

# Maintenance Treatment With Proton Pump Inhibitors for Reflux Esophagitis in Pediatric Patients: A Systematic Literature Analysis

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## ABSTRACT

**Objectives:** Short-term treatment with a proton pump inhibitor (PPI) is effective for healing reflux esophagitis and improving reflux symptoms in pediatric patients. Our aim was to assess the efficacy and tolerability of maintenance PPI treatment after healing of reflux esophagitis in pediatric patients.

**Materials and Methods:** Systematic searches of MEDLINE, Excerpta Medica database, and recent conference abstracts.

**Results:** Five studies evaluated the efficacy of PPI maintenance therapy (6- to 90-month follow-up) in pediatric patients after healing of reflux esophagitis. Three found no relapse of reflux esophagitis or reflux symptoms during PPI maintenance therapy; however, a low relapse rate (1/14) was also found in the placebo group of the only prospective controlled study. Two of the 5 studies (both prospective) reported relapse of reflux esophagitis at half the original healing dose of omeprazole (7 of 51 patients relapsed after 3 months; 8 of 32 within 21 months), which resolved again in most patients when the healing dose or higher was given. Four studies evaluated relapse of reflux esophagitis and/or reflux symptoms after stopping PPI therapy. Reflux symptoms recurred in 18% to 76% of patients across all 4 studies. In the 4 studies that assessed the safety of PPI maintenance therapy, adverse events were infrequent and of low severity.

**Conclusions:** Pediatric patients with gastroesophageal reflux disease and certain chronic comorbidities appear to have the greatest need of maintenance PPI treatment after healing of reflux esophagitis. In patients requiring maintenance therapy, PPIs appear to be well tolerated and effective in maintaining remission of reflux esophagitis and reflux symptoms.

**Key Words:** gastroesophageal reflux disease, maintenance treatment, pediatric, proton pump inhibitor, reflux esophagitis

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Gastroesophageal reflux disease (GERD), defined as troublesome reflux symptoms and/or complications (1), is considered to be a chronic disease in adults (2). A recent Cochrane review

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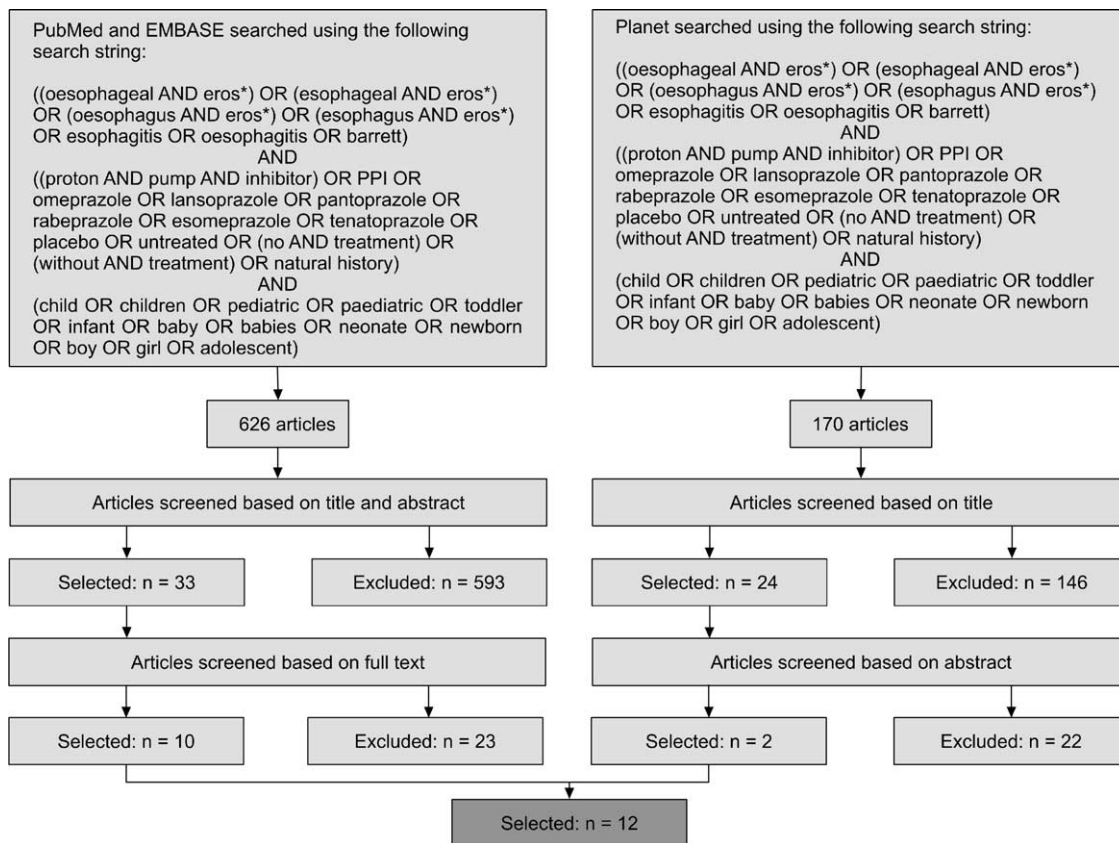
showed that in adults, proton pump inhibitors (PPIs) are significantly superior to placebo in maintaining remission after healing of reflux esophagitis (relative risk of relapse 0.26; 95% confidence interval [CI] 0.19–0.36 for long-term treatment with a healing dose and 0.46 [95% CI 0.38–0.57] for a maintenance dose [half the healing dose]) (3). The authors concluded that these data support the long-term treatment of reflux esophagitis with PPIs to prevent relapse of reflux esophagitis. In addition, PPIs have been shown to be well tolerated in adults during treatment for up to 11 years (4).

Although the benefits of short-term treatment with PPIs in pediatric patients with reflux esophagitis have been demonstrated (5–7), there are few data on long-term maintenance treatment with PPIs in this population. The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition recently copublished clinical practice guidelines relating to the diagnosis and management of pediatric gastroesophageal reflux. Although the guidelines advocate the short-term use of PPIs in children older than 1 year for the relief of GERD symptoms, the issue of maintenance therapy is not discussed in depth (8). This systematic review was originally conducted as part of a response to a written request from the US Food and Drug Administration for esomeprazole data in pediatric patients. Its aim was to review the available literature on reflux esophagitis in pediatric patients, to answer the following specific research questions: Is maintenance PPI treatment after healing of reflux esophagitis effective and well tolerated in pediatric patients? and Is maintenance PPI treatment needed in pediatric patients with reflux esophagitis and can the population of pediatric patients in need of treatment be defined?

## MATERIALS AND METHODS

Systematic searches of PubMed (all years until October 2008), Excerpta Medica database (all years until October 2008), and the Planet database (1990–October 2008) were conducted. (Planet is a database maintained by AstraZeneca that contains records from abstracts including information on PPIs that have been presented at key medical conferences). The search string used in the present review was an amended version of that used in a Cochrane review that assessed maintenance treatment for reflux esophagitis in adults (3) (QUORUM diagram shown in Fig. 1). The search string was modified to include only PPI medication terms; symptom-related terms and general GERD terms were removed and pediatric-specific terms were added.

Studies were identified that reported the effectiveness of PPIs in maintaining resolution of reflux symptoms and healed reflux esophagitis in pediatric patients, the relapse of reflux symptoms and/or reflux esophagitis in pediatric patients after discontinuing PPI treatment, and overall tolerability of PPI maintenance therapy in pediatric patients.



**FIGURE 1.** QUORUM diagram showing the selection of articles relevant to assessing the safety and therapeutic benefit of proton pump inhibitor maintenance treatment for reflux esophagitis. \*Wild card search term.

The articles identified through the search strategy were screened (on the basis of title and abstract) using the inclusion and exclusion criteria shown in Table 1. Publications for which relevance could not be determined from the title or abstract alone were obtained as full-text versions and screened in the same way. The screening process was performed by 2 independent reviewers, who resolved disagreements through discussion.

and/or reflux symptoms in pediatric patients during maintenance PPI therapy. Five reported outcomes for patients who stopped PPI therapy and were then followed up. One article reported an observational study of infants who were assigned to the placebo arm of a study. Another reported long-term outcomes in patients receiving PPIs. Four articles reported adverse events during maintenance PPI therapy.

**RESULTS**

**Trial Characteristics**

A total of 12 relevant studies (10 articles and 2 abstracts) were identified. Five of these reported relapse rates for reflux esophagitis

**Efficacy Of Maintenance Treatment With PPIs in Pediatric Patients With GERD After Healing of Reflux Esophagitis**

Of the 5 relevant studies identified, 1 was a prospective placebo-controlled study (9), 2 were prospective single-treatment

**TABLE 1.** Inclusion and exclusion criteria for articles identified from the search string

Inclusion criteria	Exclusion criteria
Clinical trial (abstract or full paper)	Review, editorial, practice guidelines, case studies, animal studies
Contains safety or efficacy data on the use of PPIs	Contains no safety or efficacy data on the use of PPIs
Contains data on treatment of pediatric patients (ages 1–17 y)	Contains no data on treatment of pediatric patients
Reflux esophagitis assessed by endoscopy or histology	Reflux esophagitis not assessed by endoscopy or histology
Contains data on maintenance therapy with PPIs or on follow-up of patients stopping PPI treatment after healing	Contains no long-term/follow-up data

PPI= proton pump inhibitor.

studies (10,11), and 2 were retrospective studies (12,13). Details of the studies are summarized in Table 2.

In the only placebo-controlled prospective study, by Boccia et al (9), 46 children were randomly assigned after healing of reflux esophagitis (defined as at least grade II according to the Hetzel et al classification [14]) to 6-month maintenance therapy with omeprazole,  $0.7 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$  (single daily dose) ( $n = 16$ ), ranitidine,  $10 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$  (divided into 2 doses) ( $n = 16$ ), or placebo ( $n = 14$ ). Histological, endoscopic, and symptomatic scores were assessed 3 months after discontinuation of maintenance therapy. Reflux esophagitis and reflux symptoms did not relapse in any of the 16 patients taking omeprazole during the 6-month treatment and subsequent follow-up (9). However, only 1 patient had relapse of reflux esophagitis (grade II according to the Hetzel et al classification) in the placebo arm, and there were no relapses in the ranitidine arm, suggesting that the natural propensity to relapse was inherently low in this pediatric population. It is notable that this study specifically excluded children with chronic conditions such as cerebral palsy, repaired esophageal atresia, neurological impairment, or repaired tracheoesophageal fistula.

In the first of 2 retrospective studies (12), regular endoscopic assessments during a mean follow-up of 4.4 years showed that healed reflux esophagitis was maintained in all 15 children while taking omeprazole (doses used during the follow-up period were not specified; reflux esophagitis was defined as at least grade II according to the Hetzel et al classification). The second study (13) was a retrospective chart review of 31 children who received >6 months of omeprazole maintenance therapy for reflux esophagitis. Endoscopy was repeated in these patients until reflux esophagitis was healed, and then annually thereafter. In all of the patients, reflux esophagitis significantly improved (details not specified), as did their reflux symptoms. These improvements were sustained during omeprazole maintenance treatment (mean dose  $1.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ , range  $0.6\text{--}3.3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ ) during a mean follow-up of 31 months (range 6–90 months). In both of these studies, the majority of patients had chronic conditions such as cerebral palsy, repaired esophageal atresia, neurological impairment, or repaired tracheoesophageal fistula.

Relapses of reflux esophagitis were studied in 2 prospective single-arm studies. In the first study (10), 7 of 51 neurologically impaired children showed recurrence of reflux symptoms and reflux esophagitis (defined as at least grade I according to the Savary-Miller classification [15]) after 3 months of maintenance treatment using omeprazole at half the dose initially used to heal reflux esophagitis and resolve reflux symptoms (20 mg/day for children who were at least 20 kg in weight, 10 mg/day for children <20 kg). Reflux symptoms and reflux esophagitis resolved again in these patients when omeprazole treatment was increased to the original healing dose for 3 months. The second prospective study investigated the healing and maintenance of reflux esophagitis (defined as at least grade II according to the Hetzel et al classification) in 57 children. The healing portion of this study has been fully published (6), and the maintenance phase has been published in abstract form (11). The maintenance phase of this study has not yet been published as a full article, but comprehensive details were available from the clinical study report (study code I-678). After healing of reflux esophagitis, 46 patients entered a 21-month maintenance phase at half the healing dose of omeprazole ( $0.35\text{--}1.75 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ ). Twenty-four of these children had no other underlying disease, 15 had neurological impairments, and 7 had repaired esophageal atresia. Thirty-two patients completed the 21-month maintenance phase. Patients did not complete the maintenance phase for the following reasons: nontreatment-related adverse event ( $n = 4$ ), fundoplication ( $n = 2$ ), patient withdrawn by investigator because of relapse ( $n = 1$ ), discontinuation of omeprazole

treatment by noninvestigator physician ( $n = 1$ ), laboratory measures or biopsy missing ( $n = 2$ ), lost to follow-up ( $n = 3$ ), and asymptomatic ( $n = 1$ ). During the maintenance period, reflux esophagitis relapsed in 8 patients (not including the patient who relapsed and was then withdrawn from the study for this reason). Four had relapse of reflux esophagitis only, and 4 had relapse of both reflux esophagitis and reflux symptoms. The reflux esophagitis healed again in 5 of these patients when the omeprazole dose was increased to the healing dose or higher. At the end of the study, reflux esophagitis had healed in 26 of the remaining patients, 3 had no final endoscopy but were asymptomatic, and 3 had reflux esophagitis. One of the 3 patients who finished the study unhealed had been healed when the dose of omeprazole was increased to the healing dose but relapsed again when the dose was then decreased to half this dose.

Further indirect evidence for the efficacy of PPI maintenance therapy is provided by a study that screened hospital databases for records from pediatric patients with GERD who took PPIs continuously for at least 9 months (16). In 166 individuals (mean age at time of index 7.8 years, range 4 weeks–17 years), the median number of symptoms declined significantly from 3 (interquartile range 2) at first presentation to 1 (interquartile range 1) on the last encounter. The median follow-up between presentation and last encounter was 3 years, during which PPIs (omeprazole [85%], lansoprazole [4.2%], omeprazole + lansoprazole [6%]) were used for a median period of 2.75 years, omeprazole at a median dose of  $1.1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ , and lansoprazole at a median dose of  $1.4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ . All of the patients who were followed up underwent esophageal endoscopy at some point during the study period. Although reflux esophagitis (classification system not reported) was endoscopically confirmed in 81 (48.8%) of these 166 patients, specific details for rates of healing or relapse of reflux esophagitis were not given. Seventy-nine percent of the patients had comorbid conditions such as neurological disorders, esophageal atresia or tracheoesophageal fistula, or chronic lung disorders.

## Relapse of Reflux Esophagitis and Reflux Symptoms After Stopping PPI Therapy

Studies showing endoscopic and symptomatic outcomes after stopping PPI therapy in pediatric patients with GERD give an indication of whether PPI maintenance treatment is needed in this population. Two of the 4 studies identified by the search criteria collected data on relapse of reflux esophagitis after stopping PPI treatment, and all 4 reported relapse of reflux symptoms. These studies are summarized in Table 3. This section also incorporates data from the previous section that are relevant to this particular issue.

In the first of 2 prospective studies that assessed relapse of reflux esophagitis after stopping PPI treatment, 10 children with reflux symptoms and reflux esophagitis (at least grade II according to the Hetzel et al classification) underwent 3-month-long treatment with omeprazole (40 mg/day [children weighing  $\geq 30 \text{ kg}$ ] or 20 mg/day [children <30 kg]) (17). At the end of this treatment, reflux esophagitis had improved to grade I or 0 in 9 patients and grade II in 1 patient. Upon discontinuation of treatment (time period not specified), 6 of 10 patients had symptomatic relapse for an unspecified duration of follow-up, 3 (30%) of whom also experienced relapse of reflux esophagitis (grade I) that prompted initiation of maintenance therapy. It should be noted that despite the presence of healed reflux esophagitis in most of these patients, histological abnormalities persisted, which, the authors suggest, may have been an indicator of incomplete healing. In the study by Boccia et al (9) described in the previous section, patients were followed up for

TABLE 2. Summary of studies reporting relapse rates for reflux esophagitis and/or reflux symptoms in pediatric patients during PPI maintenance therap

Reference	Study population characteristics							
	n	Healing treatment	Comorbidity	Previously failed treatment	Ages, y	Completers n	Maintenance treatment	Length of treatment
Bohmer et al (10)	52	Omeprazole (40 mg/d for children $\geq 20$ kg; 20 mg/d for children $< 20$ kg) for 3 mo	All NI	Cisapride 17%; ranitidine 23%; fundoplication 100%	Mean 15.4, range 4–19	51	Omeprazole (20 mg/d for children $\geq 20$ kg; 10 mg/d for children $< 20$ kg)	3 mo
Hassall (11)	46	Omeprazole (0.7–3.5 mg $\cdot$ kg $^{-1} \cdot$ d $^{-1}$ ) for 3 mo	33% NI, 15% EA	H <sub>2</sub> RA/prokinetic 49%; fundoplication 5%; H <sub>2</sub> RA/prokinetic; and fundoplication 1.8%	$< 7$ , n = 20; 7–12, n = 16; 12–16, n = 10	32	Omeprazole at half healing dose (0.35–1.75 mg $\cdot$ kg $^{-1} \cdot$ d $^{-1}$ )	21 mo
Pashankar et al (12)	18	Omeprazole (mean dose 1.2 mg $\cdot$ kg $^{-1} \cdot$ d $^{-1}$ , range 0.8–2.3 mg $\cdot$ kg $^{-1} \cdot$ d $^{-1}$ ) for 3–9 mo	56% EA/TF, 33% NI, 11% CP	Fundoplication 100%	Mean 7.8, range 2.4–17	15	Omeprazole (mean dose 1.2 mg $\cdot$ kg $^{-1} \cdot$ d $^{-1}$ )	Mean
Pashankar and Israel (13)	31	Omeprazole (mean dose 1.5 mg $\cdot$ kg $^{-1} \cdot$ d $^{-1}$ , range 0.6–3.3 mg $\cdot$ kg $^{-1} \cdot$ d $^{-1}$ ); time frame not given	23% EA/TF, 61% CP	H <sub>2</sub> RA 71%; fundoplication 29%	Mean 7.5, range 1–14	31	Omeprazole (dose not given)	6–90 mo
Boccia et al (9)	46	Omeprazole (1.4 mg $\cdot$ kg $^{-1} \cdot$ d $^{-1}$ ) for 3 mo	Patients with EA, TF, CP, or NI excluded	Not reported	Median 9, range 2.5–14	44	Omeprazole 0.7 mg $\cdot$ kg $^{-1} \cdot$ d $^{-1}$ (16 patients), ranitidine 10 mg $\cdot$ kg $^{-1} \cdot$ d $^{-1}$ (16 patients), or placebo (14 patients)	6 mo

CP = cerebral palsy; EA = repaired esophageal atresia; H<sub>2</sub>RA = histamine 2 receptor antagonist; NI = neurological impairment; PPI = proton pump inhibitor; TF

\* Reflux esophagitis defined as at least grade I according to the Savary-Miller classification (15).

† Reflux esophagitis defined as at least grade II according to the Hetzel et al classification (14).

TABLE 3. Relapse of reflux esophagitis and reflux symptoms after stopping PPI therapy

Reference	Study population	Age, y	n	Treatment	Healed reflux esophagitis,* n	Relapse after PPI cessation	
						Reflux esophagitis, n (%)	Reflux symptoms, n (%)
Krischer et al (19)	Chronic comorbidity not reported All refractory to antacids, H <sub>2</sub> RAs, and prokinetic drugs	Mean 9.3, range 1–15	11	8–12 wk with omeprazole at 20 mg/d	8	—	2/11 (18%)
Cucchiara et al (18)	No chronic comorbidities All unresponsive to H <sub>2</sub> RAs and cisapride	Median 6.6, range 1.5–12	21	8 wk with omeprazole 1 mg · kg <sup>-1</sup> · d <sup>-1</sup>	18	—	16/21 (76%)
De Giacomo et al (17)	All refractory to H <sub>2</sub> RAs and prokinetic drugs 20% cerebral palsy	Median 6.3, range 2–9	10	3 mo with omeprazole (40 mg/d [children of at least 30 kg] or 20 mg/d [children <30 kg])	10	3/10 (30%)*	6/10 (60%)
Boccia et al (9)	Previous failed treatments not reported No chronic comorbidities Healed reflux esophagitis after 3-mo omeprazole (1.4 mg · kg <sup>-1</sup> · d <sup>-1</sup> )	Median 9, range 2.5–14	48	6-mo maintenance with omeprazole 0.7 mg · kg <sup>-1</sup> · d <sup>-1</sup> (16 patients), ranitidine 10 mg · kg <sup>-1</sup> · d <sup>-1</sup> (16 patients), or placebo (14 patients)	46	1/46 (2.2%) <sup>†</sup> at 3 mo	12/46 (26%) at 30 mo

EA = esophageal atresia; GERD = gastroesophageal reflux disease; H<sub>2</sub>RA = histamine 2 receptor antagonist; NI = neurological impairment; PPI = proton pump inhibitor.

\*Reflux esophagitis defined as at least grade I according to the Hetzel et al classification (14).

<sup>†</sup>Reflux esophagitis defined as at least grade II according to the Hetzel et al classification (14).

30 months after stopping maintenance therapy with omeprazole, ranitidine, or placebo. One patient showed relapse of reflux esophagitis 3 months after stopping maintenance therapy and received further treatment. An additional 12 patients (25%) had reflux symptoms after stopping maintenance therapy, all of which were deemed “sufficiently mild to discontinue treatment.” However, no endoscopies were performed at the 30-month follow-up, making it impossible to determine whether reflux esophagitis also remained in remission in this time frame.

Additional 3 studies assessed only relapse of reflux symptoms (and not reflux esophagitis) after discontinuing PPI maintenance treatment. In the first study (18), 21 patients ages 1.5 to 12 years (median age 6.6 years) with recurrent reflux esophagitis (at least grade II according to the Hetzel et al classification) were prospectively followed during an 8-week treatment with omeprazole, 1 mg · kg<sup>-1</sup> · day<sup>-1</sup>. Treatment resulted in dramatic improvement or complete disappearance of both reflux symptoms and reflux esophagitis. Reflux symptoms recurred in 16 (76%) patients (severity and frequency not specified) within 2 months after ending PPI therapy.

In a second study (19), 11 children (mean age 9.3 years, range 1–15 years) with severe reflux esophagitis (defined as at least grade II according to the Hetzel et al classification) that was unresponsive to treatment with Gaviscon, cimetidine/ranitidine, and/or cisapride received omeprazole, 20 mg/day, for 8 to 12 weeks. All of the patients had significant symptom relief, and resolution of reflux esophagitis was observed in 8 who underwent endoscopy. However, reflux symptoms recurred in 2 patients (18%) at an unspecified time after stopping omeprazole treatment.

Although they did not directly assess relapse following treatment discontinuation, the studies by Bohmer et al (10) and Hassall (11), described in detail in the previous section (Table 2), provide evidence that reducing the PPI dose can provoke relapse of reflux esophagitis and reflux symptoms in some pediatric patients. In both of these studies, patients experienced

relapses when the healing dose of PPI was halved for maintenance therapy. In addition, most of these patients showed rehealing/resolution of symptoms when the dose was increased again.

Although histological esophagitis is not classified as reflux esophagitis according to the recently published Definition of GERD in Pediatric Patients (20), studies that assessed histological esophagitis provide some supportive evidence for the need for maintenance PPI therapy. In 1 prospective study, histological esophagitis was defined as more than 2 eosinophils per high-power field and basal zone hyperplasia of >20%, or the presence of >2 neutrophils per high-power field. Patients with reflux esophagitis (defined as at least grade II according to the Hetzel et al classification) were excluded. In this study, 17 pediatric patients (mean age 10.7 years, range 2–17 years) with persistent histological esophagitis despite treatment with histamine-2 receptor antagonists were treated for 8 to 12 weeks with a mean healing omeprazole dose of 0.7 mg · kg<sup>-1</sup> · day<sup>-1</sup> (range 0.26–1.35 mg · kg<sup>-1</sup> · day<sup>-1</sup>). One patient had mild developmental delay and 2 patients had repaired esophageal atresia and tracheoesophageal fistula. After this treatment, histological esophagitis had healed in 6 patients (21). Five of the 6 patients had a relapse of reflux symptoms after treatment was stopped (time frame not specified); the sixth was lost to follow-up.

Some indirect evidence for the need for maintenance treatment is also provided by a study of 19 infants (ages 2.8–6.0 months) with histological esophagitis (assessed by papillary height and basal layer thickness) who were in the placebo arm of a trial (22). Symptoms and esophageal histology were assessed at baseline and at 2, 4, 6, and 12 months into the study; infants were given the active drug if both symptoms and histology were unimproved at any 1 visit. After 12 months, 6 patients required rescue and 3 withdrew. Although symptoms improved in all of the 10 infants who did not require the active drug, esophageal biopsies were abnormal at every assessment.

## Tolerability of Maintenance PPI Therapy in Pediatric Patients With Reflux Esophagitis

Four studies of PPI treatment in pediatric patients with previously healed reflux esophagitis reported rates of adverse events. In the study by Hassall et al (16), PPIs were used in 86 patients (52%) for 0.75 to 3 years and 80 patients (48%) for 3 to 11 years; omeprazole was the most commonly prescribed PPI (91%), followed by lansoprazole (10%). Only 6 adverse events potentially related to PPI use (nausea, vomiting, diarrhea, rash, agitation, and irritability) were recorded among 4 children, 3 of whom were taking omeprazole. A subgroup of 62 patients in this study had >1 set of gastric biopsies during routine clinical care. Assessment of these biopsies showed that these children did not develop atrophic gastritis, carcinoid tumors, or clinically significant enterochromaffin cell–like hyperplasia (23). In a retrospective study of 113 children receiving continuous lansoprazole or omeprazole (mean ages 6.7 and 8.3 years, respectively) for at least 1 year (64% lansoprazole [mean dose  $1.42 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ ], 22% omeprazole [mean dose  $1.15 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ ]), adverse events were reported by 12% of children; diarrhea (5%) and constipation (4%) were the most common (24). No clinically apparent adverse events were observed in the study by Pashankar et al (12). In addition, in the study from Hassall (11), omeprazole was well tolerated and no serious adverse events could be attributed to the drug.

There was 1 death in the Hassall study (11) (data retrieved from the I-678 clinical study report) after 21 months on omeprazole, 15 mg/day. The patient was already severely ill, had a history of glycogen storage disease, and experienced a 24-hour period of nausea and vomiting, extremely low blood glucose levels, and subsequent death from cardiac arrest. A causal relation with omeprazole treatment was not found. Among other treatments, the patient was taking cisapride. Overall, in this study, omeprazole was well tolerated and there were no serious adverse events that could be attributed to the drug.

## DISCUSSION

Few studies have documented the efficacy of maintenance treatment with PPIs in pediatric patients after healing of reflux esophagitis. The small number of studies identified in the present review suggests that PPI maintenance therapy in pediatric patients ages 1 to 17 years is associated with low relapse rates for reflux esophagitis (0%–25%) and reflux symptoms (0%–34%) for follow-up durations of 6 to 90 months. Indeed, no relapses of reflux esophagitis in 6-month to 4.4-year follow-up were reported during PPI treatment in 3 of the 5 studies reviewed. In the remaining 2 studies, relapse of reflux esophagitis (14% and 25%) and reflux symptoms (14% and 34%) (after 3- and 21-month follow-up) occurred only when half the healing dose was used but resolved again in most patients when the healing dose or higher was given. The relapse rates observed for reflux symptoms and reflux esophagitis in patients receiving suboptimal PPI doses suggest that long-term therapy at the full maintenance dose is needed in some children. In studies in which patients stopped PPI treatment after healing, rates of relapse of reflux esophagitis and reflux symptoms were variable (2.2% and 30% (9,17) for reflux esophagitis; 18%–76% for symptoms (9,17–19)). (The duration of follow-up was 2 and 3 months in 2 studies, and not specified in the other 2 studies.) In the studies that reported tolerability data, adverse events associated with maintenance PPI treatment appeared to be infrequent and of low severity. Thus, the evidence indicates that maintenance therapy, when required, should provide a favorable benefit-to-risk ratio.

Differences in relapse rates between studies may be accounted for by the different patient populations involved. The lowest rates of relapse of reflux esophagitis and reflux symptoms in prospective studies were seen in the Boccia et al study (9). A distinguishing feature of this study was the exclusion of pediatric patients with chronic comorbidities such as repaired esophageal atresia or tracheoesophageal fistula and neurological impairment. In contrast, 48% to 100% of patients in the maintenance phases of the remaining studies had these conditions (Table 2). This finding is consistent with the recent Global Definition of GERD in Pediatric Patients, which identified these disorders as predisposing to chronic, severe GERD (20). The recent joint clinical practice guidelines produced by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition for the diagnosis and management of pediatric gastroesophageal reflux attributes the recurrence of symptoms after repeated trials of PPI withdrawal to chronic-relapsing GERD and recommends long-term PPI therapy or surgery as therapeutic options in such situations (8). The low relapse rates observed by Boccia et al (9) suggest that reflux esophagitis in pediatric patients who do not have certain chronic comorbidities may require only PPI healing treatment and not maintenance therapy. Conversely, patients with reflux esophagitis who have underlying predisposing disorders are likely to need long-term PPI maintenance treatment. This view is supported by the study of Hassall et al, which found that 131 (79%) of 166 patients (mean age 7.8 years) taking PPIs for longer than 9 months had these underlying conditions (16). However, the only other study (18) of pediatric patients with GERD that excluded patients with chronic comorbidities reported far higher rates of reflux symptom relapse than Boccia et al (9) (76% compared with 26%). In this study, the frequent relapse of reflux symptoms may be attributed to the inclusion (due to selection bias) of a large proportion of patients who were refractory to non-PPI treatment. Therefore, the population of this study may have been enriched with individuals with a propensity to relapse.

In adults, GERD is recognized as a chronic disease requiring long-term maintenance PPI therapy (2,25). There is evidence that the symptomatic manifestation of reflux disease is different in infants (younger than age 1 year) compared with children and adolescents (1–17 years). Specifically, a large proportion of infants have regurgitation (due to volume reflux) that spontaneously resolves with age (20), whereas GERD in childhood appears to have a manifestation similar to that of GERD in adults, with symptoms persisting for many years (26–28). However, reflux esophagitis appears to be the same disease in pediatric patients as young as 2 months as it is in adults. This has been demonstrated in short-term studies of reflux esophagitis healing, which show that esomeprazole is efficacious for healing reflux esophagitis in pediatric patients (29,30) and adults (31–34). Furthermore, the physical description of reflux esophagitis is the same in pediatric and adult patients (20).

The data presented in the present review suggest that the clinical presentation of reflux esophagitis is similar in pediatric and adult GERD populations, but it is difficult to determine the chronicity of reflux esophagitis in the pediatric population. Rates of relapse of reflux esophagitis in the absence of PPI treatment in adults are generally higher than those found for pediatric patients in the present review. In particular, the Cochrane review found that on average (across 9 studies), 78.8% of adult patients taking placebo experienced relapse of reflux esophagitis in 12- to 52-week follow-up, compared with 21.7% of patients in PPI treatment groups (3). However, the paucity of pediatric studies and small patient numbers in the studies that have been performed make it difficult to draw firm conclusions. As discussed above, results from these pediatric

studies indicate that GERD may be more persistent in children with comorbidities such as neurological impairment, repaired esophageal atresia, or tracheoesophageal fistula.

One of the studies (11) reviewed in this article reported that reflux esophagitis and reflux symptoms often recurred in the absence of each other, suggesting a “disconnection” between these 2 outcomes. This is consistent with data showing that approximately one third of adults with reflux esophagitis do not have typical reflux symptoms or are asymptomatic (35,36) and that GERD without reflux esophagitis is also common. This is supported in the pediatric age group in the study by Orenstein et al (22), which showed that infants with abnormal esophageal biopsy in the placebo arm of a treatment trial never had normal biopsies in 1 year of follow-up, despite resolution of reflux symptoms. It is possible that some of the patients in other studies reviewed in this article, who only reported long-term symptomatic endpoints after stopping PPI treatment, could have had relapse of reflux esophagitis.

The main strength of the present review is the use of unbiased systematic search criteria. The search string used was a modified version of that used in the highly regarded Cochrane review, which addressed similar questions of PPI maintenance therapy in the adult GERD population. In addition, these systematic search criteria were applied across a range of databases, including a conference abstracts database, ensuring wide coverage of the international medical literature.

A major limitation of the literature in this area is the small number of well-designed standardized studies from which to draw conclusions. The prospective studies in particular included small numbers of patients, and definitions of reflux symptoms and reflux esophagitis were not consistent across studies. Moreover, some long-term studies investigated only the relapse of reflux symptoms and did not monitor reflux esophagitis endoscopically. Few studies included placebo groups because of the ethical difficulties associated with the inclusion of placebo groups in pediatric study populations. Given this limitation, clinical practice databases such as the UK General Practice Research Database and The Health Improvement Network are useful resources for investigating GERD in children (37). Finally, some of the studies were reported only in abstract form, which meant that the full details of exclusion criteria and methodology were not available. Full publication of such studies is obviously important to allow comprehensive comparisons to be made between studies.

In conclusion, this review highlights the paucity of data on PPI maintenance therapy in pediatric patients with healed reflux esophagitis. Maintenance PPI treatment in this age group appears to be required by children with certain chronic disorders (neurological impairment, repaired esophageal atresia, or tracheoesophageal fistula). The sparse available data suggest that in pediatric patients who need maintenance therapy, PPIs are effective in preventing relapse of reflux esophagitis and are well tolerated.

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