# Efficacy of Proton-Pump Inhibitors in Children With Gastroesophageal Reflux Disease: A Systematic Review

**Rachel J. van der Pol, Marije J. Smits, Michiel P. van Wijk, Taher I. Omari, Merit M.Tabbers, Marc A. Benninga**

**Pediatrics, 2011 May;127(5):925-35.**

# INTRODUCTION:

- **GERD** = GER that causes troublesome symptoms and/or complications.

- Diagnosis: medical history, physical examination, pH monitoring, intraluminal impedance monitoring (pH-MII) and/or endoscopy.

- GERD was diagnosed in 12.3% of North American infants & in 1% of other pediatric age groups, with health care costs ~US $2386 /patient /6 months.

- Use of PPIs for the treatment of GERD in children has increased enormously.

  Effectiveness and safety of PPIs for pediatric GERD?

→ a systematic review

# METHODS:

- Authors searched PubMed, Embase, the Cochrane Database of Systematic Reviews for randomized controlled trials & crossover studies investigating efficacy, safety of PPIs in children (0 -18 years) with GERD for reduction in GERD symptoms, gastric pH, histologic aberrations, reported adverse events.
- Exclusion: asthmatic patients, mentally retarded children, cystic fibrosis, eosinophilic esophagitis, surgical therapy, previous use of any other therapy besides PPIs (histamine H2 receptor antagonist, antacids, prokinetics).

# The Delphi list: a standardized list for RCTs

| Study Population | Blinding | Analysis |
|---|---|---|
| Was a method of randomization performed? | Was the outcome assessor blinded? | Were point estimates and measures of variability presented for the primary outcome measures? |
| Was the allocation of treatment concealed? | Was the care provider blinded? | Did the analysis include an intention-to-treat analysis? |
| Were the groups similar at baseline regarding the most important prognostic indicators (age, gender, disease duration, disease severity)? | Was the patient blinded? | Was the withdrawal/drop-out rate at <20% and equally distributed? |
| Where both inclusion and exclusion criteria specified? | | |

**High quality ⚜≥ 6 points.**

# RESULTS:

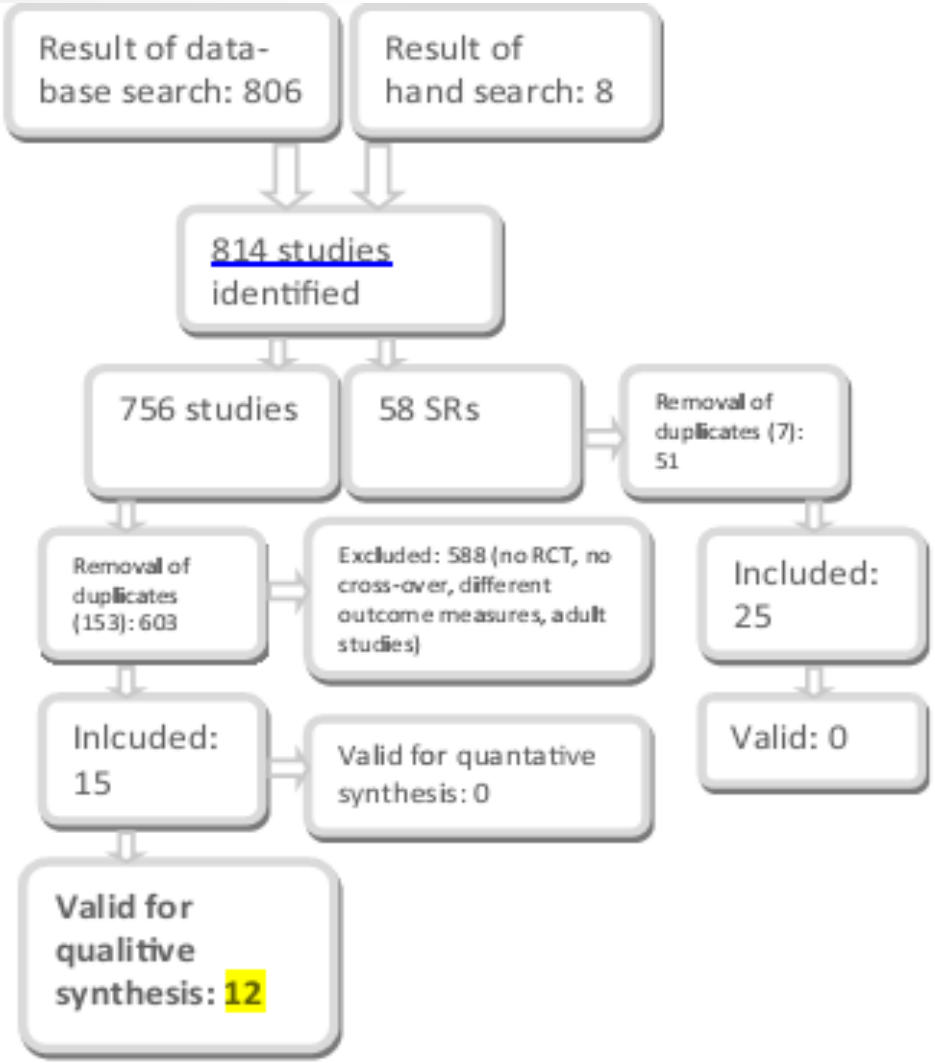


FIGURE 1
Search strategy.

-10 RCTs,
2 crossover trials:
9 in a general pediatric department,
2 in a pediatric gastroenterology department,
1 in a tertiary hospital
+895 participants
(0-17 years old)
-The mean score for overall methodologic quality was 7.6.

| Study and Quality | Setting, Participants, Diagnosis | Intervention (No. of Participants, Age, Mean ± SD) | Control Intervention (No. of Participants, Age, Mean ± SD) | Follow-up | Outcome Measures and Results |
|---|---|---|---|---|---|
| Moore et al[28] (2003), high quality (9) **infants** | Pediatric gastroenterology clinic; irritable/crying/spilling infants (3–12 mo old) with a reflux index of ≥5% on pH monitoring and/or abnormal esophageal endoscopy/histology | Omeprazole: <10 kg, 10 mg/d, or >10 kg, 2 × 10 mg/d; placebo ($n$ = 15, NS per group, 5.1 ± 2.0 mo) | Placebo, omeprazole ($n$ = 15, NS per group, 5.1 ± 2.1 mo) | 4 wk (LFU: 4 of 34 [6%]) LFU loss to follow-up | Reduction in reflux index: omeprazole, −8.9 ± 5.6; placebo, −1.9 ± 20 ($P$ < .001); change in cry/fuss score: omeprazole, 191 ± 120; placebo, 201 ± 100 ($P$ = .4); change in visual analog score of infant irritability: omeprazole, 5.0 ± 3.1; placebo, 5.9 ± 2.1 ($P$ = .214); baseline vs period 2 (placebo and omeprazole): baseline, 6.8 ± 1.6; period 2, 4.8 ± 2.9 ($P$ = .008) |
| Orenstein et al[30] (2009), high quality (9.5) | General pediatric clinic; infants (4–51 wk old) with symptomatic GERD, 3 times I-GERQ-MH screening (score not stated); crying/fussing/irritability 1 h after <25% of feeds; no response to conservative therapy | Double-blind period: lansoprazole: ≤10 wk, 0.2–0.3 mg/kg per d, or >10 wk, 1.0–1.5 mg/kg per d; open-label period: lansoprazole ($n$ = 81, 4–49 wk, mean: NS) | Double-blind period: placebo; open-label period: lansoprazole ($n$ = 81, 4–51 wk, mean: NS) | Before treatment: 1–2 wk; double-blind: 1–4 wk; open-label: 2–4 wk; after treatment: 30 d (LFU: 2 of 162 [1.2%]) | Responder status: >50% reduction from baseline in feeding-related crying: lansoprazole, 54%; placebo, 54% (not significant); changes in GERD symptoms: lansoprazole, −20; placebo, −20 (not significant); improvement of GAS: lansoprazole, 56%; placebo, 51% (not significant); mild/moderate AEs: lansoprazole, 62%; placebo, 46% ($P$ = .058); most frequent AE, upper respiratory tract infection: lansoprazole, 22%; placebo, 21%; serious AEs: lansoprazole, 12%; placebo, 2% ($P$ = .032); most frequent AE, lower respiratory tract infection: lansoprazole, 12%; placebo, 2%; mild/moderate TRAEs: lansoprazole, 15%; placebo, 16% (not significant) |
| Winter et al[31] (2010), high quality (8) | General pediatric clinic; postterm infants (≥28 d to <12 mo old) and preterm infants (corrected age: 44 wk to <12 mo old) with GSQ-I score > 16; clinical diagnosis of suspected, symptomatic, or endoscopy-confirmed GERD | Open-label period: pantoprazole: 1.2 mg/kg per d; double-blind period: pantoprazole ($n$ = 52, 5.15 ± 2.81 mo) | Open-label period: pantoprazole; double-blind period: placebo ($n$ = 54, 5.04 ± 2.81 mo) | Before treatment: 2–4 wk; open-label: 4 wk; double-blind: 4 wk (LFU: 0 of 106 [0%]) | Withdrawal rate: pantoprazole, 6; placebo, 6 (not significant); change in weekly GERD symptom scores: pantoprazole, −2.39 ± 2.47 ($P$ < .001); placebo, −2.52 ± 2.7 ($P$ < .001); no significant changes between groups; mild/moderate AEs, upper respiratory infection most common, pantoprazole, 13%; placebo, 13% (not significant); TRAEs: NS |
| Omari et al[27] (2007), high quality (7) | General pediatric (inpatient) department; preterm infants (34–40 wk PMA) with reflux symptoms; reflux index of >5% on pH monitoring | Omeprazole: 0.7 mg/kg per d; placebo ($n$ = 5, 34–40 wk PMA, 36.1 ± 0.7 wk) PostMenstrual Age | Placebo; omeprazole ($n$ = 5, 34–40 wk PMA, 36.1 ± 0.7 wk) | 2 wk (LFU: not stated) | Change in gastric acidity: omeprazole, 13.9 ± 5.1; placebo, 53.8 ± 6.8 ($P$ < .0005); esophageal acid exposure: omeprazole, 19.0 ± 4.5; placebo, 4.9 ± 3.4 ($P$ < .01); acid GER episodes: omeprazole, 59.6 ± 26.7; placebo, 119.4 ± 20.9 ($P$ < .05); change of GER symptom-assessment charts, symptom-assessment score: no significant changes; blood samples on days 6 and 13: blood chemistry or complete blood count (no significant alteration) |
| Khoshoo and Dhume[29] (2008), high quality (6) | Pediatric gastroenterology clinic; infants (3–7 mo old) with an I-GERQ-R score of ≥16 over a 1-wk period | Lansoprazole: 15 mg/d (Lan1) or 2 × 7.5 mg/d (Lan2) ($n$ = 15, 4.80 ± 1.18 mo [Lan1]; $n$ = 15, 4.30 ± 1.01 mo [Lan2]) | HF ($n$ = 15, 4.60 ± 0.99 mo) **Hydrolyzed Formula** | 2 wk (LFU: 0 of 45 [0%]) | Improvement of >30% in I-GERQ-R scores: Lan1, before, 26.6 ± 2.8; after, 20.6 ± 4.2; Lan2, before, 26.9 ± 3.7; after, 20.0 ± 3.3; HF, before, 25.9 ± 3.3; after, 25.8 ± 3.2; HF vs Lan1 or Lan2, $P$ < .05 |

**Efficacy** assessed by symptoms such as cryng/irritability and spilling, in questionnaire outcomes (I-GERQ-MH [Infant Gastroesophageal Reflux Questionnaire Medical History], GSQ-I[GERD Symptom Questionnaire Infants], I-GERQ-R [Infant Gastroesoph-ageal Reflux Questionnaire Revised] ), and/or in pH monitoring.

- Compared with a placebo:
  omeprazole not effective in reducing GERD symp-toms / 2 studies; lanzoprazole & pantoprazole equally effective /2 studies. In a study: lansoprazole more effective than hydrolyzed formula.
- One of the 5 studies did reveal a significant decrease in irritability over time in the PPI and placebo groups.
- Omeprazole was more effective compared with placebo in reducing gastric acidity (shown by pH-monitoring).
- 3 studies reported AEs: 1 study found no AEs, 1 study found mild-to-moderate AEs, 1 study found a significant difference in the frequency of serious AEs (lower RTI)-not related to treatment.

| Study and Quality | Setting, Participants, Diagnosis | Intervention (No. of Participants, Age, Mean ± SD) | Control Intervention (No. of Participants, Age, Mean ± SD) | Follow-up | Outcome Measures and Results |
|---|---|---|---|---|---|
| Tolia et al[32] (2006), high quality (8.5) | General pediatric practice; children (5–11 y old); endoscopy-proven GERD with a CSS of >16 on the GASP-Q | Pantoprazole: 10 mg/d ($n$ = 19, 8.50 ± 1.65 y) | Pantoprazole: 20 or 40 mg/d ($n$ = 18, 8.2 ± 1.48 y [20 mg/d]; $n$ = 16, 7.60 ± 1.89 y [40 mg/d]) | Before: 2 wk treatment: 8 wk; after: 2 wk (LFU: 1 of 53 [2%]) | Change in GASP-Q in mean CSS: 10 mg/d, 129.2 vs 28.1; 20 mg/d, 134.6 vs 32.7; 40 mg/d, 132.3 vs 42.9 ($P$ < .001); ISS, all 3 doses: belly pain, difficulty swallowing, nausea, pain after eating (all $P$ < .001); chest pain ($P$ < .006); PGA: disease improvement in all 3 doses ($P$ < .001); CSS, ISS, and PGA: differences in mean score between groups: not significant; AEs: NS; mild or moderate TRAEs, most common: 10 mg/d, headache (3); 20 mg/d: abdominal pain (1) and increased appetite (1); 40 mg/d, headache (1); differences between groups: not significant |
| Gilger et al[33] (2008), high quality (7.5) | General pediatric practice; children (1–11 y old) with endoscopy- or histology-confirmed reflux esophagitis | Esomeprazole: <20 kg, 5 mg/d, or >20 kg, 10 mg/d ($n$ = 26, mean NS [5 mg/d]; $n$ = 31, mean NS [10 mg/d]) | Esomeprazole: <20 kg, 10 mg/d, or >20 kg: 20 mg/d ($n$ = 23, mean NS [10 mg/d]; $n$ = 29, mean NS [20 mg/d]) | 8 wk (LFU: 0 of 109 [0%]) | AEs: $n$ = 82; TRAEs, most common: diarrhea (3), headache (2), and somnolence (2); differences between groups, not significant; PGA vs baseline, $P$ < .005 (all groups); change in symptoms according to PGA: parents scores vs baseline, $P$ < .01 (all groups); assessment by parents, significant differences between groups: NS |
| Boccia et al[34] (2007), high quality (7.5) | General pediatric practice; children (32–170 mo old) with GERD and reflux esophagitis in endoscopy-confirmed remission treated with omeprazole (1.4 mg/kg per d) for 3 mo | Omeprazole: 50% of starting dose (1.4 mg/kg per d) ($n$ = 16, 86 ± [NS] mo) | Ranitidine: 10 mg/kg per d or no treatment (No) ($n$ = 16, 98 ± [NS] [ranitidine]; $n$ = 14, 105 ± [NS] mo [No]) | Open label: 3 mo; double-blind: 6 mo; follow-up: 33 mo (LFU: 2 of 48 [4%]) | Change in endoscopic healing and symptom score (daily dairy parents and at each clinical visit); no statistically significant difference between groups; significant reduction in histological ($P$ = .02), endoscopic ($P$ = .01), and symptomatic scores ($P$ = .004) in all study groups compared with baseline |
| Borrelli et al[35] (2002), low quality (5) | General pediatric practice: children (1–12 y old) with GERD symptoms combined with results of pH monitoring and/or moderate esophagitis shown on endoscopy | Lansoprazole: 2 × 1.5 mg/kg per d; lansoprazole + alginate (LanAL); ($n$ = 10, mean NS [lansoprazole]; $n$ = 12, mean NS [LanAL]) | Alginate: 2 mL/kg per d ($n$ = 10, mean NS) | 8 wk (LFU: 4 of 36 [11%]) | Change in clinical symptom scores: alginate, 4.2 ± 0.9; lansoprazole, 4.3 ± 1.2; LanAl, 3.0 ± 1.1; LanAl vs alginate and lansoprazole, $P$ < .05; alginate/lansoprazole/LanAl vs baseline, $P$ < .01; reduction in esophageal acid exposure time: alginate, 6.1 ± 1.9; lansoprazole, 5.5 ± 1.5; LanAl, 3.8 ± 0.7; LanAl vs alginate and lansoprazole, $P$ < .05; alginate/lansoprazole/LanAl vs baseline, $P$ < .01; intragastric acidity: alginate, 2.5 ± 0.6; lansoprazole, 3.9 ± 0.3; LanAl, 4.2 ± 0.8; lansoprazole and LanAl vs baseline, $P$ < .01; Al vs baseline, $P$ = .08; endoscopic healing: all groups (significance NS) |
| Cucchiara et al[36] (1993), low quality (5.5) | General pediatric practice; children (6 mo to 13.4 y old) with GER esophagitis based on pH monitoring, endoscopy, and histology; unresponsive to ranitidine (2 × 8 mg/kg per d) and cisapride (3 × 0.8 mg/kg per d). | Omeprazole: 40 mg/d per 1.73 m$^2$ body surface area ($n$ = 16, mean NS) | Ranitidine: 20 mg/kg per d ($n$ = 16, mean NS) | 8 wk (LFU: 2 of 32 [6%]) | Reduction in median gastric pH: omeprazole, 60.1 (9.3–81); ranitidine, 37.4 (0–56.7) ($P$ < .05); change in symptom score: omeprazole, 9.0 (0–18) ($P$ < .01); ranitidine, 9.0 (6–12) ($P$ < .001); significant difference between groups: NS; omeprazole, 2.0 (0–6) ($P$ < .01); ranitidine, 2.0 (2–6) ($P$ < .01); change in esophagitis score (by endoscopy and histology): significant difference between groups: NS |

**Children**

**Individual Symptom Scores**

**Physician's Global Assessment**

**Efficacy** assessed by symptoms in questionnaire outcomes (Gastroesophageal Reflux Assessment of Symptoms in Pediatrics Questionnaire), and/or in pH monitoring, and/or endoscopy.

- PPIs were equally effective (2 dose-finding studies, 3 other studies compared PPIs with other antireflux therapies (ranitidine & alginates)).
- When comparing the different groups to baseline, GERD symptoms were significantly reduced in all groups.

- 2 studies reported that PPIs were more effective at reducing gastric acidity than alginate or ranitidine, but the reduction of macroscopic and histologic scores during endoscopy were similar in all study groups (PPI versus ranitidine or alginate) compared with baseline.

- The most common reported **TRAEs** included headache (n=6) and diarrhea (n=3)

# Adolescents

| Study and Quality | Setting, Participants, Diagnosis | Intervention (No. of Participants, Age, Mean ± SD) | Control Intervention (No. of Participants, Age, Mean ± SD) | Follow-up | Outcome Measures and Results |
|---|---|---|---|---|---|
| Tsou et al[37] (2006), high quality (9) | General pediatric practice; adolescents (12–16 y old) with a CSS of >16 on the GASP-Q, clinical diagnosis of suspected symptomatic, or endoscopy-proven GERD | Pantoprazole: 20 mg/d ($n$ = 68, 13.9 ± 1.37 y) | Pantoprazole: 40 mg/d ($n$ = 68, 14.1 ± 1.37 y) | 8 wk (LFU: 6 of 136 [4%]) | Change in GASP-Q in mean CSS: CSS, 20 mg/d, 177.7 vs 67.2 ($P$ < .001); 40 mg/d, 174.1 vs 58.2 ($P$ < .001); no significant changes between study groups; AEs: NS (no serious AEs); mild/moderate TRAEs: 20 mg/d, 59 (87%); 40 mg/d, 53 (78%); most common: headache (35%), infection (23%), and pharyngitis (19%); no significant differences between groups |
| Gold et al[38] (2007), high quality (8.5) | General pediatric practice; adolescents (12–17 y old) with clinical diagnosis of GERD based on medical history, physical examination, pH monitoring, and/or endoscopy and biopsy | Esomeprazole: 20 mg/d ($n$ = 76, mean NS) | Esomeprazole: 40 mg/d ($n$ = 73, mean NS) | 8 wk (LFU: 4 of 149 [3%]) | AEs: 113; TRAEs (14.9% of patients): most common: headache (8%), abdominal pain (3%), and diarrhea (2%); no significant differences between groups; reduction of GERD symptoms according to PGA: no significant changes between groups; symptoms were significantly reduced compared with baseline ($P$ < .0001) |

## Efficacy of the PPIs was assessedby symptom assessments or questionnaires (Gastroesophageal Reflux Assessment of Symptoms in Pediatrics Questionnaire)

- PPIs were equally effective in reducing GERD symptoms (dose-finding studies).
- GERD symptoms were significantly reduced in different groups compared to baseline.
- AEs, TRAEs included: headache (35%), infection (23%), pharyngitis (19%) / 1 study and in other: headache (8%), abdominal pain (3%), and diarrhea (2%)

# DISCUSSION:

- PPIs are not effective in reducing GERD symptoms in infants.
- Placebo-controlled studies are lacking in children and adolescents, but shown PPIs to be equally effective in reducing GERD symptoms (controls: alginates, ranitidine, different-dosage PPIs).
- PPIs are effective in reducing gastric acidity in all age groups. However, the effect of PPIs on histologic aberrations in children with GERD is unclear (only 3 studies reported on the differences in histologic scores between the studied groups, and no differences were found in 2 of them).
- On balance, short-term use of PPIs was well tolerated (although 1 lower RTI). Evidence to ensure safety is still lacking.

- Well-designed RCTs (the placebo-controlled trials), with a high methodologic quality were sparse, small sample sizes, heterogeneous: ethical problem? invasive procedures, taking place in non-academic centers…
- Pharmacodynamics, pathophysiology, symptom presentation might differ substantially between children and adults. Evidence of effectiveness of PPIs in adults cannot be extrapolated to children. It could be unethical to prescribe drugs without convincing evidence for efficacy of therapy in the age group to be treated.

# Drawbacks of studies:

- **First:** in 2 infant RCTs (crossover design): Immediate withdrawal of PPIs may trigger a rebound effect of hypersecretion of gastric acid, thereby influencing study results.
- **Second:** in 2 infant studies: use of a PPI before randomization could have influenced study outcome.
- **Third:** 1 study lacked data with respect to follow-up → whether GERD symptoms relapsed over time?
  Using a reflux questionnaire for the inclusion of patients without other tools to diagnose GERD may not be of good value in the prediction of severity of GERD.
- **Fourth:** the studies involved children and adolescents, were not placebo-controlled, which makes the results difficult to interpret.
  In another study: both study groups were treated with a PPI before random assignment during 3 months, which also could have influenced the study results.

# CONCLUSIONS:

- If the primary aim is to treat GERD symptoms, PPIs should not be prescribed in infants and PPIs have potential adverse effects, unless there is documented disease or with careful monitoring.

- Although PPIs seem to be well tolerated during short-term use, evidence supporting the effectiveness and safety of PPIs is lacking in the treatment of GERD in children and adolescents.

- Large, well-designed, placebo-controlled, randomized trials with well-chosen end points are necessary to evaluate the effect and safety of PPIs in the entire pediatric age range.