SYSTEMATIC REVIEWS AND META-ANALYSES

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Efficacy of Proton Pump Inhibitor Drugs for Inducing Clinical and Histologic Remission in Patients With Symptomatic Esophageal Eosinophilia: A Systematic Review and Meta-Analysis

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BACKGROUND & AIMS: **Proton pump inhibitor (PPI) therapy might lead to clinical and histologic remission in a significant proportion of patients with symptomatic esophageal eosinophilia (>15 eos/high-power field). We aimed to evaluate systematically the efficacy of PPI therapy for these patients.**

METHODS: **A search in MEDLINE, EMBASE, and SCOPUS databases, and the American Gastroenterological Association Institute, American College of Gastroenterology, and United European Gastroenterology meetings abstract books, was performed. Primary outcomes were clinical response and histologic remission (<15 eos/high-power field) after PPI therapy. Secondary outcomes were the influence on the response to PPIs of age group, study design/quality, PPI type, doses and interval dosing, and pH monitoring results. Data were pooled using a random-effects model.**

RESULTS: **Thirty-three studies (11 prospective studies) comprising 619 patients with symptomatic esophageal eosinophilia (188 children and 431 adults) were included. PPI therapy led to a clinical response in 60.8% (95% confidence interval, 48.38%–72.2%; $I^2 = 80.2$) and histologic remission in 50.5% (95% confidence interval, 42.2%–58.7%; $I^2 = 67.5$) of patients. No differences were observed regarding the study population (children vs adults), the type of publication, or its quality. PPIs were nonsignificantly more effective in prospective studies (52.6% vs 39.1%) administered twice daily compared with once daily (55.9% vs 49.7%), and with pathologic pH monitoring (65.4% vs 49.3%). A significant publication bias in favor of studies reporting histologic responses to PPIs was observed.**

CONCLUSIONS: **PPI therapy induces clinicohistologic remission in half of patients with symptomatic esophageal eosinophilia. This finding should be interpreted with caution because of poor-quality evidence, heterogeneity, and publication bias.**

Keywords: Eosinophilic Esophagitis; Proton Pump Inhibitors; Omeprazole; Esomeprazole; Lansoprazole; Rabeprazole; Systematic Review; Meta-Analysis.

Eosinophilic esophagitis (EoE) is a chronic immune-mediated inflammatory disorder, defined symptomatically by esophageal dysfunction and histologically by esophageal eosinophil–predominant inflammation.[1] Despite first characterized as a distinct clinicopathologic disorder 20 years ago,[2,3] EoE just recently has become recognized as the most prevalent cause of chronic esophageal symptoms among children and young adults.[4–6] Because the presence of esophageal eosinophilia is not specific, EoE consensus guidelines require clinical and/or histologic unresponsiveness to a 4- to 8-week proton pump inhibitor (PPI) trial, with other alternative causes of esophageal eosinophilia ruled out as well.[1,7–9] This requirement initially was introduced intending to eliminate gastroesophageal reflux disease (GERD) as an alternative cause of eosinophil infiltration.[7] However, it became clear that the relationship between esophageal eosinophilia, EoE, and GERD was much more complex,[10] so the description of a third diagnostic category, proton pump inhibitor esophageal eosinophilia (PPI-REE), was needed.

Abbreviations used in this paper: **CI, confidence interval; EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; hpf, high-power field; PPI, proton pump inhibitor; REE, responsive esophageal eosinophilia.**

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This condition was reported in 2006 in a series comprising 2 children and an adult with clinical, endoscopic, and histologic features of EoE, but who completely responded to a course of PPI therapy.[11] Two retrospective series in children also suggested the existence of patients with presumptive EoE who responded to PPI therapy.[12,13] In 2011, a prospective series evaluated the efficacy of systematic PPI therapy in EoE patients, of whom 50% achieved complete remission on PPI therapy.[14] Since then, interest in this novel entity has rocketed and several retrospective and prospective studies in both children and adults consistently have shown that at least a third of patients with suspected EoE eventually receive a diagnosis of PPI-REE.[15]

A review in 2013 indicated that the rates of symptom improvement (from 25% to 80%) and histologic remission (from 33% to 61%) on PPI therapy notably varied, depending on the study design and patient population.[16] Of note, response to PPI therapy was significantly higher in patients with pathologic pH monitoring.[16] However, data on PPI-REE have not been analyzed systematically yet to evaluate the quality of available evidence, many of the unsolved issues regarding the PPI trial (the length of treatment, type of PPI, dose, and frequency of dosing), differences between children and adults, or the accuracy of clinical phenotypes that could predict responsiveness to PPI therapy.

The aim of our study was to conduct a systematic review and meta-analysis of the efficacy and consistency of PPI therapy in inducing clinical and histologic remission of patients with a presumptive diagnosis of EoE, in both children and adults.

Methods

This systematic review has been registered in the PROSPERO International prospective register of systematic reviews (www.crd.york.ac.uk/PROSPERO; register no. CRD42015017569), and was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statements.[17]

Study Selection

A systematic literature search was performed independently by 2 researchers (A.A. and A.J.L.) in 3 major bibliographic databases (PUBMED, EMBASE, and Scopus) through December 2014. The search was not restricted to English language articles. To best estimate the magnitude of the effect of PPI therapy, according to the Cochrane Handbook for Systematic Reviews on Interventions,[18] we recovered all of the studies that would provide original data to answer our research question, regardless of their design. A predetermined protocol was used in accordance with the quality of reporting meta-analyses of observational studies in epidemiology.[19]

Comprehensive search criteria were used to identify articles dealing with EoE in children and adults. We consulted the thesauri for MEDLINE (Medical Subject Heading) and EMBASE (EMTREE) using the following search strategy: ("eosinophilic esophagitis" OR "eosinophilic oesophagitis") AND ("omeprazole" OR "lansoprazole" OR "pantoprazole" OR "rabeprazole" OR "esomeprazole" OR proton pump inhibitors[pharmacological action]"). For the SCOPUS database, only free text searches with truncations were performed. We also examined the reference lists from retrieved articles and abstracts of conference proceedings (annual abstract books from the American Gastroenterological Association (Digestive Disease Week), American College of Gastroenterology, and United European Gastroenterology meetings, through December 2014) to identify additional relevant studies. Two reviewers (J.M.-I. and A.A.) independently screened the database search for titles and abstracts. If any of the reviewers believed that a title or abstract met the study eligibility criteria, the full text of the study was retrieved.

Inclusion Criteria

All included patients showed esophageal symptoms plus esophageal eosinophilic infiltration greater than 15 eos/high-power field (hpf) at baseline endoscopy, performed off PPI therapy. Randomized controlled trials, observational prospective and retrospective studies, and case-series reports were included if original data on clinical and/or histologic efficacy or effectiveness after PPI therapy were provided. Studies evaluating all kinds of PPI drugs at any dosage providing objective quantitative data on PPI efficacy in terms of clinical and/or histologic response were included. Clinical response was defined by improvement/remission of esophageal symptoms after PPI therapy, depending on the investigators' specific criteria. Histologic remission was defined by an esophageal eosinophil peak count less than 15 eos/hpf after PPI therapy.

Exclusion Criteria

Our analysis excluded studies that used PPIs simultaneously with another therapeutic alternative capable of reducing esophageal inflammation (topical and systemic steroids and/or immunomodulatory drugs and/or dietary modifications). Review articles on the treatment of EoE that did not provide original data on PPI therapy, clinical guidelines, and consensus documents were excluded. Studies not performed on human beings or providing duplicate information (ie, repeated abstracts presented at different congresses or abstracts published later as a full report) also were excluded. Subsets of cases or controls from a previously published article by the same investigators were excluded as well.

Quality Assessment

Cohort studies, case series, and case reports were evaluated for quality if the article described the diagnostic criteria considered for EoE, all patients' demographic data, the type and dose of PPI drug assessed, as well as the treatment length, and any additional therapeutic interventions. Likewise, peak eosinophil counts had to be stated specifically in the text as well as the time frames and the clinic or clinics in which the study was performed. Quality assessment was checked with a specific evaluation form for observational studies developed by our group and based on the Strengthening the Reporting of Observational Studies in Epidemiology statement.[20] The study was considered to be at low risk for bias if each of the bias items could be categorized as low risk. On the contrary, studies were judged to have a high risk of bias if even one of the items was deemed high risk. Two investigators (A.J.L. and J.M.-I.) independently provided each eligible study with an overall rating of high, low, or unclear risk of bias, and, if disagreements emerged, a third reviewer (A.A.) was consulted.

Data Extraction

Three reviewers (A.J.L., A.A., and J.M.-I.) independently extracted relevant information from each eligible study using a standardized data extraction sheet and then proceeded to cross-check the results. The data extracted included the trial study areas, the last name of the first author, publication year, type and dose of PPI assessed, age and sex of study participants, sample size, methodologic design, and study period, whenever possible. At the same time, data on the key outcomes, including eosinophil count reduction to fewer than 15 eosinophils/hpf and symptomatic improvement, were extracted from all included studies. Disagreements between reviewers regarding data extraction were resolved through discussion. The authors of the various studies were contacted by e-mail for additional information if necessary.

Statistical Analysis

Response percentages for PPI therapies were summarized with the aid of a fixed-effects or random-effects meta-analysis weighted for the inverse variance following DerSimonian and Laird's method. Summary estimates, including 95% confidence intervals (CIs), were calculated for the rate of reduction of peak eosinophil counts to fewer than 15 eosinophils/hpf, and for symptomatic improvement, whenever possible.

Heterogeneity between studies was assessed by a chi-square test (Cochran Q statistic) and quantified with the I^2 statistic. Generally, I^2 was used to evaluate the level of heterogeneity, assigning the categories low, moderate, and high to I^2 values of 25%, 50%, and 75%, respectively.[21] Publication bias was evaluated with the aid of a funnel plot, the asymmetry of which was assessed with the Egger[22] and Harbord tests.[23]

For the primary outcomes, planned subgroup analyses were performed based on the type and dose of PPI drug used, its prescription (once daily vs twice daily), and the population considered (adults vs children). A sensitivity analysis was performed with regard to quality (risk of bias) and type of document (full-length article vs abstract presented at conference proceedings). All calculations were made with StatsDirect statistical software version 2.7.9 (StatsDirect Ltd, Cheshire, UK).

All authors approved the final version of the manuscript, including the authorship list.

Results

The search strategy yielded 1008 references; 961 were excluded after examining the title and abstract because they did not fulfill the inclusion criteria. Among the remaining 47 documents retrieved for complete evaluation, 14 were excluded because of a lack of data for calculations (11 documents) or either repeated or duplicated information (3 documents). Finally, 33 studies (comprising 28 full reports[11–14,23–46] and 5 abstracts[47–52]) were included in the quantitative summaries of our systematic review (Figure 1). Most of the research retrieved consisted of observational studies and case reports or series, with only 2 randomized controlled trials developed on this topic. The characteristics of the included studies are summarized in Table 1.

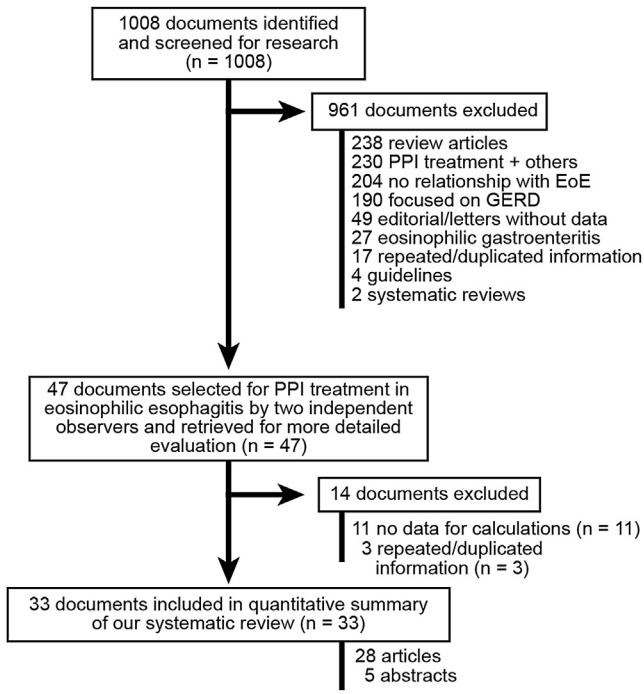

Figure 1. Flowchart for the process of identifying studies that were included and excluded from the systematic review.

Table 1. Demographics and Characteristics of Studies Included in Our Systematic Revision and Meta-Analysis

Study	N	Population	Type of PPI	Dose, *mg*	Treatment duration	Study design	Inclusion period	Male %	Histologic remission cases, n (%)	Clinical remission cases (%)
Nurko et al,[24] 2004	8	Children	Unspecified	NR	>4 wk	Retrospective	1990–2002	87	NR	6/8 (75)
Cury et al,[25] 2004	1	Children	Lansoprazole	NR	NR	Case report	NR	100	0/1 (0)	0/1 (0)
Potter et al,[26] 2004	12	Adult	Unspecified	NR	NR	Retrospective	1999–2002	NR	NR	3/12 (25)
Ngo et al,[11] 2006	3	Children	Omeprazole	10[a]	8 wk	Case report	NR	66.7	1/1 (100)	NR
		Children		20	8 wk				1/1 (100)	1/1 (100)
		Adult		20[a]	Several weeks				1/1 (100)	NR
Nantes et al,[27] 2009	3	Adult	Unspecified	NR	NR	Retrospective	2002–2008	NR	0/3 (0)	3/3 (100)
Sayej et al,[12] 2009	36	Children	Unspecified	1–2 mg/kg/d	12 wk	Retrospective	2003–2008	63.9	14/36 (38.9)	28/36 (77.8)
Gortani et al,[48] 2009	1	Children	Lansoprazole	15	6 wk	Case report	NR	100	1/1 (100)	1/1 (100)
Dranove et al,[13] 2009	43	Children	Unspecified	NR	NR	Retrospective	1999–2006	67.4	17/43 (39.5)	37/43 (86)
Garrean et al,[47] 2009	64	Adult	Unspecified	NR	NR	Retrospective	NR	NR	16/64 (25)	NR
Peterson et al,[28] 2010	15	Adult	Esomeprazole	40	8 wk	Clinical trial	2005–2006	80	6 /12 (50)	3/12 (25)
Jung et al,[29] 2010	2	Adult	Omeprazole	20	8 wk	Retrospective	2006–2008	NR	NR	1/2 (50)
Molina-Infante et al,[14] 2011	35	Adult	Rabeprazole	20[a]	8 wk	Prospective	2008	71.4	26/35 (74.3)	26/35 (74.3)
Abe et al,[30] 2011	6	Adult	Unspecified	NR	NR	Retrospective	2006–2009	71.4	3/6 (50)	5/6 (83.3)
Fujiwara et al,[31] 2012	5	Adult	Rabeprazole	10	8 wk	Prospective	2010–2011	100	3/5 (60)	3/5 (60)
Dohil et al,[32] 2012	3	Children	Lansoprazole	15[a]	12 wk	Case series	NR	66.7	1/1 (100)	1/1 (100)
			Lansoprazole	20[a]	12 wk				1/1 (100)	0/1 (0)
			Lansoprazole	30	NR				1/1 (100)	0/1 (0)
Levy et al,[33] 2012	1	Adult	Omeprazole	40[a]	6 wk	Case report	NR	0	0/1 (0)	0/1 (0)
Francis et al,[34] 2012	18	Adult	Esomeprazole	40[a]	6 wk	Prospective	2009–2010	63.2	11/18	5/18
Cohen-Sabban et al,[49] 2012	23	Children	Unspecified	NR	NR	Retrospective	2007–2008	56.5	NR	7/23 (30.4)
Vazquez-Elizondo et al,[35] 2013	60	Adult	Omeprazole	20[a]	8 wk	Prospective	2008–2012	65	34/60 (56.7)	43/60 (71.7)
Tomomatsu et al,[36] 2013	6	Adult	Unspecified	NR	NR	Retrospective	2010–2011	66.7	NR	2/6 (33.3)
Schroeder et al,[37] 2013	35	Children	Unspecified	1–2 mg/kg/d	8 wk	Retrospective	2000–2011	NR	8/35 (22.9)	8/35 (22.9)
Rea et al,[38] 2013	25	Children	Unspecified	NR	8 wk	Prospective	2005–2011	80	15/25 (60)	NR
Moawad et al,[39] 2013	21	Adult	Esomeprazole	40	8 wk	Clinical trial	2008–2010	90.5	7/21 (33.3)	NR
Lee et al,[40] 2013	6	Adult	Unspecified	NR	4–8 wk	Retrospective	2006–2011	66.7	5/6 (83.3)	2/6 (33.3)
Martinek et al,[50] 2013	26	Adult	Unspecified	20[a]	Long term	Prospective	NR	69.2	NR	25/26 (96.2)
Dellon et al,[41] 2013	66	Adult	Unspecified	20–40[a]	8 wk	Prospective	2009–2011	72.7	24/66 (36.4)	NR
Yilmaz et al,[42] 2014	2	Children	Esomeprazole	20	48 wk	Case report	NR	100	0/1 (0)	1/1 (100)
			Unspecified	NR	12 wk				0/1 (0)	1/1 (100)
Mangla et al, 2014[51]	17	Adult	Unspecified	High dose[a]	8 wk	Prospective	2013	82.4	11/17 (64.7)	NR
Lipka et al, 2014[43]	1	Adult	Rabeprazole	20[a]	4 wk	Case report	NR	0	1/1 (100)	1/1 (100)
Molina-Infante et al, 2014[44]	53	Adult	Omeprazole	40[a]	8 wk	Prospective	2010–2013	77.4	23/53 (43.4)	23/53 (43.4)
Dhaliwal et al, 2014[45]	6	Children	Unspecified	1 mg/kg/d[a]	NR	Retrospective	1999–2006	NR	5/6 (83.3)	6/6 (100)
Van Rhijn et al. 2014[46]	16	Adult	Esomeprazole	40[a]	8 wk	Prospective	NR	81.3	8/16 (50)	NR
Yamada et al, 2014[52]	3	Children	Unspecified	NR	NR	Case series	2005–2013	NR	3/3 (100)	NR

NR, not reported.
[a]Twice daily.

Overall, data from 619 patients (188 children and 431 adults) receiving any kind of PPI at any dose were retrieved, with study populations ranging from 1 to 66 cases. Of note, the type and doses of PPI used were not reported in the majority of included patients (383 of 619; 61%). The remaining documents assessed different PPI drugs, including omeprazole (n = 119), esomeprazole (n = 71), rabeprazole (n = 41), and lansoprazole (n = 5).

An overall favorable clinical response after PPI treatment given at any dose was reported for 60.8% (95% CI, 48.38%–72.2%; $I^2 = 80.2\%$) of patients, with a similar benefit for children and adults (64.9% vs 56.2%) (Table 2).

The overall effectiveness for inducing histologic remission of EoE (defined as the reduction of peak eosinophil counts to <15 eosinophils/hpf) for any PPI administered at any dosage was 50.5% (95% CI, 42.2%–58.7%; $I^2 = 67.5\%$) (Figure 2*A*), with no significant differences between pediatric and adult patients (54.1% vs 49.6%) (Figure 2*B* and *C*), and with a similar number of studies performed for both populations (Table 2). The heterogeneity of results among the different retrieved studies was high, according to I^2 statistic values.

Subgroup Analysis

Study design and risk of bias. An analysis of subgroups categorized according to risk of bias and type of document was performed (Table 2). Most of the selected studies were considered to be of low/medium-low quality (conversely, with a high/medium-high risk of bias), but the efficacy of PPI therapy to induce histologic remission of EoE showed no differences regarding that obtained by high/medium-quality studies (51.7% vs 50.6%, respectively).

The overall efficacy rate of 50.5% (95% CI, 42.2%–58.7%) for PPIs in inducing histologic remission of esophageal eosinophilia did not change significantly when case reports (with ≤ 3 patients) were excluded (47.48%; 95% CI, 39.5%–55. 53%) or case reports plus abstracts were excluded (48.33%; 95% CI, 40.5%–56.36%). A high heterogeneity (I^2) remained after excluding abstracts and case reports.

When only clinical response was considered as the study end point, a higher efficacy was reported in the research with a higher risk of bias (63% vs 51.6%).

Regarding the type of publication, no significant differences were noted for research published as full reports compared with abstracts (49.7% vs 62.9%, respectively).

Because the study design directly correlates with risk of bias, results from research using prospective and retrospective methods were analyzed separately (Figure 3) after excluding the results from 13 individual patients reported as case reports (including 1–3 individual patients). Summary estimates for the effectiveness of PPI therapy to achieve histologic remission of EoE in prospective studies (including randomized controlled trials) was 52.6% (95% CI, 44.4%–60.7%; $I^2 = 52.8\%$), which was slightly superior ($P = .146$) to that of

Table 2. Summary of Histologic Remission Rates, Clinical Remission/Improvement, 95% CIs, and I^2 Statistics (Inconsistency) for Proton Pump Inhibitor Therapy for Children and Adults With Eosinophilic Esophagitis

PPI therapy	Histologic remission (%)	n	I^2	Clinical response (%)	n	I^2
Overall	50.5 (42.2–58.7)	27	67.5	60.8 (48.38–72.2)	26	80.2
Adults	49.6 (40.1–59.2)	17	65.5	56.2 (41.4–70.4)	15	78.3
Children	54.1 (37.7–70)	11	69.6	64.9 (43.4–83.6)	11	83.8
Subgroups according to PPI used						
PPI unspecified	44.9 (33.9–56)	13	69.1	65.6 (46.6–82.4)	13	86.7
Omeprazole	53.5 (35.3–71.1)	4	59.9	55.7 (34.2–76.2)	5	66.6
Lansoprazole	70.2 (18.7–99.9)	3	57.1	44 (10.1–81.7)	3	23.2
Rabeprazole	72.3 (58.3–84.3)	3	0	72.3 (58.3–84.3)	3	0
Esomeprazole	46.8 (35.3–58.4)	5	2.6	33.3 (14.7–55.2)	3	31.2
Subgroups according to quality						
Medium/high	51.7 (43–60.3)	10	54.8	51.6 (34.4–68.5)	6	80.2
Low/low–medium	50.6 (37–64.2)	17	70	63 (46.9–77.7)	20	80.7
Subgroups according to type of publication						
Full text	49.7 (41.3–58)	23	62.3	56.4 (44.7–67.8)	24	77.7
Abstract	62.9 (27.1–92)	4	83.8	-	2	-
Subgroups according to doses						
Once daily	49.7 (28.9–54)	7	17.1	51.1 (29.3–72.7)	7	24.8
Twice daily	55.9 (46–65.6)	13	59.9	68 (51.5–82.5)	9	82.2
Subgroups according to design						
Prospective	52.6 (44.4–60.7)	11	52.8	59.1 (39.3–77.5)	7	87.4
Retrospective	39.1 (26.6–52.4)	8	66	59.9 (41–77.4)	12	84.3
Case report/case series	66.2 (34.7–91.3)	8	58.2	69 (40.7–91.1)	7	22.4
Subgroups according to pH monitoring						
Normal	49.3 (24.2–74.6)	7	82.7	-	-	-
Pathologic gastroesophageal reflux	65.4 (44.5–83)	6	61.7	-	-	-

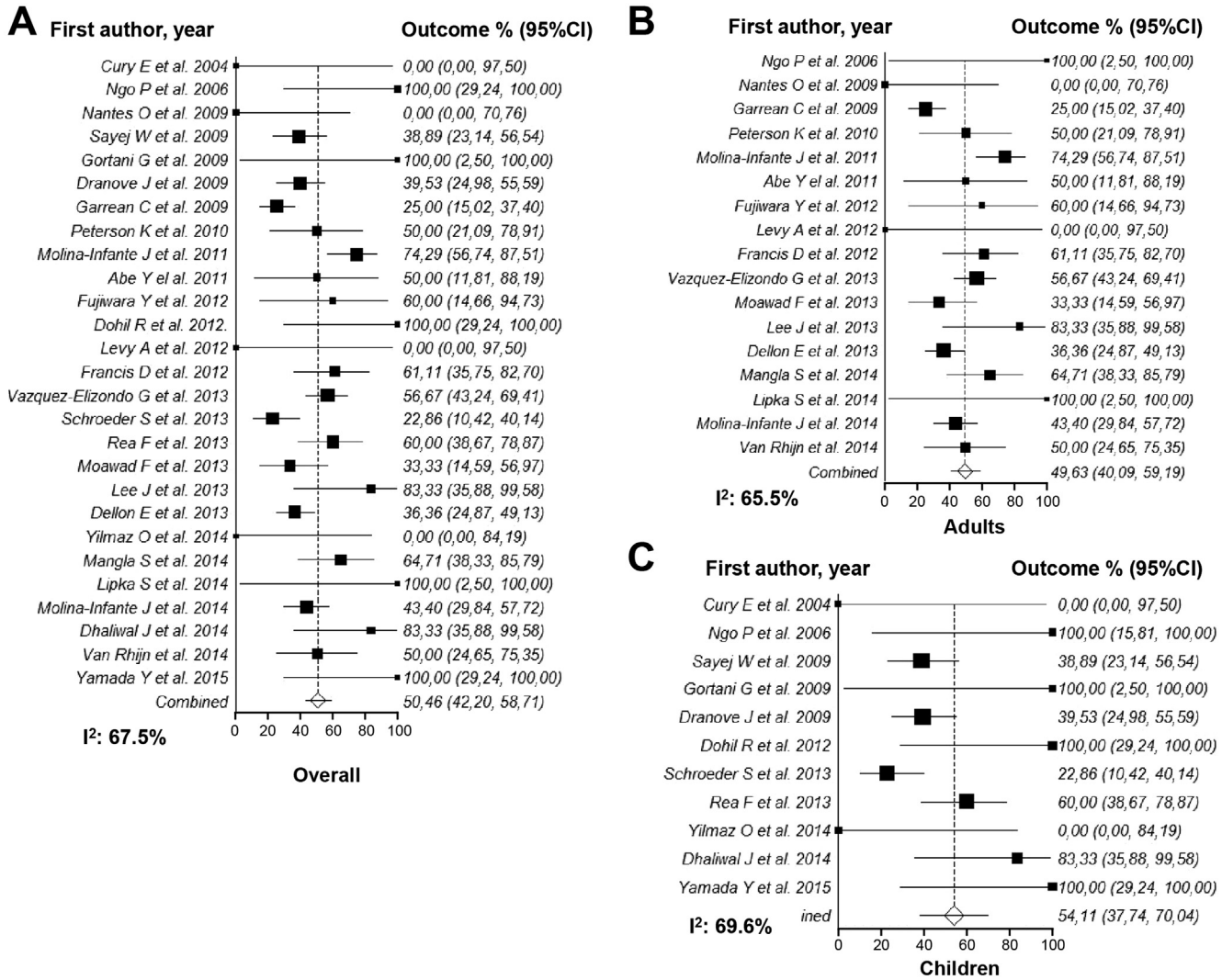

Figure 2. (*A*) Overall combined effects of PPI therapy for inducing histologic remission in patients with symptomatic esophageal eosinophilia. Percentage of histologic improvement after a PPI therapy was extracted from each article/abstract and 95% CIs were calculated using the exact binomial method. A random-effects model was used to calculate the overall effect size. The I^2 statistic indicates intrastudy heterogeneity. Subgroup analyses for studies exclusively including (*B*) adult and (*C*) pediatric patients.

retrospective studies (39.1%; 95% CI, 26.6%–52.4%; $I^2 = 66\%$).

Proton pump inhibitor type and doses. The differential efficacy rates for the distinct PPIs were assessed. Lansoprazole and rabeprazole showed the highest efficacies in inducing histologic disease remission (70.2% and 72.3%, respectively), compared with omeprazole and esomeprazole (53.5% and 46.8%, respectively). The limited number of studies using each PPI drug, their small sample size, and the heterogeneity among individual studies prevented finding significant differences.

A nonstatistically significant trend toward a higher efficacy for achieving histologic remission was found when PPIs were given twice daily compared with once-daily dosages (55.9% vs 49.7%; $P = .96$) (Figure 4*D* and *C*, respectively).

Esophageal pH monitoring. Finally, the overall efficacy rates of PPI therapy in inducing histologic remission of EoE trended to be nonsignificantly higher in the presence of pathologic pH monitoring (65.4%), compared with those patients showing normal esophageal acid exposure time (49.3%) (Figure 4*A* and *B*).

Publication Bias

The funnel plot analysis for studies reporting the histologic remission of EoE after PPI therapy showed a statistically significant publication bias in favor of studies reporting the effectiveness of this intervention, with a P value of .002, according to the Egger test and a P value of .047 according to the Harbord test (Supplementary Figure 1*A*).

For studies reporting the efficacy of PPIs for improving clinical symptoms of EoE, the funnel plot did not show obvious asymmetry (Supplementary Figure 1*B*), and the Egger test ($P = .155$) and Harbord test ($P = .797$) likewise indicated no evidence of publication bias.

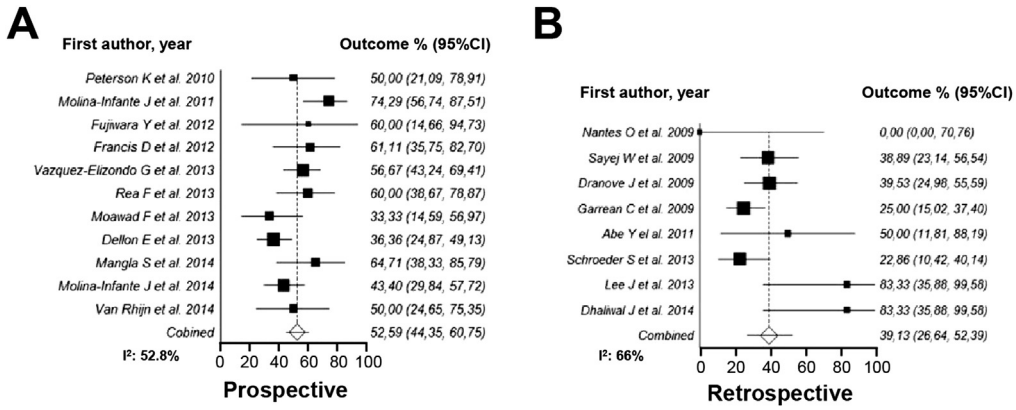

Figure 3. Subgroup analysis of studies evaluating the efficacy of PPI therapy in inducing histologic remission in patients with symptomatic esophageal eosinophilia in (*A*) prospective studies and (*B*) retrospective studies. I^2 denotes intrastudy differences or statistical heterogeneity.

Discussion

The present systematic review and meta-analysis shows that PPIs are effective drugs for achieving complete remission in half of patients with symptomatic esophageal eosinophilia compatible with EoE. Interestingly, the prevalence of histologic remission on PPI therapy reported here is slightly higher than that reported in a previous nonsystematic review article, especially in children (23%–40%).[16] This discrepancy likely is related to the inclusion of case reports and abstracts because the previous review only included series including 4 or more patients. However, our 50% histologic remission rate was consistent in further

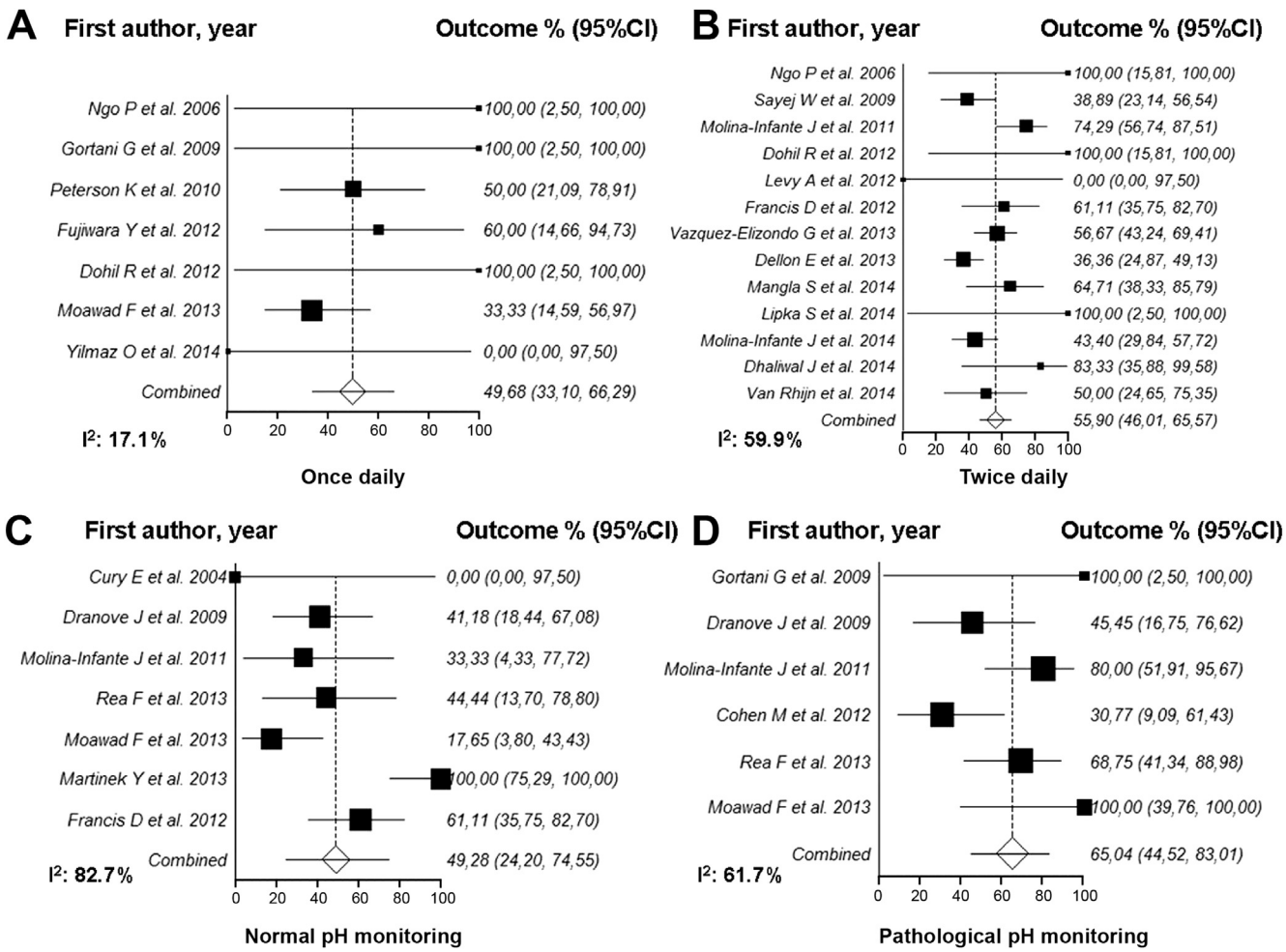

Figure 4. Subgroup analysis of studies evaluating the efficacy of PPI therapy in inducing histologic remission in patients with symptomatic esophageal eosinophilia in (*A*) patients with an absence of GERD as determined by normal pH monitoring, (*B*) patients with evidence of GERD determined by pathologic pH monitoring, (*C*) studies using a PPI dose once daily, and (*D*) studies using PPI doses twice daily. I^2 denotes intrastudy differences or statistical heterogeneity.

subanalyses along the study, regardless of the study population (children vs adults), type of study (full text vs abstract), and quality of the study (medium/high vs low/low-medium). When articles were broken down into case reports, retrospective studies, and prospective studies, prospective studies showed a steady 52% rate of histologic remission. Similarly, clinical remission was reported consistently in approximately 60% of patients after PPI therapy, irrespective of the evaluated subset of patients or drugs used.

Regarding the main outcomes in this meta-analysis depending on the type of PPI used, data were mixed, with lansoprazole and rabeprazole showing a nonsignificantly higher histologic remission rate (70%), accompanied by an identical symptom remission rate in the case of rabeprazole. These data, however, should be viewed with caution because they come from only 6 studies comprising 46 patients,[14,25,32,43,48] and most of them were case reports or retrospective studies. Among these studies, a prospective study published in 2011 (using rabeprazole 20 mg twice daily for 8 weeks) also was included, which reported a 75% histologic remission rate.[14] It should be noted that this notably high response rate was reported in unselected patients undergoing upper endoscopy owing to nonspecific upper gastrointestinal symptoms. In this study, the histologic remission rate in patients with an EoE phenotype (dysphagia/food bolus impaction, >15 eos/hpf and typical endoscopic findings) was 50%, which interestingly coincides with the rates reported in the present research.

Our results highlight a growing interest in PPI-REE, but mostly limited to gastroenterologists attending adult patients. Compared with the 2013 review article[16] (which included 152 children and 106 adults), the present study shows a minimal increase in pediatric cases (n = 188), which contrasts with an almost 4-fold increase in adult patients (n = 431) in a 2-year timeframe. Despite all available guidelines,[1,7–9] including the first specific for EoE in children, recommending a PPI trial in all patients with suspected EoE,[9] we paradoxically found 1 single prospective study addressing PPI-REE in a pediatric population.[38] Our findings suggest there are no relevant differences between children and adults regarding PPI-REE, but this issue should be addressed adequately in high-quality prospective pediatric studies.

As for specific information for the initial PPI trial in PPI-REE patients (type of PPI, doses, duration, and interval dosing), the present study underscores the poor quality of available literature on PPI-REE (61% of evaluated articles did not report the type of PPI used and 33% did not report the length of administration, respectively). In addition, some studies did use any kind of PPI drug within a wide range of doses[12,13,41,45] and the reported duration of PPI therapy also was variable. These limitations clearly hamper statistical analyses for PPI-REE and may explain the lack of significant associations. Nevertheless, we observed a nonsignificant trend to higher histologic response to PPI therapy when they were administered twice a day, compared with once a day administration. This observation may suggest that the effect of PPI therapy in PPI-REE is not dose-dependent, but instead shows a positive correlation with sustained therapeutic drug levels. Whether splitting the dose of PPIs may improve cure rates in PPI-REE owing to either more adequate acid suppression or sustained anti-inflammatory effects, and whether this finding applies for long-term PPI therapy in PPI-REE patients, should be elucidated in further studies.

Of note, our study also corroborates the lack of accuracy of esophageal pH monitoring to predict PPI-REE. These data were reviewed 2 years ago with 3 adult studies and 1 pediatric study, comprising 102 patients.[16] Although PPI-REE was reported in patients with either normal or pathologic acid exposure, the response to PPI therapy was higher in patients with documented GERD (70%) compared with patients with negative esophageal pH monitoring (29%). After the addition of 39 additional patients (66% pediatric and 33% adults) from a total of 9 studies, our results showed an even higher response to PPI therapy in patients with normal pH monitoring (49%), with a nonsignificant difference compared with patients with pathologic pH monitoring (65%).

One of the major strengths of the present study was the search strategy, conducted by means of an exhaustive literature search in 3 major databases and abstract books from the 3 major gastroenterology congresses. Moreover, recovered studies were critically appraised, according to their methodologic aspects, and different investigators independently extracted the data from the studies included. Compared with the nonsystematic review published in 2013,[16] we were able to identify 9 additional studies with 146 patients reported before February 2013 that had not been included in this previous review.

However, several limitations should be acknowledged for an adequate interpretation of the results. To begin with, the quality of the available evidence on PPI-REE is low, with 66% of retrieved studies being retrospective or case reports. The remaining third of the reports consisted of 2 randomized controlled trials and prospective series, all but one performed in adult patients. As mentioned previously, missing data regarding PPI therapy were common and prevented us from drawing conclusions on the most effective PPI drug and doses. Notwithstanding the fact that our results were mostly consistent, moderate to high statistical heterogeneity was observed. We believe that the shortage of good quality studies (two thirds consisting of retrospective series/case reports with small sample size) might have played a major role in the heterogeneity. Second, we detected a risk of bias in favor of studies reporting on the effectiveness of PPI therapy in achieving histologic remission of EoE. In this regard, it is undeniable that negative results are harder to publish and this limitation might have blurred the real response to PPI therapy. We used an eosinophil density of fewer

than 15 cells/hpf after PPI therapy as the criteria for a histologic response. However, a hpf constitutes a non-standardized measure that widely varies among individual studies[53] and therefore the possibility of failures in the response assessment in original documents remains. Regarding assessment of clinical response, another drawback is the lack of structured or objective tools to assess symptoms in most of the studies; because no validated instrument was used to assess changes in symptoms induced by PPI therapy, improvements can be attributed to adaptive strategies of the patient to cope with the disease, and not only to the effect of PPI on esophageal inflammation. In addition, the variations in diagnostic criteria for EoE along the almost 20-year period covered by our systematic review (regarding the eosinophil count threshold and exclusion of proton pump inhibitor–responsive esophageal eosinophilia) were not taken into account.

In conclusion, the present study proves that PPI therapy is an effective treatment that induces histologic and clinical remission in half of patients with symptomatic esophageal eosinophilia suggestive of EoE. Our results support the concept of PPIs as the first-line therapy in both children and adults for this subset of patients. Other effective alternatives, such as dietary or topical steroid therapy, likely might be set aside as second-line treatment, owing to long-term safety concerns (topical steroid therapy) and impairment of quality of life and nutritional inadequacy (dietary interventions). Our data reinforce the lack of accuracy of esophageal pH monitoring to predict responsiveness to PPI therapy, therefore the performance of this test before histologic re-evaluation on PPI therapy should be discouraged. More quality evidence on pediatric PPI-REE is needed urgently. Further high-quality prospective studies should aim to determine the best PPI drug, dose, and interval dosing for an initial PPI trial in EoE patients. Additional research is needed to clarify a handful of unsolved issues related to PPI therapy in PPI-REE, including its sustained effect and optimal dosing in the long term, the influence of the CYP2C19 genotype, its ability to reverse esophageal fibrotic remodeling, as well as aspects related to cost-effectiveness and quality of life issues.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2015.07.041.

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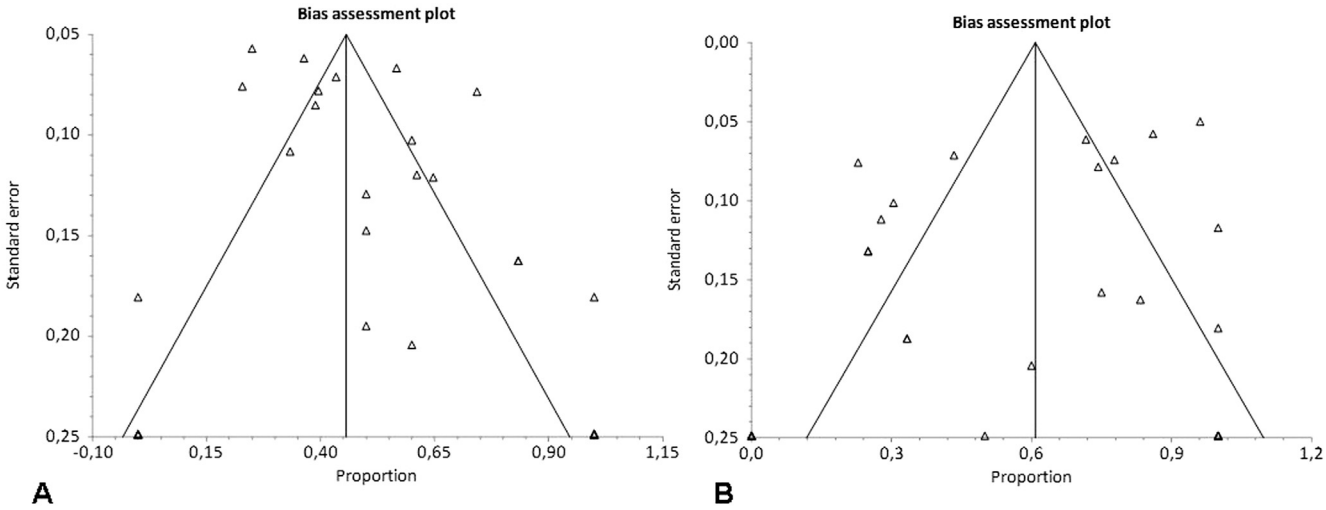
Conflicts of interest
The authors disclose no conflicts.



Supplementary Figure 1. Begg funnel plot of studies on the efficacy of PPI therapy for inducing (*A*) histologic remission and (*B*) clinical improvement in patients with symptomatic esophageal eosinophilia. The *solid line* in the center is the natural logarithm of pooled remission rates, and the 2 *oblique lines* are pseudo–95% confidence limits.