

Escalating incidence of eosinophilic esophagitis: A 20-year prospective, population-based study in Olten County, Switzerland

To the Editor:

Eosinophilic esophagitis (EoE) is an emerging, chronic, IL-5–driven inflammatory disorder of the esophagus, clinically characterized by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation.¹ Several reports suggest that EoE has been diagnosed with a dramatically increasing frequency over the last years in Westernized countries.²⁻⁴ Whether this reflects a true increase in incidence or just an increased awareness of this disease is currently unknown. So far, the vast majority of studies addressing this pivotal epidemiological question rely on retrospective analyses of pathology or endoscopy databases.^{2,5-7} Here, we evaluated the epidemiology of EoE by prospectively conducting a population-based long-term study in a geographically and socioeconomically defined indicator area in Switzerland with approximately 90,000 inhabitants. Two gastroenterologists (A. S. and P. H.) and 1 pathology center serve this area. Since 1989, adult and pediatric patients with EoE from Olten County were consecutively entered into the Swiss EoE database (SEED) if they fulfilled the following criteria: (1) proton pump inhibitor (PPI)-refractory esophagus-attributed symptoms (high-dose PPI trial of >4 weeks or gastroesophageal reflux disease (GERD) exclusion by pH-metry before the EoE diagnosis), (2) eosinophilic esophageal peak infiltration of 24 or more eosinophils per hpf, and (3) exclusion of other diseases associated with esophageal eosinophilia. This standardized diagnostic workup has been maintained since 1989 (see [Methods](#) and [Statistical analysis](#) in this article's Online Repository at www.jacionline.org).

Forty-six patients were diagnosed with EoE in Olten County between 1989 and 2009. The age at diagnosis ranged from 9 to 77 years (mean \pm SD, 41 \pm 16), including 3 pediatric patients (<16 years). The majority (76%) of patients with EoE were males. Seventy percent of patients with EoE had a clinical history suggestive of allergic disease, of which allergic rhinoconjunctivitis was the most prominent form (63%) (see [Table E1](#) in this article's Online Repository at www.jacionline.org). The majority of patients presented with reddish longitudinal furrows (72%) and whitish exudates (63%). Five patients (11%) had esophageal strictures. The median peak eosinophil esophageal count was 53 per hpf (interquartile range [IQR], 29-85) (see [Table E2](#) in this article's Online Repository at www.jacionline.org).

Annual incidence rates were calculated as an average of a 3-year interval (see [Table E3](#) in this article's Online Repository at www.jacionline.org) and are shown together with the cumulative prevalence ([Fig 1](#)). An average annual EoE incidence rate of 2.45 per 100,000 inhabitants was found. A marked increase in the annual EoE incidence rate in the period from 2004 to 2009 was observed. A Poisson regression analysis revealed that significantly more EoE cases per 100,000 population were diagnosed between 2000 and 2009 compared with those diagnosed between 1989 and 1999 (relative rate, 2.53; 95% CI, 1.51-4.25; $P = .0004$). The rate of upper endoscopies was higher in the period between 2000 and 2009 compared with the period between 1989 and 1999 (rate ratio, 1.63; 95% CI, 1.43-1.86; $P = .001$). However, the increase in EoE incidence was more pronounced (factor 2.53, 153% increase)

than the increase in the number of upper endoscopies (factor 1.63, 63% increase) between the 2 time periods, taking into account the opening of a second gastroenterology practice (P. H.) in 1998 in Olten County. The EoE incidence was lower in women than in men (relative risk, 0.585; 95% CI, 0.331-1.034; $P = .065$) in the last 21 years.

In 2009, a cumulative EoE prevalence of 42.8 per 100,000 inhabitants was calculated as 39 patients with EoE were living in the Olten County area by the end of 2009 (46 patients were diagnosed from 1989 to 2009, 6 patients moved to another area during this time, and 1 patient died of pancreatic cancer).

The median diagnostic delay, defined as the time interval from the onset of EoE-attributed symptoms to EoE diagnosis, was 2 years (IQR, 1-7 years; range, 0-23 years) between 1989 and 2009. There was no relevant change over time between the diagnostic delay from 1989 to 1999 (median, 3 years; IQR, 2-5; range, 2-5) compared with 2000 to 2009 (median, 2 years; IQR, 1-7 years; range, 0-23; $P = 1.0$). In a logistic regression analysis, young age (<40 years) at EoE diagnosis was associated with "long diagnostic delay," which was defined as the time period over the 50th percentile (>2 years) (see [Table E4](#) in this article's Online Repository at www.jacionline.org).

By using a prospective population-based assessment strategy, we were able to detect an increase in EoE incidence and prevalence in Olten County over the last 20 years. It is likely that this change reflects a true increase in EoE's incidence and prevalence because it occurred in the face of a constant diagnostic delay and in the absence of any EoE awareness programs.

Our study fulfilled several methodologic quality criteria for a properly designed population-based study. First, 2 experienced gastroenterologists with high awareness of EoE serve the area of Olten County and have been using the same diagnostic procedures for the entire duration of the study. Second, EoE diagnosis was based on both clinical and histopathologic features and biopsy specimens were processed and examined in a single pathology center by pathologists with an extensive experience in examining EoE biopsies. Third, all patients with EoE were followed up with regard to residence status and survival. Fourth, Olten County has not undergone any relevant demographic or medical system changes in the past decades and the indicator area was left epidemiologically untouched as no EoE awareness programs were conducted. Finally, the stable diagnostic delay over the last 2 decades is indicative of the epidemiologically naive character of Olten County. This suggests that the results of our study are truly reflective of EoE epidemiology in Olten County during the last 20 years.

Patients with EoE in Olten County were predominantly young males (male/female, 3:1) with disease-specific characteristics similar to those described in other EoE patient populations.^{3-5,7,8} The annual *incidence* increased in the last 6 years (4.4-7.4 per 100,000 inhabitants per year). These findings are comparable with retrospective analyses from other geographically confined regions in the United States and Australia and provide solid evidence for a significant increase in EoE incidence.^{3,8}

On the basis of EoE's increasing incidence and its nonfatal nature, we also observed a pronounced increase in prevalence. Currently, we count 43 patients with EoE per 100,000 inhabitants. This prevalence rate may represent an underestimate as our

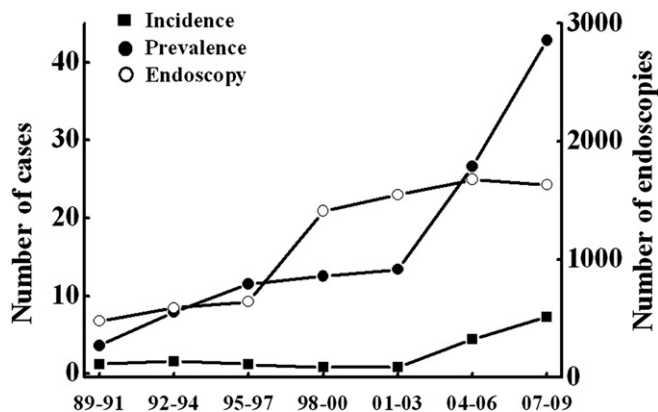


FIG 1. Incidence and prevalence of EoE: incidence rates per 100,000 inhabitants per year calculated as an average of a 3-year interval are shown. The cumulative prevalence was calculated per 100,000 inhabitants at the end of the respective 3-year interval. The number of total upper endoscopies in Olten County is shown per year as an average of a 3-year interval.

diagnostic criteria required higher levels of esophageal eosinophilic infiltration relative to the current consensus recommendations.¹ While EoE is not a routinely diagnosed disease, its incidence and prevalence rates may one day approach those found for ulcerative colitis and Crohn disease, which are estimated to have an incidence rate of 4 to 15 patients per 100,000 and a prevalence rate of 50 to 250 patients per 100,000 inhabitants in developed countries.⁹ The substantial diagnostic delay suggests that gastroenterologists, allergists, and general practitioners who encounter EoE need to be better informed to facilitate diagnosis and to initiate adequate treatment of this relatively new disease.

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Petr Hruz, MD, PhD^{a,*}
 Alex Straumann, MD^{a,*}
 Christian Bussmann, MD^b
 Pius Heer, MD^c
 Hans-Uwe Simon, MD, PhD^d
 Marcel Zwahlen, PhD^e
 Christoph Beglinger, MD^a
 Alain M. Schoepfer, MD^f
 for the Swiss EoE study group

From ^athe Department of Gastroenterology and Hepatology, University Hospital Basel, Switzerland; ^bthe Department of Pathology, Kantonsspital, Lucerne, Switzerland; ^cPrivate Practice for Gastroenterology, Olten, Switzerland; ^dthe Institute of Pharmacology and ^ethe Institute of Social and Preventive Medicine, University of Bern, Switzerland; and ^fthe Department of Gastroenterology and Hepatology, CHUV, University Hospital Lausanne, Switzerland. E-mail: phruz@uhbs.ch.

*These authors contributed equally to this work.

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Low prevalence of IgE to cross-reactive carbohydrate determinants in beekeepers

To the Editor:

N-glycans from plant and insect glycoproteins can induce extensive IgE cross-reactivity.^{1,2} IgE antibodies against these glycans, commonly known as cross-reactive carbohydrate determinants (CCDs), may interfere with *in vitro* tests for allergy diagnosis.² The cause of CCD sensitization is a matter of debate. *N*-glycans are ubiquitous in nature and represent the most common set of epitopes to which humans are exposed.² From the initial descriptions of CCDs, Hymenoptera stings have been proposed as a cause of CCD sensitization.¹ Serial determinations in patients with Hymenoptera venom allergy showed that CCD-specific IgE (sIgE) levels increased in parallel with the culprit venom-sIgE levels after a sting.³ In patients with suspected respiratory allergy, a history of Hymenoptera stings was associated with CCD-sIgE-positivity.⁴ The level of CCD-sIgE is higher in atopic than in nonatopic individuals^{4,5} and is highest among patients who are allergic to Hymenoptera venoms.⁶ For an in-depth understanding of the role of Hymenoptera venom exposure on CCD sensitization, we investigated the prevalence and factors associated with CCD-sIgE among beekeepers, a population that is heavily exposed to stings.

In this cross-sectional study, the 320 members of the Sociedad de Apicultores (Beekeeping Association) of Lugo (Spain) were invited to participate via a personal letter. A total of 158 individuals consented to participate in the study, which was approved by the Regional Ethics Committee. Three individuals who were already diagnosed as having Hymenoptera venom allergy undergoing specific immunotherapy were excluded. The study thus contained 155 individuals (125 males; median age, 57 years; range, 23-88 years). All participants completed a physician-administered structured questionnaire that included items related to residence, occupational activity, smoking, alcohol consumption, beekeeping activities, sting episodes, and reactions to stings. Reactions were classified as none, small local, large local (with a diameter >10 cm and peaking at 24-48 hours), or systemic. Skin prick tests to a standard panel of common inhalant allergens, including mites and pollens, were performed

METHODS

Olten County: Population characteristics and health care system

Olten County is situated in the northwestern part of Switzerland—an industrialized European country. This part of Switzerland has been mainly urbanized for the last 50 years. Olten County contains 35 communities and is geographically well defined by a surrounding state border. On December 31, 2009, the total number of inhabitants in Olten County was 91,125. Of this population, 71,588 (78.56%) were indigenous residents while 19,537 (21.44%) were mainly Caucasian immigrants. Of the total number of inhabitants, 49.4% (n = 45,016) were males and 50.6% (n = 46,109) were females.

According to the 1994 Federal Health Insurance Act, any person living in Switzerland is obliged to purchase a basic health insurance policy. The health insurance provider covers 90% of the medical service costs, and the remaining 10% have to be paid by the patients. The medical service in Olten County is maintained by approximately 50 family physicians, working in general practices. Two board-certified gastroenterologists (A. S. T., P. H. [since 1998]), working in a referral practice in Olten City in close proximity to each other, are responsible for the gastroenterological service in the area. Patients with gastrointestinal complaints first contact their family physician and are then, if necessary, referred for further evaluation to 1 of the 2 gastroenterologists. Both gastroenterologists rely on a single pathology center (C. B.).

Of note, Olten County has not undergone any relevant demographic or medical system changes in the past decades. With the intention to prevent any epidemiological interference, the decision was made to implement neither public nor medical education programs/campaigns focusing on EoE. Therefore, Olten County can be considered epidemiologically naive with respect to EoE epidemiology.

Diagnostic procedures performed in patients suspected of having EoE

Except for patients with obvious dysphagia for reasons such as esophageal neoplasia or severe GERD strictures, all patients referred for a diagnostic workup for esophageal symptoms, such as dysphagia, odynophagia, or chest pain suspected of esophageal origin, underwent the following standardized diagnostic procedures. Detailed medical history was taken, including clinical history of allergic disease, travels to tropical destinations, and family history suggestive of allergic disease and swallowing difficulties. All patients underwent a physical examination. Blood samples were drawn for differential blood count and total serum IgE measurements. Upper endoscopy was performed in all patients, and biopsies were taken from the proximal and the distal parts of the esophagus (at least 4 samples from each part of the esophagus—total ≥ 8 specimens). All biopsy specimens were histologically examined. All levels of the biopsy were surveyed, and the eosinophils in the most densely infiltrated area were counted in 5 consecutive hpfs (Carl Zeiss MicroImaging GmbH, Jena, Germany; Axiophot, Plan-Neofluar 40, ocular magnification $\times 10$, area of microscopic field 0.3072 mm²). The histological findings were classified according to the following criteria: number and

distribution of intraepithelial eosinophils, presence or absence of eosinophilic microabscesses, intercellular edema, papillary height, and thickness of the basal zone of the squamous epithelium. Additional examinations, such as allergy testing (skin prick test), computed tomography scan, barium or gastrographin swallow, pH monitoring, motility studies, and endosonography, were performed if necessary. This standardized diagnostic workup has been maintained since 1989.

Database characteristics

Adult and pediatric patients were entered into SEED if they fulfilled the following criteria: (1) PPI-refractory esophagus-attributed symptoms, (2) eosinophilic esophageal peak infiltration of 24 or more eosinophils per hpf, (3) exclusion of other diseases associated with esophageal eosinophilia, and (4) signed informed consent for database inclusion. The SEED consists of 11 demographic and 15 disease-specific items (clinical, laboratory, and endoscopic findings), as well as 13 items relating to therapeutic procedures and complications.

Patients with EoE were included in the Olten County database if they fulfilled the above criteria and were also residents of Olten County. Patients with EoE leaving Olten County were removed from the Olten County database.

Statistical analysis

Data of patients with EoE from Olten County were entered into an Excel sheet (Microsoft Excel 2003). The statistical analyses were performed by using a statistical package program (Stata Vs 9, College Station, Tex). Results of parametric numerical data are presented as mean \pm standard deviation and range. Nonparametric data are presented as median and IQR, comprising the values from the 25th and 75th percentile. Fisher exact test (2-sided) or the χ^2 test were used to explore associations of categorical data in 2 independent groups. The Wilcoxon rank sum test was used to explore associations of nonparametric numerical data in 2 independent groups, and the t test was used for parametric numerical data. For the analysis of annual rates of EoE diagnoses and upper endoscopies, the entire Olten County population was considered to be at risk. We calculated sex-specific incidence rates by using official population figures for men and women for Olten County. To analyze time trends of rates, we used Poisson regression models that model the number of cases with a logarithmic link function and the logarithm of the population figures as an offset variable. We report incidence rate ratios and 95% CIs. The association of risk factors and a prolonged diagnostic delay (defined as time interval >50 th percentile) was analyzed by means of logistic regressions, in which the dependent (outcome) variable was whether a patient had experienced a long diagnostic delay or not. The variables tested as potential risk factors, that is, the independent variables, were age at diagnosis (<40 years vs ≥ 40 years), gender (male vs female), interval of first diagnosis (2000-2009 vs 1989-1999), positive EoE family history (yes vs no), and presence of clinical history suggestive of allergic disease (yes vs no). Each independent variable was first tested individually. Then, all the independent variables with a *P* value of $\leq .25$ in the 1-by-1 analysis were entered together in a multivariable logistic regression model. A *P* value of $< .05$ was considered statistically significant.

TABLE E1. Characteristics of patients with EoE in Olten County

| Variable | Patients (n = 46) |
|--|--------------------------|
| Age at EoE diagnosis (y), mean \pm SD (range) | 41 \pm 16 (9-77) |
| Male gender | 35 (76%) |
| Smoking status | 8 (17%) |
| Positive EoE family history | 8 (17%) |
| EoE symptoms at diagnosis (may be in more than 1 category) | |
| Dysphagia | 43 (93.5%) |
| Necessity of endoscopic bolus removal | 9 (19.6%) |
| EoE-associated chest pain* | 15 (32.6%) |
| Symptoms of coexisting GERD† | 4 (8.7%) |
| Singultus | 1 (2.2%) |
| Clinical history suggestive of allergies | |
| No allergies | 14 (30.5%) |
| Rhinoconjunctivitis | 29 (63.1%) |
| Asthma | 14 (30.5%) |
| Rhinoconjunctivitis and asthma | 12 (21.8%) |
| Oral allergy syndrome | 4 (8.7%) |
| Urticaria | 1 (2.2%) |

*Patient description for EoE-associated chest pain: not associated with swallowing, localized, retrosternal burning, itching, or pressure.

†Patient description for coexisting GERD: retrosternal, ascending burning pain, PPI responsive.

TABLE E2. Endoscopic, histologic, and laboratory characteristics of patients with EoE in Olten County

| Variable | Patients (n = 46) |
|--|--------------------------|
| Endoscopic features (may be in more than 1 category) | |
| White exudates | 29 (63%) |
| Furrowing | 33 (71.7%) |
| Corrugated rings | 20 (43.5%) |
| Loss of vascular pattern | 38 (82.6%) |
| Felinization | 4 (8.7%) |
| Crepe paper | 8 (17.4%) |
| Peak eosinophil counts (entire esophagus) | |
| 24-30 | 5 (11%) |
| 31-50 | 8 (17%) |
| >51 | 33 (72%) |
| Peak eosinophil counts, proximal esophagus | |
| Median, IQR | 50, 28-80 |
| Peak eosinophil counts, distal esophagus | |
| Median, IQR | 59, 30-100 |
| Peak eosinophil counts, entire esophagus | |
| Median, IQR | 53, 29-85 |
| Blood work | |
| Eosinophilia, patients tested (% of total patients) | 37 (80.4%) |
| Total serum IgE, patients tested (% of total patients) | 36 (78%) |
| Serum IgE, median, IQR | 162, 41-304 |

TABLE E3. EoE incidence and cumulative prevalence (95% CIs) evaluated in 3-y intervals

| 3-y Interval | Incidence per 100,000 inhabitants (95% CI) | Cumulative prevalence per 100,000 inhabitants (95% CI) |
|---------------------|---|---|
| 1989-1991 | 1.2 (0.25-3.52) | 3.6 (0.75-10.56) |
| 1992-1994 | 1.6 (0.42-3.98) | 7.9 (3.27-16.77) |
| 1995-1997 | 1.1 (0.24-3.36) | 11.5 (5.51-21.14) |
| 1998-2000 | 0.7 (0.09-2.74) | 12.5 (7.05-23.82) |
| 2001-2003 | 0.7 (0.09-2.71) | 13.4 (8.60-26.40) |
| 2004-2006 | 4.4 (2.30-7.77) | 26.6 (18.89-42.38) |
| 2007-2009 | 7.4 (4.48-11.34) | 42.8 (36.96-67.33) |

Incidence is shown per 100,000 inhabitants per year as mean of a 3-y interval.
Cumulative prevalence was calculated per 100,000 inhabitants at the end of the time interval.

TABLE E4. Logistic regression modeling evaluating "long diagnostic delay," defined as the time interval >2 y from first symptoms to EoE diagnosis with potential risk factors

| Item | Diagnostic delay > 2 y from first symptoms to EoE diagnosis | | | | | |
|-----------------------------|---|------------|---------|----------------------------------|------------|---------|
| | Univariate logistic regression | | | Multivariate logistic regression | | |
| | OR | 95% CI | P value | OR | 95% CI | P value |
| Age at diagnosis (y) | 6.43 | 1.66-24.86 | .007 | 6.28 | 1.44-27.28 | .014 |
| <40 | | | | | | |
| ≥40 | | | | | | |
| Gender | 0.88 | 0.21-3.65 | .863 | | | |
| <i>Male</i> | | | | | | |
| Female | | | | | | |
| First diagnosis | 0.88 | 0.21-3.65 | .863 | | | |
| 2000-2009 | | | | | | |
| 1989-1999 | | | | | | |
| Positive EoE family history | 8.08 | 0.85-77.1 | .069 | 5.36 | 0.49-59.13 | .171 |
| Positive | | | | | | |
| Negative | | | | | | |
| Atopic diseases | 0.563 | 0.15-2.06 | .384 | | | |
| <i>Yes</i> | | | | | | |
| No | | | | | | |

The italicized binary item denotes to which specification the odds ratio (OR) and CI refer.