Published in final edited form as:

Dig Dis Sci. 2015 November ; 60(11): 3181–3193. doi:10.1007/s10620-015-3723-8.

Esophageal Food Impaction and Eosinophilic Esophagitis: A Retrospective Study, Systematic Review, and Meta-Analysis

Girish S. Hiremath¹, Fatimah Hameed¹, Ann Pacheco¹, Anthony Olive¹, Carla M. Davis², and Robert J. Shulman^{1,3}

Girish S. Hiremath: hiremath@bcm.edu

¹Pediatric Gastroenterology, Hepatology and Nutrition, Texas Children's Hospital, Baylor College of Medicine, 6701, Fannin Street, 1010.00, Houston, TX 77030, USA

²Pediatric Allergy and Immunology, Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA

³Children's Nutrition Research Center, Houston, TX, USA

Abstract

Background—Esophageal food impaction (EFI) can be the initial presentation of eosinophilic esophagitis (EoE). EoE is characterized by persistent esophageal eosinophilia (EE). Both EFI and EE are related to a variety of conditions. To date, the relationship between EFI, EE, and EoE remains unclear.

Aims—To review our institutional experience with EFIs and combine our knowledge with the existing literature to conduct a systematic review and meta-analysis for delineating the relationship between EFI, EE, and EoE.

Methods—We reviewed medical records of 72 children with EFI presenting to our emergency center between 2007 and 2013. PubMed, EMBASE, and Scopus databases were screened from inception until July 2014 to identify studies linking EFI and EoE. Included studies were methodically assessed for the quality and strength of association between EFI and EoE.

Results—Our institutional experience highlighted the possibility of proton-pump inhibitor therapy-responsive EE (PPI-REE) as an underrecognized risk factor for EFI. A systematic review of 14 studies, including ours, revealed that most studies did not eliminate other causes of EFI or EE. The meta-analysis revealed that esophageal biopsies were obtained from 54 % (40–68) of individuals presenting with EFI, and the overall EoE-attributable EFI among those who were biopsied was 54 % (43–65). Substantial heterogeneity was noted among the studies.

Discussion—PPI-REE is an underestimated risk factor for EFI. The quality of existing evidence linking EFI and EoE is limited by several important factors. Future studies with robust design are warranted to delineate the relationship between EFI, EE, and EoE.

Correspondence to: Girish S. Hiremath, hiremath@bcm.edu.

Electronic supplementary material The online version of this article (doi:10.1007/s10620-015-3723-8) contains supplementary material, which is available to authorized users.

Conflict of interest: None.

Keywords

Eosinophilic esophagitis; Dysphagia; Epidemiology; Meta-analysis

Introduction

Esophageal food impaction (EFI) is a gastrointestinal emergency known to affect all ages worldwide. EFI patients presenting to an acute care center require urgent evaluation and often endoscopic intervention to remove the impacted food. The endoscopic disimpaction can be performed by any of several subspecialists (e.g., gastroenterologists, surgeons, or otolaryngologists) and is unique to each institution [1].

Intrinsic factors such as anatomical malformations (e.g., esophageal diverticulum, rings, and webs), dysmotility (e.g., achalasia), and mucosal inflammation as a result of exposure to gastric refluxate as observed in gastroesophageal reflux disease are known risk factors for EFI. There is an increasing awareness that EFI and symptoms suggestive of esophageal dysfunction can be the initial presentation of eosinophilic esophagitis (EoE) [2, 3].

EoE is an increasingly prevalent, allergen/immune-mediated, clinicopathological condition affecting the esophagus. Similar to EFI, EoE has been reported in all age groups worldwide. Histopathologic examination of the esophageal tissue biopsies obtained from EoE patients reveals an eosinophil-predominant inflammation [≥ 15 eosinophils per high-power field (eos/hpf)] which persists after adequately excluding other causes of esophageal eosinophilia (EE) such as gastroesophageal reflux [4–7]. Several recent studies have described patients with proton-pump inhibitor (PPI)-responsive esophageal eosinophilia (PPI-REE) [8, 9]. Typically PPI-REE patients account for about 35–50 % of patients who initially present with clinical and histopathologic features consistent with EoE, but the EE completely resolves in response to high-dose PPI therapy for 2 months. The results from a recently published transcriptome analysis suggest that PPI-REE represents a continuum of the same pathogenic allergic mechanisms that underlie EoE [10]. Yet, to date, the relationship between EFI, EE, and EoE remains poorly defined.

In order to examine the relationship between EFI, EE, and EoE, we performed a systematic review and meta-analysis of the existing publications. Because of the limited data available, we also reviewed our experience with EFI and its association with EE and EoE, and combined our data with the existing literature. For compiling the bibliographic search for the systematic review and meta-analysis, we formulated our research question using *PICO* acronym [11], wherein *P* (participants) represented subjects presenting to the emergency care setting with symptoms and/ or signs consistent with EFI; *I* (intervention) was an endoscopic procedure with or without biopsies to relieve food impaction and assess potential causes of EFI, respectively; *C* (comparison or reference standard) using guidelines for diagnosis of EoE or as defined by the authors of each study; and *O* (outcome) as the diagnosis of EoE.

Methods

Retrospective Review of Our Data

We identified patients presenting with symptoms suggestive of EFI (e.g., dysphagia, chest pain, foreign body sensation, choking, or drooling) to the Texas Children's Hospital Emergency Center between January 2007 and December 2013. To optimize the sensitivity of our case finding strategy, cases of EFI were identified by screening our electronic medical record and endoscopy records (The Clinical Outcomes Research Initiative database) using the International Classification of Diseases (ICD)—9th Revision, Clinical Modification code (935.1) and current procedural terminology codes (CPT) (43215, 43247, 31511). The ICD-9 and CPT codes were constant over the study time frame, and there were no changes to the billing practice.

The electronic medical records then were reviewed by F.H. to identify cases of EFI. A random review of the dataset was completed by G.H. to assess the variability in data acquisition. The study was approved by the Baylor College of Medicine Institutional Review Board.

The medical records of patients presenting with EFI resulting from non-food materials (e.g., coins) were not considered. On confirmation of EFI, pertinent demographic, clinical, endoscopic, and histologic features were recorded in predefined data collection forms. To understand the clinical course and unique characteristics of EFI patients, they were grouped as: (1) EFI not requiring endoscopic removal—defined as children who were able to either cough or vomit the food bolus or in whom the food bolus spontaneously traversed into the stomach with relief of symptoms; (2) one-time EFI requiring endoscopic removal; and (3) recurrent EFI—defined as ≥ 2 EFIs over the study duration. To understand the practice patterns in our institution, we used the treating physicians' diagnosis of EoE which was formulated by the presence of a suggestive clinical presentation, pertinent endoscopic findings, and histologic examination of esophageal tissue demonstrating ≥ 15 eos/hpf.

Systematic Review and Meta-Analysis

Literature Search—PubMed, EMBASE, and Scopus databases were searched from inception to September 2014 for articles in English containing one or more of the following keywords or phrases: “esophageal impaction,” “food bolus impaction,” “EE,” and “EoE.” The reference lists of the retrieved articles were reviewed for identification of additional articles. Relevant authors were contacted to acquire missing or additional information as necessary.

Study Selection—Studies providing the number of patients presenting with EFI requiring endoscopic removal, undergoing esophageal biopsies at the time of endoscopic removal or during follow-up, and diagnosed with EoE, as defined by each author, were included.

Small case series, individual case reports, and abstracts reporting EFI cases diagnosed with EoE were disqualified due to limited statistical validity. Furthermore, publications providing food impaction rates and not providing esophageal biopsy and/or EoE rates, describing number of EoE patients presenting with EFI, reporting non-food material esophageal

impactions (e.g., coins), and comparing therapeutic interventions to remove and/or disimpact the impacted food material were excluded.

Data Abstraction—Two authors (G.H., A.P.) evaluated articles for eligibility and quality, and abstracted the data independently according to the meta-analysis of observational studies in epidemiology guidelines [12]. A standard data extraction form was designed to collect relevant information from the studies which met our inclusion criteria. To ensure the quality of evidence linking EFI and EoE, each study was assessed for the measures taken to eliminate other causes of EFI and EE, the findings on esophageal biopsies, and the diagnostic criteria used by the authors to diagnose EoE. Any disagreement between authors in data abstraction was resolved by discussion and review of the publication(s).

Statistical Methods—Descriptive statistics were used to summarize the findings of our retrospective study. Wilcoxon rank-sum test was used to compare continuous variables, and Fisher's exact test was used to compare categorical variables.

For meta-analysis of proportions, the biopsy rates in patients presenting with EFI and undergoing endoscopic removal and the proportion of biopsied patients who were diagnosed with EoE were calculated and the confidence intervals were based on exact binomial procedures. The results are presented as proportions [effect size (ES)] with corresponding 95 % confidence intervals (CI).

Both the fixed- and random effects models were calculated. The fixed effects model assumes that all included studies come from a common population and the point estimate is not significantly different between the studies. This assumption is tested by the “heterogeneity test” or the I^2 statistic. The percentage of observed total variation across studies due to real heterogeneity rather than chance is calculated as: $100 \% \times (Q - df)/Q$, where Q is Cochran's heterogeneity statistic and df , the degrees of freedom. Negative values of I^2 were considered to be equal to zero so that I^2 was between 0 and 100 %. A value of 0 % was considered to indicate no observed heterogeneity, and larger values represented increasing heterogeneity. If this test yields a P value ≤ 0.05 , then the random effects model is considered appropriate. If the P value for a heterogeneity test is >0.05 , then the fixed effects model is considered suitable [13]. Presence of a publication bias was examined by inspecting for asymmetry of the funnel plots (plotting the proportion against the standard error of the proportion), and the statistical significance was assessed by the Begg's method and the Egger's test separately for studies included in analysis of the biopsy rates in EFI as well studies included in EoE-attributable EFI [14, 15].

In our two-step analysis plan, in order to understand the reported relationship between EFI and EoE, we initially performed overall and subgroup analyses [Age (Adults vs. Pediatrics), Location [United States of America (USA) vs. non-USA], and Specialty [GI alone vs. Non-GI ((non-GI) or (GI + non-GI)) performing food bolus disimpaction] using the authors' definitions. Subsequently, in an attempt to place the results in the context of current guidelines for diagnosis of EoE, we compared the data from studies that met the current diagnostic criteria for EoE to those not meeting the current diagnostic criteria [16].

All statistical analyses were performed on Stata version 10.2 (StataCorp LP, College Station, TX). The statistical significance was determined at $P = 0.05$ using two-tailed tests.

Results

Retrospective Study

Figure 1 and Table 1, and Supplementary Table 1, summarize the results from our retrospective study. A total of 985 children presented with esophageal impaction during the 7-year study period. Of those, 72 (7 %) [n (%)] children had EFI. These 72 children had a total of 95 EFI events. Sixteen (22 %) children had recurrent EFIs with a total of 39 (42 %) events.

Our cohort consisted predominantly of Caucasian (69 %) males (73 %), with a median (range) age of 11 (1–18) years. A history of esophageal malformation with corrective surgery (e.g., tracheoesophageal fistula, esophageal atresia) was the most common predisposing factor, particularly among children presenting with recurrent EFIs. Prematurity, asthma, and food allergies were other commonly associated comorbidities.

The majority of children presented with a combination of symptoms, with the sensation of food being stuck (54 %) and vomiting (41 %) being two of the most common, especially in children with recurrent EFIs. The sensation of food being stuck and pain during swallowing were commonly reported both by children with EFI not requiring endoscopic removal (39 and 35 %, respectively) and those with EFI requiring endoscopic removal (36 and 21 %, respectively). Drooling, chest pain, and choking were other common presenting symptoms.

While 23 (32 %) children either coughed or vomited the food bolus or were able to pass the food bolus into the stomach and did not require any endoscopic intervention, the remaining 46 (68 %) children required endoscopic intervention. At our institution, the gastroenterology, surgery, or otolaryngology service, per a predetermined schedule, are consulted by the emergency center to manage EFI patients. Endoscopic removal was most commonly performed by the gastroenterologists (61 %) using a flexible endoscope. The surgery (18 %) and otolaryngology (21 %) services frequently used rigid endoscope to remove EFIs. Meat was the most common cause of EFI, and other materials included bone fragment(s), vegetables (e.g., corn, potato), fruits (e.g., grape, apple), and nuts (e.g., peanut). Midesophagus followed by the proximal esophagus was the common site of impaction. In most of the cases, the esophagus endoscopically looked normal or mildly erythematous. Other notable endoscopic features were furrowing, rings, white exudates, and mucosal tears. Narrowing of the esophageal lumen at the anastomotic site was reported in 44 % of children with recurrent EFIs. No complications related to endoscopy were reported. Esophageal biopsies were obtained from 24 (73 %) children with EFI requiring endoscopic removal with a median (range) of five biopsies. A significantly higher proportion of gastroenterologists obtained esophageal biopsies compared to surgeons or otolaryngologists (85 vs. 29 vs. 17 %, respectively; $P = 0.05$).

The histologic examination revealed that 13 (54 %) children had ≥ 15 eos/hpf. Nine (38 %) children had between 5 and 15 eos/hpf, and 2 (8 %) children had a histologically normal

esophagus. Based on their clinical presentation and intraepithelial eosinophil count, 8 (62 %) children were diagnosed with EoE and initiated on acid-blocker therapy and/or swallowed steroids by their treating physicians. Only 2 (25 %) children, both placed on acid-blocker therapy after initial EGD, received a follow-up endoscopy with biopsies at 6 and 12 weeks, respectively. The histologic examination in both cases (100 %) revealed complete resolution of EE, suggesting that they had PPI-REE.

Systematic Review

Details of the search strategy and the characteristics of studies included in the systematic review are shown in Fig. 2 and Table 2, respectively. PubMed, EMBASE, and Scopus database searches led to retrieval of 540 publications. After screening of the titles and abstracts, 486 of these were excluded for being duplicates and/or being irrelevant to our study, and 54 (11 %) publications were evaluated by retrieving the full text. Thirteen (23 %) of these publications met our inclusion criteria and were systematically reviewed. Eleven (85 %) out of 13 publications were retrospective studies, and 2 (15 %) were prospective studies. The publications included data ranging from 1988 to 2010.

Endoscopic Findings Related to EFI—Meat was the most commonly reported impacted food substance, and this did not differ by age, disimpaction by subspecialty, or geographic origin of the study. Mucosal abnormalities, especially EoE-pertinent endoscopic features such as furrowing, trachealization, and white exudates, were described by the majority of studies. In some studies, the decision to obtain an esophageal biopsy was taken in response to visible mucosal abnormalities.

The majority of the publications (85 %) described measures taken to exclude anatomical and/or neuromuscular causes of EFI. Esophageal strictures either as a result of a previous surgical intervention (e.g., esophageal atresia or tracheoesophageal fistula repair) or secondary to peptic injury were the most common anatomical conditions associated with EFI in children and adults, respectively. Other commonly associated anatomical conditions were esophageal web, Schatzki's ring, previous esophageal resection, previous antireflux surgery, narrowing as a result of EoE, esophageal ulcer, or an esophageal stent. Esophageal neoplastic conditions such as esophageal carcinoma and Barrett's esophagus were commonly associated with EFI, particularly in adults.

Four out of 13 studies (31 %) (1 pediatric study and 3 adult studies) reported an association between EFI and swallowing and/or esophageal neuromuscular disorders such as achalasia, neuromuscular disorder of swallowing, or nonspecific esophageal motility disorders.

EFI and Esophageal Eosinophilia—Five (38 %) studies described measures taken to identify other causes of EE. One of these five studies was a prospective study, and non-EoE causes of EE were not included in this study. The remaining four were retrospective, and 3 out of these 4 studies presented data between 2000 and 2011 and were published in or after 2011. Only 1 study clearly described their process of eliminating other causes of EE.

EFI and Esophageal Biopsies—Eight (62 %) out of 13 studies described characteristics of esophageal sampling. While 7 of these 8 provided the location(s) from where the

esophageal biopsies were obtained, only three studies provided the number of biopsies obtained during EFI removal. Only three studies provided both number and location of esophageal biopsies obtained during the EFI removal.

Criteria Used to Diagnose EoE—Only 3 of 13 (23 %) studies met most of the current criteria used to diagnose EoE, and the remaining 10 studies did not clearly elaborate on one or more criteria. Most of the studies (77 %) used clinicopathological criteria to diagnose EoE. However, there was notable variability in the peak eos/hpf employed to diagnose EoE. Three studies (30 %) used >20 eos/hpf, 1 (10 %) study used >15–20 eos/hpf, and the remaining 6 (60 %) used 15 eos/hpf as the cutoff value to diagnose EoE. Other histologic features noted were: eosinophil microabscess, extracellular eosinophil granules, basal cell hyperplasia, dilated intracellular spaces, and subepithelial or lamina propria fibrosis. Three studies (23 %) did not clearly describe the criteria they used to diagnose EoE.

Meta-Analysis

The summary data of each study and the results of overall and subgroup analyses are presented in Tables 3 and 4, and Figs. 3 and 4, and Supplementary Figures 1–8. We were not able to include the Lao et al. [17] study in our meta-analysis as they reported no EoE-attributable EFI. Sperry et al. [18] presented separate data for adult and pediatric age groups; hence, they were treated as two independently analyzable units. For the study by Mahesh et al., we combined the separate data ranges (i.e., 1996–2010) as our intent was not to examine the change in prevalence of EFI attributable to EoE.

Overall Analysis—The overall analysis included 14 analyzable reports, including 1070 cases of EFI and 223 cases of EoE-attributable EFI. The overall pooled biopsy rate in patients presenting with EFI was 54 % (40–68) [proportion (95 % CI)], and the EoE-attributable EFI rate among those who were biopsied at EFI removal was 54 % (43–65).

Subgroup Analyses

Age: The biopsy rates among adults trended to be lower than the biopsy rates in children [percentage (95 % confidence intervals): 48 % (26–70), ($n = 815$) vs. 59 % (43–74), ($n = 255$)], yet the EoE-attributable EFI rates between adults and children were comparable [52 % (37–67), ($n = 148$) vs. 55 % (37–73), ($n = 75$)].

Location: While the biopsy rate among studies conducted in the USA was significantly lower when compared to studies reported from outside of the USA [49 % (31–68), ($n = 605$) vs. 63 % (42–81), ($n = 465$), respectively; $P = 0.05$], the EoE-attributable EFI rates were significantly higher in studies reported from the USA compared to those reported from outside the USA [64 % (53–74), ($n = 117$) vs. 38 % (21–57), ($n = 106$), respectively; $P = 0.05$].

Subspecialty: The biopsy rate among gastroenterologists was significantly higher than among other subspecialists [62 % (40–82), ($n = 545$) vs. 47 % (27–66), ($n = 525$), respectively; $P = 0.05$]. However, the frequency of EoE-attributable EFI was identical between the two groups [55 % (39–71), ($n = 131$) vs. 52 % (35–69), respectively, ($n = 92$)].

Adherence to Current EoE Diagnostic Criteria: Although the biopsy rates among studies not meeting the EoE diagnostic criteria were significantly higher compared to studies meeting the diagnostic criteria [60 % (44–76), ($n = 631$) vs. 39 % (16–64), ($n = 439$); $P = 0.05$, respectively], the EoE rates between these two groups were comparable [56 % (40–72), ($n = 162$) vs. 51 % (42–61), respectively ($n = 61$)]. The heterogeneity among studies that adhered to the current diagnostic guidelines and analyzed for EoE-attributable EFI requiring endoscopic removal was not significant ($I^2 = 0$ %; $P = 0.64$). The calculated EoE-attributable EFI by random effects model and the fixed effects model were identical, and the results from the fixed effects model are presented above.

Publication Bias—On visual inspection, the funnel plots designed for studies included in analysis of biopsy rates in EFI (Supplementary Figure 9a and 9b) and studies included in EFI attributable to EoE appeared slightly asymmetric (Supplementary Figure 10a and 10b), suggesting possibility of a publication bias. However, these observations did not attain statistical significance, indicating that there was no statistically significant publication bias [(biopsy rates in EFI: Begg's test: Adjusted Kendall's score ($P-Q$) = 6; $P = 0.76$ (continuity corrected); Egger's test: Bias = 4.93; $P = 0.09$); (EFI attributable to EoE: Begg's test: Adjusted Kendall's score ($P-Q$) = 13; $P = 0.51$ (continuity corrected); Egger's test: Bias = 1.32; $P = 0.48$)].

Discussion

We reviewed our institutional experience of EFI and combined it with the existing literature to attempt to elucidate the relationship between EFI, EE, and EoE. To our knowledge, this is the first study to perform a comprehensive review of the existing evidence linking EFI and EoE, and to perform a meta-analysis to determine what proportion of EFI may be attributable to EoE. We focused on elucidating the relationship between EFI and not on esophageal impactions per se (which would also include non-food material) since the presence of non-food items in the esophagus may be a consequence of a volitional action.

In order to add to the current literature and our systematic review/meta-analysis, we reviewed the medical records of 72 children with EFI presenting to our institution. These cases represented 7 % of esophageal impactions over a period of 7 years. The presentations were consistent with the demographic, clinical, and endoscopic features described in a previous study of pediatric patients [19]. The majority of children were Caucasian, male, with meat impaction, and they described the sensation of food being stuck or pain while swallowing. Importantly, gross endoscopic evaluation revealed a normal looking or only mildly irritated esophageal mucosa in approximately 30 % children. As in our study, anatomical abnormalities as a result of esophageal malformations and related surgical complications have been reported previously [18], and in our experience, about 1 in 3–5 EFIs requiring endoscopic removal and recurrent EFIs were attributable to anatomical malformations and their related complications.

Most of the EFIs requiring endoscopic removal in our center were performed by the gastroenterologists. The biopsy rates were significantly higher in EFI requiring endoscopic removal performed by gastroenterologists when compared to the EFI requiring endoscopic

removal performed by the other two services. Similar experience has been described in previous reports, and this possibly is attributable to a combination of factors including increased awareness among gastroenterologists toward mucosal causes of EFIs and variability in practice wherein the surgeons or the ENT specialists do not routinely biopsy.

Our systematic review revealed that the quality of the existing evidence linking EFI and EoE is limited by several important factors. The data offered in most of the studies, including our own, were gathered via a retrospective study design which has several inherent limitations. There was lack of standardization in the manner in which the information (e.g., endoscopic features, the number and location of biopsies obtained, and measures taken to eliminate other causes of EE, eos/hpf required for diagnosis, etc.) was defined and analyzed. When compared to the criteria delineated in the updated guidelines for diagnosis of EoE, large numbers of studies excluded anatomical and/or neuromuscular causes for EFI, but a relatively small number of studies clearly described measures taken to eliminate other causes of EE which is essential in discriminating EoE from PPI-REE.

Using conservative estimates (lower bounds of 95 % CI) from our overall analyses, about 1 in 3 cases with EFI were biopsied at the time of the endoscopic intervention, and about half of those biopsied had EoE. These observations concur with findings from two prospective studies included in this review [20, 21]. Long-standing EoE can result in a progression from an inflammatory to a fibrostenotic phenotype and contribute to EFI, especially in adults [22, 23]. However, our meta-analysis revealed that the EoE-attributable EFI rates were comparable between both adults and children, suggesting that perhaps EoE- or EE-related acute mucosal changes also play an important role in EFI in addition to esophageal remodeling resulting from long-standing EoE. It was interesting to note that, despite lower biopsy rates among studies reported from the USA, significantly higher rates of EoE-attributable EFIs were observed. This may likely be a result of a combination of better identification of appropriate cases for biopsy and/or a higher prevalence of EoE in the USA compared to the other reporting countries.

While significantly higher biopsy rates were noted among gastroenterologists, we did not find high EoE rates compared to other subspecialists. This probably is as a result of the “others” group combining data from multiple subspecialists including gastroenterologists. Finally, despite several recent studies meeting the criteria for establishing a diagnosis of EoE having significantly lower biopsy rates compared to the studies which did not meet current criteria establishing a diagnosis of EoE, EoE-attributable EFI was identical in both these groups and also was comparable to the overall EoE-attributable EFI rates.

EoE is a relatively new clinical entity, and our understanding of this condition has improved significantly, especially in the past decade. As a result, the conceptual definition and diagnostic guidelines have evolved. For example, it is recognized now that other causes of EE need to be excluded—in particular, PPI-REE [24, 16, 25]. There is growing evidence that long-standing eosinophil-induced inflammation can lead to dysmotility and/or narrowing of the esophagus via edema and/or deposition of subepithelial fibrotic tissue, which eventually causes narrowing of the esophageal lumen. Whereas it is highly plausible that EoE is likely a major risk factor for EFI, the results from our in-depth analysis suggest

that the quality of the existing evidence linking EFI and EoE is limited by lack of clarity on several key factors which play a central role in establishing a diagnosis of EoE.

Our own study and systematic review/meta-analysis underscore the need to create awareness among physicians caring for patients with EFI to obtain adequate numbers of biopsies from multiple levels in the esophagus irrespective of the gross endoscopic findings [26]. In addition, recent reports have highlighted that diagnosis of EoE in patients with known anatomical (such as tracheoesophageal fistula after surgical repair) and/or neuromuscular conditions (such as achalasia) is often missed or delayed, resulting in delayed institution of specific therapy [27–29]. Therefore, it is important to consider esophageal biopsies in all patients presenting with EFI. The benefits of performing routine mucosal biopsies during EFI removal must be balanced against the risk of complications (such as perforation). While the risk of perforation is known to be minimal with the flexible endoscope, an increased risk of perforation with the rigid endoscope, especially in the distal esophagus, has been reported [30].

This systematic review and meta-analysis has several strengths. It is the first study to methodically evaluate the existing literature linking EoE and EFI through July 2014. We performed an exhaustive literature search, sought to obtain additional data from authors, rigorously assessed studies in accordance with current guidelines for conducting a systematic review and meta-analysis, and used robust statistical methods to quantitatively synthesize the abstracted data. However, our study also has limitations. The most prominent ones being the significant degree of heterogeneity between the included studies likely as a result of methodological differences as noted above. Mirroring this, we also noted significant statistical heterogeneity (except in more recent studies) among the studies in our meta-analyses. A number of studies were retrospective, with their inherent limitations. It is possible that we might have introduced selection bias by excluding a small number of statistically invalid studies and/or by limiting our search to reports published in English only which could have resulted in us missing relevant studies published in other languages.

In summary, our systematic review reveals that the quality of evidence linking EoE and EFI is limited by lack of clarity on several key factors crucial to ascertain the diagnosis of EoE. Hence, the exact relationship between EFI and EE or EoE remains undefined. There appears to be a need for greater awareness among physicians (particularly non-gastroenterologists) caring for patients with EFI of the need for esophageal biopsies during endoscopic removal of EFI. Data from prospective studies designed to strictly adhere to the EoE diagnosis guidelines would allow us to better understand the optimal EFI biopsy strategies and the precise relationship between EFI, EE, and EoE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

G.H. is supported by NIH Training Grant (T32 DK007664). The support of the Texas Medical Center Digestive Disease Center (P30 DK56338) also is acknowledged.

References

1. Crockett SD, Sperry SL, Miller CB, et al. Emergency care of esophageal foreign body impactions: timing, treatment modalities, and resource utilization. *Dis Esophagus*. 2013; 26:105–112. [PubMed: 22458738]
2. Hudson S, Sampson C, Muntz HR, et al. Foreign body impaction as presentation of eosinophilic esophagitis. *Otolaryngol Head Neck Surg*. 2013; 149:679–681. [PubMed: 23959816]
3. Mahesh VN, Holloway RH, Nguyen NQ. Changing epidemiology of food bolus impaction: is eosinophilic esophagitis to blame? *J Gastroenterol Hepatol*. 2013; 28:963–966. [PubMed: 23425056]
4. Shi YN, Sun SJ, Xiong LS, et al. Prevalence, clinical manifestations and endoscopic features of eosinophilic esophagitis: a pathological review in China. *J Dig Dis*. 2012; 13:304–309. [PubMed: 22624553]
5. Vindigni C, Villanacci V, Marini M, et al. Eosinophilic esophagitis: an Italian experience. *Rev Esp Enferm Dig*. 2010; 102:15–19. [PubMed: 20187680]
6. O'Donnell S, Kelly OB, Breslin N, et al. Eosinophilic oesophagitis: an Irish experience. *Eur J Gastroenterol Hepatol*. 2011; 23:1116–1121. [PubMed: 21946074]
7. Jensen ET, Kappelman MD, Martin CF, et al. Health-care utilization, costs, and the burden of disease related to eosinophilic esophagitis in the United States. *Am J Gastroenterol*. 2015; 110:626–632. [PubMed: 25267327]
8. Dellon ES. Epidemiology of eosinophilic esophagitis. *Gastroenterol Clin North Am*. 2014; 43:201–218.
9. Molina-Infante J, Rivas MD, Hernandez-Alonso M, et al. Proton pump inhibitor-responsive oesophageal eosinophilia correlates with downregulation of eotaxin-3 and Th2 cytokines overexpression. *Aliment Pharmacol Ther*. 2014; 40:955–965. [PubMed: 25112708]
10. Wen T, Dellon ES, Moawad FJ, et al. Transcriptome analysis of proton pump inhibitor-responsive esophageal eosinophilia reveals proton pump inhibitor-reversible allergic inflammation. *J Allergy Clin Immunol*. 2015; 135:187e4–197.e4. [PubMed: 25441638]
11. Richardson WS, Wilson MC, Nishikawa J, et al. The well-built clinical question: a key to evidence-based decisions. *ACP J Club*. 1995; 123:A12–A13. [PubMed: 7582737]
12. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA*. 2000; 283:2008–2012. [PubMed: 10789670]
13. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*. 2003; 327:557–560. [PubMed: 12958120]
14. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994; 50:1088–1101. [PubMed: 7786990]
15. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997; 315:629–634. [PubMed: 9310563]
16. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol*. 2011; 128:3 e6–20.e6. quiz 21–2. [PubMed: 21477849]
17. Lao J, Bostwick HE, Berezin S, et al. Esophageal food impaction in children. *Pediatr Emerg Care*. 2003; 19:402–407. [PubMed: 14676489]
18. Sperry SL, Crockett SD, Miller CB, et al. Esophageal foreign-body impactions: epidemiology, time trends, and the impact of the increasing prevalence of eosinophilic esophagitis. *Gastrointest Endosc*. 2011; 74:985–991.
19. Hurtado CW, Furuta GT, Kramer RE. Etiology of esophageal food impactions in children. *J Pediatr Gastroenterol Nutr*. 2011; 52:43–46. [PubMed: 20975581]
20. Desai TK, Stecevic V, Chang CH, et al. Association of eosinophilic inflammation with esophageal food impaction in adults. *Gastrointest Endosc*. 2005; 61:795–801. [PubMed: 15933677]
21. Kerlin P, Jones D, Remedios M, et al. Prevalence of eosinophilic esophagitis in adults with food bolus obstruction of the esophagus. *J Clin Gastroenterol*. 2007; 41:356–361. [PubMed: 17413601]

22. Dellon ES, Kim HP, Sperry SL, et al. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. *Gastrointest Endosc.* 2014; 79:577 e4–585.e4. [PubMed: 24275329]
23. Schoepfer AM, Safroneeva E, Bussmann C, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. *Gastroenterology.* 2013; 145:1230–1236. e1–2. [PubMed: 23954315]
24. Furuta GT, Liacouras CA, Collins MH, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology.* 2007; 133:1342–1363. [PubMed: 17919504]
25. Dellon ES, Gonsalves N, Hirano I, et al. ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). *Am J Gastroenterol.* 2013; 108:679–692. quiz 693. [PubMed: 23567357]
26. Nielsen JA, Lager DJ, Lewin M, et al. The optimal number of biopsy fragments to establish a morphologic diagnosis of eosinophilic esophagitis. *Am J Gastroenterol.* 2014; 109:515–520. [PubMed: 24445569]
27. Gorter RR, Heij HA, van der Voorn JP, et al. Eosinophilic esophagitis after esophageal atresia: is there an association? Case presentation and literature review. *J Pediatr Surg.* 2012; 47:e9–e13. [PubMed: 22703825]
28. Oliveira C, Zamakhshary M, Marcon P, et al. Eosinophilic esophagitis and intermediate esophagitis after tracheoesophageal fistula repair: a case series. *J Pediatr Surg.* 2008; 43:810–814. [PubMed: 18485944]
29. Mandaliya R, DiMarino AJ, Cohen S. Association of achalasia and eosinophilic esophagitis. *Indian J Gastroenterol.* 2013; 32:54–57. [PubMed: 23054948]
30. Wennervaldt K, Melchior J. Risk of perforation using rigid oesophagoscopy in the distal part of oesophagus. *Dan Med J.* 2012; 59:A4528. [PubMed: 23171748]
31. Byrne KR, Panagiotakis PH, Hilden K, et al. Retrospective analysis of esophageal food impaction: differences in etiology by age and gender. *Dig Dis Sci.* 2007; 52:717–721. [PubMed: 17253139]
32. Vannelli PM, Youssef NN, Oppenheimer JJ, et al. Exploring the link between eosinophilic esophagitis and esophageal foreign bodies in the pediatric population. *Pract Gastroenterol.* 2007; 31:81.
33. Kirchner GI, Zuber-Jerger I, Endlicher E, et al. Causes of bolus impaction in the esophagus. *Surg Endosc.* 2011; 25:3170–3174. [PubMed: 21487866]
34. Antoniou D, Christopoulos-Geroulanos G. Management of foreign body ingestion and food bolus impaction in children: a retrospective analysis of 675 cases. *Turk J Pediatr.* 2011; 53:381–387. [PubMed: 21980840]
35. Diniz LO, Towbin AJ. Causes of esophageal food bolus impaction in the pediatric population. *Dig Dis Sci.* 2012; 57:690–693. [PubMed: 21948341]
36. El-Matary W, El-Hakim H, Popel J. Eosinophilic esophagitis in children needing emergency endoscopy for foreign body and food bolus impaction. *Pediatr Emerg Care.* 2012; 28:611–613. [PubMed: 22743755]
37. Williams P, Jameson S, Bishop P, et al. Esophageal foreign bodies and eosinophilic esophagitis—the need for esophageal mucosal biopsy: a 12-year survey across pediatric subspecialties. *Surg Endosc.* 2013; 27:2216–2220. [PubMed: 23355153]

Fig. 1.
Schematic representation of retrospective study showing our experience of EFI and EoE

Fig. 2.
Flow diagram of study selection process for a systematic review and meta-analysis

Fig. 3.
Forrest plot of overall biopsy rates in patients presenting with EFI

Fig. 4.
Forrest plot of overall EoE-attributable EFI requiring endoscopic intervention

Table 1

Characteristics of children with EFI presenting to our emergency center

	Food impaction NOT requiring endoscopy Self- resolved (<i>n</i> = 23)	Food impaction requiring endoscopy	
		Single impaction (<i>n</i> = 33)	Recurrent impactions (<i>n</i> = 16)
Events	23	33	39
Age, years [median (range)]	6 (1–17)	12 (2–17)	11 (1–18) ^a
Male [<i>n</i> (%)]	20 (88)	20 (61) [‡]	1 (70)
Ethnicity [<i>n</i> (%)]			
Caucasian	12 (55)	29 (87) [‡]	10 (65)
Hispanic	5 (21)	4 (13)	4 (22)
African American	0	0	2 (13)
Asian	2 (9)	0	0
Other	3 (15)	0	0
Comorbidity [<i>n</i> (%)]			
Prematurity	0	1 (3)	2 (13)
Anatomical	1 (4)	7 (21)	6 (38)
Dysmotility	0	0	1 (3)
Asthma	2 (8)	3 (9)	0
Food allergy	0	4 (12)	0
Rhinitis	0	2 (6)	0
EoE	0	0	3 (9)
Other	Anxiety, Down's syndrome, autism	ADHD, developmental delay, aortic stenosis	CHARGE syndrome, tetralogy of fallot
Presenting symptoms			
Food stuck sensation	9 (39)	12 (36)	14 (88) [€]
Vomiting	5 (22)	9 (27)	12 (75) [€]
Painful swallowing	8 (35)	7 (21)	5 (31) [€]
Drooling	7 (30)	5 (15)	2 (13)
Choking	5 (22)	4 (12)	5 (31)
Location			
Proximal	–	11 (33)	2 (13)
Mid	–	9 (27)	11 (69)
Distal	–	8 (24)	4 (22)
Unspecified	–	5 (15)	12 (75)
Endoscopic findings			
Normal	–	8 (24)	6 (38)
Minimal erythema	–	8 (24)	6 (38)
Furrowing	–	7 (21)	3 (19)
Edema	–	4 (12)	2 (13)
White exudates	–	2 (6)	0
Rings	–	4 (12)	2 (13)

	Food impaction NOT requiring endoscopy Self- resolved (<i>n</i> = 23)	Food impaction requiring endoscopy	
		Single impaction (<i>n</i> = 33)	Recurrent impactions (<i>n</i> = 16)
Mucosal tear	–	2 (6)	0
Luminal stenosis	–	3 (9)	1 (6)
Narrowing/stricture at anastomotic site	–	1 (3)	4 (22)
Unspecified	–	5 (15)	3 (19)
Food material			
Meat (beef, chicken, pork, sausage)	8 (35)	17 (52)	8 (50)
Bone (chicken bone, pork bone)	1 (4)	4 (12)	0
Vegetables (corn, potato)	0	2 (6)	1 (6)
Fruits (grape, apple)	1 (4)	2 (6)	0
Nuts	2 (8)	1 (3)	0
Candy	5 (22)	0	0
Other (quesadilla, Hot Pocket)	1 (4)	2 (6)	0
Not specified	8 (16)	1 (3)	0
Subspeciality			
ENT		7 (21)	0
Gastroenterology		20 (61)	20 ^b
Surgery		6 (18)	6 ^b

[¥]*P* 0.05 for comparison between self-resolved group versus single-impaction group

[€]*P* 0.05 for comparison between single-impaction group versus recurrent impaction group

^a At initial presentation

^b Repeated endoscopic procedures

Table 2

Description and details of the studies included in the systematic review and meta-analysis

References	Study design	Year(s)	Excluded other causes of		Esophageal eosinophilia	Esophageal biopsies	EoE criteria
			EFI				
Lao et al. [17]	R	1/1988–12/1998	Proximal esophageal stricture ($n = 1$); esophageal web ($n = 1$); nonspecific esophageal motility disorders ($n = 4$)	No		Taken 3–5 cm above GE junction	Not described
Desai et al. [20]	P	1/2000–12/2003	Stricture ($n = 5$)	Yes		Proximal and distal	Esophageal dysfunction, EoE-related endoscopic findings, histologic features consistent with EoE, and peak intraepithelial eosinophil count of > 20 eos/hpf.
Byrne et al. [31]	R	12/1999–11/2004	Schatzki's ring ($n = 18$); stricture ($n = 18$); esophageal cancer ($n = 3$); achalasia ($n = 2$); esophageal stent ($n = 1$)	Esophagitis ($n = 9$)	Not provided		Combination of EoE-pertinent endoscopic findings and esophageal biopsies > 15 – 20 eos/hpf
Vannelli et al. [32]	R	01/2000–07/2004	No	No		Mid or distal	> 20 eos/hpf
Kerlin et al. [21]	P	07/2002–01/2004	Peptic strictures ($n = 11$); Schatzki ring ($n = 1$); post-surgical stricture ($n = 1$)	No		Two each from the proximal 1/3 and the distal 1/3	15 eos/hpf
Kirchner et al. [33]	R	4/2000–6/2008	Esophageal carcinoma ($n = 7$); Schatzki ring ($n = 4$); achalasia ($n = 3$); previous esophageal resection ($n = 3$); neurologic impairment of swallowing ($n = 2$); Zenker's diverticulum ($n = 1$); impairment of esophageal motility ($n = 1$)	Reflux esophagitis with or without peptic strictures ($n = 10$)		Upper, middle and lower	15 eos/hpf with basal zone hyperplasia, intercellular edema, and lamina propria papillae elongation
Sperry et al. [18]	R	6/2002–12/2009	Esophageal stricture ($n = 65$); hiatal hernia ($n = 59$); Schatzki's ring ($n = 38$); achalasia ($n = 28$); cancer (13); esophageal ulcer ($n = 10$); previous anti-reflux surgery ($n = 23$); Barrett's esophagus ($n = 4$); Previous esophageal atresia repair ($n = 2$); Previous tracheoesophageal fistula repair ($n = 10$); Other GI diagnoses ($n = 58$)	Lack of response to 6–8 weeks of treatment with a high-dose PPI, or a normal pH monitoring study of the distal esophagus.		Multiple sites	Clinical symptoms of esophageal dysfunction and 15 eos/hpf with basal zone hyperplasia, intercellular edema, and lamina propria papillae elongation
Hurtado et al. [19]	R	1/2005–6/2009	Esophageal stricture ($n = 13$)	No		An average of 2.6 proximal biopsies and 2.2 distal biopsies. Only 4 subjects had biopsies taken from 1 location.	Clinicopathological features such as trachealization (circular rings), white exudates, and > 20 eos/hpf in biopsies.
Antoniou et al. [34]	R	9/2002–8/2010	Stricture post esophageal atresia repair ($n = 5$); eosinophilic esophagitis ($n = 2$)	No		Not provided	Not described

References	Study design	Year(s)	Excluded other causes of EoE		Esophageal eosinophilia	Esophageal biopsies	EoE criteria
			EFI				
Diniz et al. [35]	R	1993–2009	Prior esophageal atresia repair or Nissen fundoplication (<i>n</i> = 16)	No	Not provided	Not provided	> 15 eos/hpf
El-Matary et al. [36]	R	01/2005–12/2008	Not described	Not described	Eight esophageal biopsies at minimum from 2 levels (proximal and distal)	> 15 eos/hpf	
Maresh et al. [3]	R	1996–2010	Benign peptic strictures (range 41–75 %)	No	Not provided	15 eos/hpf with/without eosinophil microabscess; superficial layering of eosinophils; extracellular eosinophil granules; basal cell hyperplasia; dilated intracellular spaces; subepithelial or lamina propria fibrosis	
Williams et al. [37]	R	01/1999–12/2011	Esophageal stricture (<i>n</i> = 11)	Disorders associated with similar clinical, histologic, or endoscopic features, particularly gastroesophageal reflux disease	Not provided	Food impaction and dysphagia in adults, and feeding intolerance and gastroesophageal reflux disease symptoms in children; 15 eos/hpf on esophageal mucosal biopsy sample	
Current study	R	2007–2013	Esophageal narrowing secondary to esophageal atresia repair (<i>n</i> = 1)	No	Multiple esophageal biopsies from different anatomical sites	Symptoms of esophageal dysfunction and 15 eos/hpf on esophageal mucosal biopsy sample	

Table 3

Characteristics of studies included in meta-analysis

References	Age (year) ^a	Location	Subspecialty	EFI (n)	Number biopsied	n (%)	IoE [n (%)]
Desai et al. [20]	42 ± 4	USA	GI	31	17 (46)	13 (76)	13 (76)
Bryne et al. [31]	18–100	USA	GI	79	13 (16)	9 (69)	9 (69)
Vannelli [32]	12 (mean) (range 9–16)	USA	GI	11	11 (100)	8 (73)	8 (73)
Kerlin et al. [21]	19–93	Australia	GI	43	29 (67)	14 (48)	14 (48)
Kirchner et al. [33]	15–88	Germany	GI	54	48 (89)	10 (21)	10 (21)
Sperry et al. [18]	9.5 ± 5.3	USA	GI + ENT	54	28 (52)	13 (46)	13 (46)
Sperry et al. [18]	58.0 ± 19.6	USA	GI + ENT	293	50 (17)	29 (58)	29 (58)
Hurtado et al. [19]	7mo.-17	USA	GI + surgery	49	12 (24)	5 (42)	5 (42)
Antoniou et al. [34]	4–14	Greece	Surgery	35	16 (46)	2 (13)	2 (13)
Diniz et al. [35]	9 (Mean)	USA	Radiology database	43	27 (63)	23 (87)	23 (87)
El-Matary et al. [36]	4.98 ± 4	Canada	GI + ENT	18	11 (61)	7 (64)	7 (64)
Williams et al. [37]	3.8 ± 2.3	USA	GI	12	6 (50)	4 (67)	4 (67)
Maresh et al. [3]	59.8 ± 2.1	Australia	GI	315	141 (45)	73 (52)	73 (52)
Current study	10 ± 5	USA	GI + ENT + surgery	33	24 (73)	13 (54)	13 (54)

^aMean ± SD, unless specified

Table 4

Results of overall and subgroup meta-analysis of proportions

Studies	Biopsy rates associated with EFI		EoE-attributable EFI		
	Cases	Proportion (95 % CI) ^a ; [I ² %]	Cases	Proportion (95 % CI) ^a ; [I ² %]	
Overall	14	1070	54 (40–68); [95]	223	54 (43–65); [76.5]
Subgroups					
Age					
Adults	6	815	48 (26–70); [97]	148	52 (37–67); [81]
Pediatrics	8	255	59 (43–74); [95]	75	55 (37–73); [77]
Location					
USA	9	605	49 (31–68) ^f ; [94]	117	64 (53–74) ^f ; [51]
Non-USA	5	465	63 (42–81); [92]	106	38 (21–57); [83]
Specialty					
GI	7	545	62 (40–82) ^f ; [95]	131	55 (39–71); [78]
Others	7	525	47 (27–66); [94]	92	52 (35–69); [77]
Adherence to current EoE diagnostic criteria					
No	10	631	60 (44–76) ^f ; [92]	162	56 (40–72); [83]
Yes ^g	4	439	39 (16–64); [95]	61	51 (42–61) ^h ; [0]

^f *P* 0.05

^a *CI* Confidence intervals,

^b results from fixed effect model