with CF (0.036%) and 28,090 with EoE (0.078%). EoE prevalence was higher in CF patients than the general population (46 in 10,000 vs. 7.8 in 10,000, $p<0.001$). Patients with CF and EoE were more likely to be male (50% vs. 33.5%, $p<0.008$), children (33.3% vs. 16.5%, $p<0.001$), and non-Hispanic (100% vs. 88.7%, $p<0.001$) than CF patients without EoE. CF with EoE patients were more likely to be children than EoE only (33.3% vs. 10.5%, $p<0.001$). Allergic conditions were generally more prevalent in CF with EoE than CF only (83.3% vs. 68.3%, $p=0.01$) and EoE only (83.3% vs. 69.3%, $p=0.014$).
Conclusion: EoE is nearly 6-times more prevalent in CF patients. Those patients had higher incidence of other atopic conditions. EoE must be considered in the differential diagnosis of patients with CF presenting with dysphagia, refractory gastroesophageal reflux, vomiting, and other esophagus-related symptoms.

Keywords: Eosinophilic esophagitis; Cystic fibrosis; Epidemiology

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic, immune mediated inflammatory process involving the esophagus leading to symptoms of esophageal dysfunction. The pathogenesis of EoE has not been completely elucidated but thought to be due to a combination of genetic,

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Conflict of Interest
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environmental, and host immune system factors [1,2]. There is a slight predominance among Caucasians and it is more frequent in males than in females (3:1). The mean age at the time of diagnosis ranges between 30–50 years in adults and 5.4–9.6 years in children [1,2]. The prevalence of EoE has been increasing and ranges from 1 to 10 cases per 10,000 persons [1,2]. The cause of the recent occurrence and dramatic rise in the frequency of EoE remain unknown, with proposed theories including the hygiene hypothesis, the Western lifestyle, dysbiosis earlier in life, environmental factors, and even the use of acid suppressive medications, especially proton pump inhibitors (PPIs) [2]. EoE has been associated with other disorders including cystic fibrosis (CF), tracheo-esophageal fistula/esophageal atresia, hypermobility syndromes, PTEN hamartoma tumor syndrome [3].

CF is an autosomal recessive (AR) disease occurring most commonly in Caucasian populations at a rate of 1 in 2,000 to 4,000 live births. It is the most common AR disease shortening the life span of mainly Caucasians. It occurs less commonly in Hispanics (1 in 9,000), African Americans (1 in 15,000), and Asian Americans (1 in 30,000). It is caused by a CF transmembrane conductance regulator gene mutation. It usually affects one or more organs, typically multiple, with the pulmonary and gastrointestinal (GI) systems being the most involved [4]. CF patients are at increased risk for gastroesophageal reflux disease (GERD) due to multiple mechanisms. These mechanisms include a higher incidence of transient lower esophageal sphincter relaxation, delayed gastric emptying, chronic cough, and chest physiotherapy [5].

There has been an identified association between CF and EoE in a case series [6] and a single center population based study [7] but large scale data is lacking. The diagnosis of EoE in patients with CF can be challenging. Dysphagia and food impaction are the most common presenting symptoms of EoE in adults while non-specific feeding difficulties and vomiting are the most common presenting symptoms in children. Other symptoms include abdominal pain, chest pain, poor weight gain, and gastroesophageal reflux symptoms. These non-specific GI symptoms, which mainly present in children, are widely prevalent in CF patients and are thought to be due to multiple factors such as GERD, medication adverse effects, pancreatic insufficiency with malabsorption, and GI dysmotility [6]. GERD is a common disorder in patients with CF, both children and adults [8,9]. GERD symptoms have been reported in up to 40% of patients with CF. When employing objective data using esophageal pH monitoring, up to 90% of CF patients with respiratory symptoms were found to have silent GERD [9]. Delayed gastric emptying has also been reported in up to one third of CF patients [10]. This high prevalence of non-specific GI symptoms in CF can make the clinical picture confusing and could potentially delay the diagnosis of EoE in CF patients.

MATERIALS AND METHODS

Database

This is a retrospective cohort analysis study utilizing a large commercial U.S. national administrative database (Explorys, IBM Explorys Solutions; IBM Inc., Armonk, NY, USA) containing comprehensive de-identified patient information from 27 healthcare networks comprising 36,111,860 active patients during our 5-year study period, from September 2014 to September 2019. Explorys collects de-identified patient data from participating institutions and utilizes a health data gateway server behind the firewall of each participating healthcare organization's electronic health record using billing inquiries. The Systematized

Nomenclature of Medicine Clinical Terms (SNOMED-CT) is used to map data categories such as diagnoses, findings, and procedures. RxNorm which is a normalized naming system for generic and branded drugs that support the semantic interoperation between drug terminologies and pharmacy knowledge base systems is used to identify prescription drugs. Explorys includes both inpatient and ambulatory patient information. To prevent the identification of individual patients by using combinations of specific SNOMED-CT codes, Explorys rounds the cohort information to the nearest 10. Since Explorys is the data set of records used in our study and the data are de-identified, the University Hospitals Institutional Review Board deems our study as exempt.

Patient selection

Using "Universe" from the search tool, all patients with CF and EoE regardless of age were identified using Explorys fast search through SNOMED-CT codes. Only active patients who had at least one clinical encounter within the time period of September 2014 to September 2019 were included. Patient cohorts were generated for all patients with a diagnosis of CF, all patients with a diagnosis of EoE, and all patients with a concurrent diagnosis of CF and EoE. Demographic (age, sex, race, ethnicity, and insurance type) and pertinent clinical information such as diagnosis, observation, procedures, prescribed drugs, blood pressure, and anthropometrics (body mass index, weight, and height) were retrieved. Cases were defined as all patients who had a concurrent SNOMED-CT diagnosis of CF and EoE (CF with EoE). Two comparison groups were used, the first group defined as all patients who had a SNOMED-CT diagnosis of CF and not EoE (CF only) and the second group defined as all patients who had a SNOMED-CT diagnosis of EoE and not CF (EoE only).

Associated medical conditions of interest

Data on multiple medical conditions associated with both CF and EoE were retrieved using SNOMED-CT diagnostic terms: associated GI disorders included GERD, heartburn, dysphagia, nausea and vomiting, failure to thrive, abdominal pain, diarrhea, weight loss, associated allergic disorders included drug allergy, rhinitis, asthma, sinusitis, dermatitis, food allergy, eczema, and urticaria.

Statistical analysis

Data is presented as counts, rates, or percentages. Prevalence was calculated by dividing the total number of patients with a clinical encounter for CF or EoE diagnosis at that time by the total number of active patients in the database from September 2014 to September 2019. Univariate analysis was performed to assess the association between CF, EoE, and other associated conditions. Chi square analysis and odds ratios with corresponding 95% confidence intervals were calculated for all patient cohorts, demographics, and associated disorders. Age-, sex-, and race-based prevalence rates were also calculated. All analyses were performed using the two-by-two study design using OpenEpi Statistical Software (Open Source Epidemiologic Statistics for Public Health, Version 3.01). Because cell counts in Explorys are rounded to the nearest 10, we approximated all cell counts between 0 and 10 to 5 in our calculation.

RESULTS

At the time of our search, the total number of patients in the database was 63,911,170. Of these, there were 36,111,860 active patients during our 5-years study period. Of those, there

were 12,950 patients with a diagnosis of CF or 3.5 in 10,000 of the active population. The prevalence of EoE was higher in patients with CF compared to the general population in the database (46 in 10,000 vs. 7.8 in 10,000, $p<0.001$). We compared the patients with CF and EoE to 2 other groups to better identify similarities and/or differences between our focus population and the other relative populations with either disease. We had a total of three cohorts: CF with EoE (n=60), CF only (n=12,890), and EoE only (n=28,090).

The CF with EoE cohort were more likely to be male as compared to CF-only (50% vs. 33.4%, $p=0.008$). There were more children and adolescents with CF and EoE as compared to CF only and EoE only (33.3% vs. 16.5% [$p<0.001$] and 10.5% [$p<0.001$], respectively). CF with EoE patients were less likely to be obese as compared to EoE only patients (8.3% vs. 38.7%, $p=0.04$, **Table 1**).

We also compared the associated signs and symptoms between the groups. Dysphagia was more common in CF with EoE patients than CF only patients (50% vs. 7.9%, $p<0.001$), but similar to EoE only patients (50% vs. 53.1%, $p=0.63$). Nausea was more common in CF with EoE than CF only patients (33.3% vs. 25%, $p<0.001$, **Table 2**). Abdominal pain was reported slightly more but not reaching significance in CF with EoE patients (50%) as compared to CF only (43.3%, $p=0.3$) and EoE only (46.9%, $p=0.63$) patients. Diarrhea and constipation were reported more frequently in CF with EoE patients (33.3% in both) than CF only (10.8%, $p<0.001$ and 19.4%, $p=0.012$) and EoE only (21.3% and 17.2%, $p=0.003$) patients (**Table 2**).

Allergic conditions in general, asthma, immunoglobulin E-mediated allergic disorders, contact dermatitis, allergic conjunctivitis, and allergic urticaria were more commonly associated with CF with EoE patients as compared to CF only patients (83.3% vs. 68.3%, 50% vs. 27.6%, 50% vs. 20%, 33.3% vs. 13.7%, 8.3% vs. 2%, and 8.3% vs. 0.85%, respectively; each $p<0.05$) and EoE only patients (83.3% vs. 69.3%, 50% vs. 28.8%, 50% vs. 32.8%, 33.3% vs. 17.6, and 8.3% vs. 0.96%, respectively; each $p<0.05$, **Table 3**).

Table 1. Demographic characteristics of the cases and the two comparison groups

Demographic characteristics	CF with EoE (n=60)	CF only (n=12,890)	EoE only (n=28,090)
Sex			
Males	30 (50.0)	4,300 (33.4)	16,800 (59.8)
Females	30 (50.0)	8,590 (66.6)	11,290 (40.2)
Age distribution			
Child/Adolescent (age <18)	20 (33.3)	2,130 (16.5)	2,970 (10.6)
Adult (age between 18 and 65)	40 (66.7)	9,000 (69.8)	21,520 (76.6)
Senior (age greater than 65)	0 (0)	1,760 (13.7)	3,600 (12.8)
Race			
Caucasian or White	50 (83.3)	10,820 (83.9)	24,600 (87.6)
African American or Black	0 (0)	1,120 (8.7)	1,420 (5.1)
Hispanic or Latino	0 (0)	770 (6.0)	130 (0.5)
Asian	0 (0)	180 (1.4)	220 (0.8)
Others	10 (16.7)	0 (0)	1,720 (6.1)
Ethnicity			
Hispanic or Latino	0 (0)	1,460 (11.3)	1,170 (4.2)
Not Hispanic or Latino	50 (83.3)	10,250 (79.5)	24,480 (87.1)
Others/Unknown	10 (16.7)	1,180 (9.2)	2,440 (8.7)

Values are presented as number (%).
Total exceeds 100% as patients may have had more than one type of insurance.
Explorys rounds cohorts to 10, and doesn't provide exact numbers when there are fewer than 10 in a group/cohort.
CF: cystic fibrosis, EoE: eosinophilic esophagitis.

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Table 2. Subgroup analysis of associated sign and symptoms

Subgroup	CF with EoE vs. CF only		CF with EoE vs. EoE only	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Dysphagia	11.64 (6.90, 19.38)	<0.001	0.88 (0.53, 1.46)	0.627
Vomiting	0.93 (0.54, 1.6)	0.810	1.56 (0.91, 2.67)	0.113
Weight loss	0.89 (0.35, 2.2)	0.859	0.88 (0.35, 2.21)	0.846
Abdominal pain	1.30 (0.78, 2.17)	0.305	1.13 (0.68, 1.87)	0.635
Diarrhea	4.13 (2.40, 7.10)	<0.001	2.35 (1.37, 4.00)	0.003
Nausea	4.13 (2.40, 7.10)	<0.001	1.46 (0.85, 2.50)	0.174
Constipation	2.06 (1.20, 3.54)	0.012	2.40 (1.40, 4.10)	0.003
Indigestion	2.57 (1.02, 6.45)	0.037	1.32 (0.52, 3.3)	0.533
Flatulence	2.04 (0.81, 5.1)	0.156	1.40 (0.55, 3.48)	0.466

CF: cystic fibrosis, EoE: eosinophilic esophagitis, OR: odds ratio, CI: confidence interval.

Table 3. Subgroup analysis of associated allergic disorders

Subgroup	CF with EoE vs. CF only		CF with EoE vs. EoE only	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Allergic condition	2.30 (1.10, 4.50)	0.010	2.20 (1.10, 4.40)	0.014
Asthma	2.60 (1.50, 4.35)	<0.001	2.14 (1.30, 3.50)	0.004
Allergic rhinitis	2.10 (1.25, 3.67)	0.008	1.06 (0.62, 1.83)	0.797
Atopic immunoglobulin E-mediated allergic disorder	4.00 (2.4, 6.6)	<0.001	2.04 (1.20, 3.40)	0.006
Contact dermatitis	2.00 (1.10, 3.40)	0.016	2.30 (1.36, 4.00)	<0.001
Allergic conjunctivitis	4.40 (1.70, 11.1)	0.009	2.14 (0.85, 5.37)	0.131
Allergic urticaria	10.56 (4.10, 26.9)	<0.001	9.36 (3.70, 23.6)	<0.001

CF: cystic fibrosis, EoE: eosinophilic esophagitis, OR: odds ratio, CI: confidence interval.

Table 4. Subgroup analysis of associated gastrointestinal disorders

Subgroup	CF with EoE vs. CF only		CF with EoE vs. EoE only	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Celiac disease	10.5 (4.10, 26.90)	<0.001	3.90 (1.50, 9.90)	0.014
Irritable bowel syndrome	2.12 (0.84, 5.31)	0.138	0.96 (0.38, 2.42)	0.995
Gastroesophageal reflux disease	2.16 (1.30, 3.6)	0.003	0.72 (0.43, 1.20)	0.221
Inflammatory bowel disease	5.48 (2.17, 13.85)	0.003	3.02 (1.20, 7.57)	0.039
Crohn's disease	7.23 (2.86, 18.3)	0.001	4.47 (1.72, 11.21)	0.008
Ulcerative colitis	10.56 (4.15, 26.90)	<0.001	5.58 (2.20, 14.00)	0.003
Eosinophilic gastritis	234.30 (65.96, 832.10)	<0.001	5.46 (2.17, 13.7)	0.003
Malnutrition	1.89 (0.75, 4.75)	0.197	6.63 (2.64, 16.6)	0.001
Clostridioides infection	3.95 (1.57, 9.93)	0.014	7.20 (2.86, 18.11)	0.001
Gastritis	5.25 (3.16, 8.74)	<0.001	1.90 (1.10, 3.20)	0.012
Gastroenteritis	3.3 (1.94, 5.72)	<0.001	2.37 (1.40, 4.07)	0.003
Obesity	0.52 (0.20, 1.30)	0.146	0.42 (0.16, 1.05)	0.045
Morbid obesity	1.47 (0.58, 3.68)	0.407	1.46 (0.58, 3.66)	0.410
Diabetes mellitus	0.42 (0.21, 0.83)	0.007	1.94 (0.98, 3.83)	0.072
Hypertensive disorder, systemic arterial	0.33 (0.16, 0.65)	<0.001	0.49 (0.25, 0.97)	0.032

CF: cystic fibrosis, EoE: eosinophilic esophagitis, OR: odds ratio, CI: confidence interval.

We also looked at the different GI disorders and found that there was an increased prevalence in the CF with EoE patients in most of the disorders as compared to ones with CF only and EoE only including malnutrition, celiac disease, inflammatory bowel disease (IBD) (including Crohn's disease and ulcerative colitis separately), eosinophilic gastritis, *Clostridioides* infections, gastritis and gastroenteritis. GERD was also more prevalent in CF with EoE patients as compared to CF only ($p<0.05$, **Table 4**).

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Table 5. Subgroup analysis of different allergies

Subgroup	CF with EoE vs. CF only		CF with EoE vs. EoE only	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Allergy to antibiotic	1.32 (0.77, 2.27)	0.308	1.67 (0.97, 2.86)	0.068
Food allergy	4.13 (2.41, 7.09)	<0.001	1.79 (1.04, 3.06)	0.040
Allergy to penicillin	0.50 (0.20, 1.26)	0.125	0.52 (0.20, 1.30)	0.150
Allergy to dairy product	3.95 (1.57, 9.90)	0.014	1.40 (0.56, 3.53)	0.452
Latex allergy	2.30 (0.91, 5.70)	0.105	2.49 (0.99, 6.23)	0.044
Allergy to contrast media	5.80 (2.28, 14.56)	0.003	5.01 (2.00, 12.58)	0.005
Aspirin allergy	4.60 (1.824, 11.58)	0.007	4.82 (1.90, 12.09)	0.006
Environmental allergy	8.90 (3.51, 22.65)	<0.001	4.23 (1.69, 10.62)	0.010
Allergy to dye	9.67 (3.80, 24.59)	<0.001	7.64 (3.04, 19.23)	<0.001
Allergy to dog dander	16.65 (6.47, 42.84)	<0.001	9.70 (3.80, 24.5)	<0.001
Allergy to house dust mite	16.65 (6.47, 42.84)	<0.001	11.00 (4.36, 27.76)	<0.001

CF: cystic fibrosis, EoE: eosinophilic esophagitis, OR: odds ratio, CI: confidence interval.

When evaluating allergies to specific substances, there was increased prevalence of allergy to food, contrast media, aspirin, environmental antigens, dye, dog dander, and house dust mites in CF with EoE as compared to CF only and EoE only patients ($p<0.05$, **Table 5**).

DISCUSSION

CF and EoE can present with similar GI symptoms especially in the younger age groups. We found that the prevalence of EoE is 46 in 10,000 in the CF population which is nearly 6 times higher than in the general population (7.8 in 10,000). This should raise the awareness of this disorder in clinicians taking care of patients with CF. Three previous reports inclusive of two case series and a single center study evaluating all associated diseases with EoE report similar results as ours [6,7,11]. Goralski et al. [6] and Mellor et al. [11] each described 3 cases of CF patients who were eventually found to have EoE. In both studies, two of their three patients were also found to have associated food allergies, which parallels the known association in the literature as well as our results.

The study by Capucilli et al. [7] evaluated 428 children who were diagnosed with EoE and found that there was an increased prevalence of CF in patients with EoE (0.9% of their EoE patients with CF as compared to 0.05% of their non EoE patients with CF). They also found that EoE patients had an increased prevalence of various atopic and non-atopic (adrenal insufficiency, autism spectrum disorder, celiac disease, connective tissue diseases, IBD, and type 1 diabetes mellitus) diseases compared to patients without EoE [7]. Our study also demonstrated similar results and our patient cohort with CF and EoE had increased prevalence of atopic disorders, IBD, and celiac disease compared to the CF alone. Interestingly, CF and EoE patients also had an increased prevalence of various atopic conditions when compared to EoE only patients. This raises the intriguing question of whether this unique group of patients with both conditions, CF with EoE, have a higher degree of atopy when compared to those with EoE or CF alone. The exact reason for this association between EoE, CF and atopic diseases is unclear but altered esophageal microbiome, dysregulated interactions between microbiota and gut mucosal immunity, could be a potential link between these conditions [12-17]. Similarly, prolonged antibiotic exposure in CF patients could predispose to atopic disorders via Th2 skewing [18,19].

Looking further at other associations, the increased prevalence of IBD and celiac disease in our patients with CF with EoE also parallels the literature. CF by itself and EoE by itself have

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been each reported to have an increased risk of IBD and celiac disease [7,20-22]. The fact that this population of CF with EoE have the increased prevalence of IBD as compared to CF only and EoE only makes this population even more unique and substantiates the increased prevalence of various underlying predisposing factors for IBD such as an increased intestinal permeability, altered mucosal immunity, and dysbiosis in this group. Malnutrition in CF patients is multifactorial and can be due to malabsorption, increased energy requirements, and decreased intake. Malnutrition can have profound negative adverse effects on pulmonary function and survival of CF patients [13]. EoE in CF patients raises additional concerns for malnutrition [6]. We did find an increased prevalence of malnutrition in CF with the EoE group when compared to the EoE only group. This highlights the malnutrition concerns in patients with CF, which could be further worsened by the dysphagia and the rest of the GI symptoms from the associated EoE. However, we did not find a significant difference in malnutrition between the CF with EoE group vs. CF only group. GERD was more prevalent in our cohort of patients with CF and EoE as compared to CF only patients, but similar to EoE only patients. This could be explained by the similar symptoms between EoE and GERD, resulting in some patients with EoE being initially diagnosed as GERD. The exact etiology of EoE remains elusive and several factors such as genetic predisposition, disruptions in epithelial barrier function, altered Th2 immunity and various environmental factors have been incriminated in the pathogenesis [23,24]. In several studies, exposure to antibiotics and PPI during early infancy has been implicated as risk factors for EoE [25-28]. Exposure to PPI early in life could lead to EoE by limiting the peptic breakdown of ingested allergens and accompanying increased gastric mucosal permeability could gastric absorption of the undigested food allergens [2]. Altered gut microbiome due to PPI exposure could also explain the increased risk with EoE.

The increased prevalence of EoE in CF patients illustrated in our cohort is significant and several factors could be responsible for this association. CF patients are at increased risk of exposure to the different antibiotics in CF patients that could alter the microbiome in the GI tract of those patients, making them more prone to different mucosal diseases including EoE [12-14]. CF patients also tend to have more GERD than the general population [29-31]. This could result in an increase in the use of PPIs which can be associated with an increase in EoE as reported previously [32].

Key points in our study include a significant increased EoE prevalence in CF patients, as well as an increase in association with atopic conditions and symptoms such as dysphagia that would suggest esophageal dysfunction in this population and can be clues to identifying CF patients who could have associated EoE.

The strengths of our study are that it is the first population based study that specifically evaluates the association between CF and EoE, and is the largest to date. Also, we highlighted the associated clinical manifestation and disorders in patients with CF with EoE when compared to the two comparison groups (CF without EoE and EoE without CF groups) to better identify this unique group of patients. Our study highlights that clinicians should have high suspicion for EoE in CF patients with those associated symptoms and disorders, and be more proactive about diagnosing those patients early on to avoid long term complications such as food impactions and esophageal strictures.

The limitations of our study is that it is a retrospective study and involves a multi-institutional database, which allows for the possibility of missing data. Our study depends on SNOMED-

CT codes and is subject to coding errors. Another limitation is that this database rounds the number of patients to the nearest 10. This may exclude a few patients with certain associated symptoms or diseases, but this may not be significant given the large population cohort. Given the retrospective nature, we could not evaluate or separately analyze the PPI-responsive EoE and this could have confounded some of our study results. Furthermore, this database also does not have a large number of pediatric patients which emphasizes the need for more pediatric studies to be pursued to further evaluate this association.

EoE and CF can present with similar GI symptoms. Given the observed increased prevalence of EoE in the CF population, treating clinicians should be vigilant in identifying those patients with CF who have symptoms concerning for EoE, especially those with the associated atopic and non-atopic disorders noted in this group, as well as those with refractory upper GI symptoms in patients with CF. More prospective studies are needed to further recognize this association in both children and adults.

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