Pediatric esophageal motility disorders: studies on (patho)physiology, diagnosis and management
Smits, M.J.

Citation for published version (APA):
CHAPTER 8

Efficacy of proton-pump inhibitors in children with gastroesophageal reflux disease: a systematic review

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

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ABSTRACT

Introduction
Use of proton-pump inhibitors (PPIs) for the treatment of gastroesophageal reflux disease (GERD) in children has increased enormously. However, effectiveness and safety of PPIs for pediatric GERD are under debate.

Objectives
We performed a systematic review to determine effectiveness and safety of PPIs in children with GERD.

Methods
We searched Pubmed, Embase, and the Cochrane database of systematic reviews for randomized controlled trials and crossover studies investigating efficacy and safety of PPIs in children aged 0 to 18 years with GERD for reduction in GERD symptoms, gastric pH, histologic aberrations, and reported adverse events.

Results
Twelve studies were included with data from children aged 0-17 years. For infants, PPIs were more effective in 1 study (compared with hydrolyzed formula), not effective in 2 studies, and equally effective in 2 studies (compared with placebo) for the reduction of GERD symptoms. For children and adolescents, PPIs were equally effective (compared with alginates, ranitidine, or a different PPI dosage). For gastric acidity, in infants and children PPIs were more effective (compared with placebo, alginates, or ranitidine) in 4 studies. For reducing histologic aberrations, PPIs showed no difference (compared with ranitidine or alginates) in 3 studies. Six studies reported no differences in treatment-related adverse events (compared with placebo or a different PPI dosage).

Conclusions
PPIs are not effective in reducing GERD symptoms in infants. Placebo-controlled trials in older children are lacking. Although PPIs seem to be well tolerated during short-term use, evidence supporting the safety of PPIs is lacking.
INTRODUCTION

Gastroesophageal reflux (GER) is characterized by the passive movement of gastric contents into the esophagus. Physiologically, GER occurs several times daily in healthy infants, children, and adults.\textsuperscript{3,5} Gastroesophageal reflux disease (GERD) in infants and children is described as GER that causes troublesome symptoms and/or complications.\textsuperscript{4,5} On the basis of a large claim database that uses International Classification of Diseases, Ninth Revision (ICD-9) codes, GERD was diagnosed in 12.3\% of North American infants and in 1\% of other pediatric age groups.\textsuperscript{6} Symptoms of GERD are often nonspecific and may vary widely from regurgitation to excessive crying and respiratory symptoms. GER has the potential to cause severe complications such as esophagitis and failure to thrive. GERD can also have a major effect on the daily life of caregivers and on health care costs, which have been estimated to be US $2386 per patient per 6 months.\textsuperscript{7} Although taking medical history and performing a physical examination will often suffice, pH monitoring, occasionally combined with intraluminal impedance monitoring (pH-MII) and/or endoscopy, can be conducted if necessary. pH-MII is able to detect non–acidic reflux events as well and is of additional value in infants because of feed-buffering.\textsuperscript{8,9}

For mild infant GERD, parental guidance and education combined with feed thickeners and/or positioning therapy will often suffice. Also, in older children and adolescents, dietary and behavioral changes frequently reduce symptoms significantly.\textsuperscript{10–12} However, when pharmacologic treatment is indicated, antisecretory agents play a key role, and proton pump inhibitors (PPIs) are on the front row. In recently published guidelines regarding pediatric GER, conducted by the European Society for Pediatric Gastroenterology Hepatology and Nutrition and the North American Society for Pediatric Gastroenterology Hepatology and Nutrition in 2009, empiric, antisecretory treatment for infants with crying and distressed behavior may be considered, although clinical recovery may be ascribed to a placebo reaction or physiologic symptom resolution with time.\textsuperscript{4} In children and adolescents with heartburn, the use of acid-suppressing agents is also recommended; however, the supporting data were extrapolated from adult studies.\textsuperscript{4} Current guidelines lack a systematic review (SR) of the available evidence. Therefore, it remains unclear whether some recommendations are based on an expert opinion of the guideline committee or on scientific evidence. A recently published SR did not include recent randomized controlled trials (RCTs) and excluded adolescents with GERD.\textsuperscript{13} PPIs (omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, rabeprazole) inhibit gastric acid secretion by selectively blocking the gastric parietal cell H+K+ ATP-ase (also called the proton pump), an enzyme that is involved in the last step of acid secretion in gastric parietal cells. Although the effectiveness of PPIs in children is under debate, PPI use in infants and children with GERD has increased enormously during the last decade.\textsuperscript{14–16} PPIs are generally well tolerated\textsuperscript{17} but have some shortcomings and may increase susceptibility to acute gastroenteritis and community-acquired pneumonia,\textsuperscript{18,19} respiratory infections,\textsuperscript{13} gastric polyps,\textsuperscript{20} and bacterial overgrowth.\textsuperscript{13} Although PPIs are widely considered the most effective acid-suppressive therapy for adults with GERD,\textsuperscript{21,22} the effectiveness and safety of PPIs in infants and children with GERD is less clear. Therefore, the aim of this study was to systematically review the current literature to investigate and
summarize the quantity and quality of the evidence for the efficacy and safety of PPIs in infants, children, and adolescents with GERD.

METHODS

Search Strategy
We searched Medline, Embase, the Cochrane Database of Systematic Reviews electronic database, and the Cochrane Controlled Trials Register for SRs, RCTs, and crossover studies from inception to May 2010. The key words used to describe the study population were “proton-pump inhibitors” (Medical Subject Headings [MESH] and all fields), “gastroesophageal reflux” (MESH and all fields), “gastroesophageal symptoms,” “extraesophageal symptoms,” “GERD,” “esophagitis” (MESH and all fields), “infant” (MESH and all fields), “child” (MESH and all fields), and “adolescent” (MESH and all fields). No language restriction was applied. Reference lists of reviews and included studies were searched by hand to identify additional studies. The full search strategy is available from the corresponding author.

Study Selection
Two reviewers (Dr van der Pol and Ms Smits) independently screened all abstracts of identified SRs for eligibility. Inclusion criteria were: (1) the study was an SR, RCT, or crossover study; (2) the study population consisted of children aged 0 to 18 years with GERD and/or esophagitis; (3) one of the aims of the study was to evaluate the efficacy, adverse effects, tolerability, safety, and/or cost-effectiveness of PPI therapy or patient satisfaction, decrease in GERD symptom score, or change in number of acid reflux episodes and/or reflux index with PPI use; (4) the intervention consisted of PPIs and was compared with placebo, no treatment, or alternative treatment; and (5) the outcome measure was “treatment success” as determined by the authors of the studies. Studies with asthmatic patients, mentally retarded children, children with cystic fibrosis, children with eosinophilic esophagitis, children who had undergone surgical therapy, or children who had had previous use of any other therapy besides PPIs (such as histamine H2 receptor antagonist, antacids, and/or protonics) were excluded.

All potentially relevant studies and the studies for which the abstracts did not provide sufficient information for inclusion or exclusion were retrieved as full articles.

Quality Assessment
The full texts of included reviews were validated by 2 assessors (Ms Smits and Dr van der Pol) independently by means of a standardized list to validate SRs. Because a valid SR was not encountered, 2 reviewers (Ms Smits and Dr van der Pol) rated the methodologic quality of all identified studies by using the Delphi list (Table 1), a standardized list for RCTs. Methodologic quality scores were calculated as a percentage of the maximum quality score on the Delphi list. High quality is defined as a score of ≥60% (i.e., ≥6 points), and low quality is defined as a score of <60%. If disagreement between
the 2 reviewers existed, consensus was formed when possible, or a third reviewer (Dr Tabbers) made the final judgment.

Data Extraction
Structured data extraction was performed from the original reports by 2 reviewers (Ms Smits and Dr van der Pol) independently. Data derived from included articles contained items such as author and year of enrollment, study setting, methods, type of participants, method of GERD assessment, type of intervention, follow-up, outcome measures, and results. If disagreement between the 2 reviewers existed, consensus was formed when possible, or a third reviewer (Dr Tabbers) made the final judgment.

RESULTS

The search strategy generated 814 titles and abstracts (see Figure 1), of which only 15 studies met our inclusion criteria. After retrieving the full-text articles, 3 articles were excluded because of the lack of a control group or different outcome measures24–26 (Figure 1). Of the included studies, 10 were RCTs and 2 were crossover trials. Data from 895 participants (0-17 years old) were included. Studies were conducted in Europe, Australia, and North America. One study was performed in a tertiary hospital on preterm infants with symptoms suggestive of GERD;27 the other trials were outpatient studies, of which 9 were performed in a general pediatric department, 2 in a pediatric gastroenterology department,28,29 and one in a tertiary medical centre.27 Quality scores and study characteristics of the included studies27–38 are listed in Table 2.

The reviewers initially agreed on 85.8% of the quality items. Prevalent shortcomings of the included studies consisted of missing point estimates and measures of variability presented for the primary outcome measure (n=8), no intention-to-treat analysis (n=5), and no blinding of the outcome assessor (n=5). The mean score for overall methodologic quality was 7.6. Because of the heterogeneity between the included studies with regard to the participants, interventions, and outcome measures, a meta-analysis was not possible. Therefore, all studies are discussed separately. Included studies were subdivided on the basis of the age of the investigated population (infants, children, and adolescents) because of the different presentations of GERD symptoms in these groups and, herewith, the possible difference in efficacy.

If safety was an outcome measure in the included studies, it was monitored by the reported adverse events (AEs). Of the reported AEs, a selection was made of treatment-related adverse events (TRAE) that were judged by the clinicians treating the subject or the authors of the conducted study. The results are presented in this way in the hereafter-described subgroups.

Infants

We identified 5 placebo-controlled studies for which the authors described the efficacy and/or safety of PPIs (lansoprazole,29,30 omeprazole,27,28 and pantoprazole31) in infants (34 weeks postmen-
strual age to 12 months) with GERD. The mean score of the methodologic quality was 7.8. Alterations of GERD were monitored by differences in symptoms such as crying/irritability and spilling,\textsuperscript{27,28,30} in questionnaire outcomes (I-GERQ-MH [Infant Gastroesophageal Reflux Questionnaire Medical History],\textsuperscript{30} GSQ-I [GERD Symptom Questionnaire Infants],\textsuperscript{31} I-GERQ-R [Infant Gastroesophageal Reflux Questionnaire Revised]),\textsuperscript{30} and/or in pH monitoring.\textsuperscript{27,28}

PPIs compared with a placebo were not effective in reducing GERD symptoms in the 2 studies that used omeprazole.\textsuperscript{27,28} Compared with placebo, lansoprazole and pantoprazole were equally effective in 2 studies\textsuperscript{30,31} for reducing GERD symptoms. In a study that used lansoprazole, PPIs were more effective compared with hydrolyzed formula.\textsuperscript{29} One of the 5 studies did reveal a significant decrease in irritability over time in the PPI and placebo groups.\textsuperscript{28} Omeprazole was more effective compared with placebo in reducing gastric acidity, as shown by pH-monitoring results.\textsuperscript{27,28}

The authors of 3 studies reported AEs:\textsuperscript{27,30,31} 1 study found no AEs,\textsuperscript{27} 1 study found mild-to-moderate AEs,\textsuperscript{31} and 1 study found a significant difference in the frequency of serious AEs (lower respiratory tract infection in the PPI group).\textsuperscript{30} In the case of the latter study, the AE was judged not to be related to treatment by the clinicians who were treating the subjects. No significant differences were detected between the studied groups in reported TRAEs.\textsuperscript{30,31}

Children

We retrieved 5 studies that reported on the effect of esomeprazole,\textsuperscript{33} lansoprazole,\textsuperscript{35} omeprazole,\textsuperscript{34,36} and pantoprazole\textsuperscript{32} in children with GERD (aged 6 months to 13.4 years). The methodologic quality of these studies had a mean score of 6.8. Efficacy was assessed by changes in GERD symptoms,\textsuperscript{33–36} questionnaire responses (Gastroesophageal Reflux Assessment of Symptoms in Pediatrics Questionnaire),\textsuperscript{32} and/or pH monitoring\textsuperscript{35,36} and/or endoscopy.\textsuperscript{34–36} Of these RCTs, 2 were dose-finding studies that used 2 PPI doses;\textsuperscript{32,33} the other studies compared PPIs by using other antireflux therapies as controls (ranitidine\textsuperscript{34,36} and alginate\textsuperscript{15}).

All studies revealed that PPIs were equally effective compared with what was given in the control groups in reducing GERD symptoms. When comparing the different groups to baseline, GERD symptoms were significantly reduced in all groups.

The authors of 2 studies\textsuperscript{35,36} reported gastric pH findings and found 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.\textsuperscript{34–36}

Mild-to-moderate AEs were described in 2 study reports.\textsuperscript{32,33} The most common reported TRAEs included headache (n=6) and diarrhea (n=3).\textsuperscript{32,33}

 Adolescents

We included 2 studies that reported on the efficacy of esomeprazole\textsuperscript{38} and pantoprazole\textsuperscript{37} in adolescents (12-17 years) with GERD. The mean score of the methodologic quality was 8.8. Efficacy of the PPIs was assessed by symptom assessments\textsuperscript{38} or questionnaires (Gastroesophageal Reflux Assessment of Symptoms in Pediatrics Questionnaire).\textsuperscript{37}
Both studies revealed that PPIs were equally effective in reducing GERD symptoms compared with what was given in the control groups. Because both of them were dose-finding studies, control groups received PPIs but in different quantities. When comparing the different groups to baseline, GERD symptoms were significantly reduced in both groups. One study did not report on AEs, only TRAEs. TRAEs in that study included headache (35%), infection (23%), and pharyngitis (19%). The other study did report on AEs and TRAEs, of which headache (8%), abdominal pain (3%), and diarrhea (2%) were the most frequently reported TRAEs. No significant differences of AEs and/or TRAEs were detected between the studied groups in both studies.

**DISCUSSION**

This SR reveals that PPIs are not effective in reducing GERD symptoms in infants. Although SRs and placebo-controlled studies are lacking in children and adolescents, randomized trials have shown PPIs to be equally effective in reducing GERD symptoms compared with their controls (alginates, ranitidine, different-dosage PPIs). It is not surprising that 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, because only 3 studies in our review 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 study did reveal a significant change in lower respiratory tract infections. Evidence to ensure safety is still lacking. AEs tend to be of a mild-to-moderate nature; headache is the most frequently reported TRAE.

Because of statistical and clinical heterogeneity of the included studies, we were not able to perform a pooled analysis with a fixed- or random-effect model. Well-designed RCTs, especially the placebo-controlled trials, with a high methodologic quality were sparse, and sample sizes were often small. Furthermore, methodologic quality scores of the included studies were determined by the Delphi list. Although this is a validated list, it lacks any consideration of the number of included subjects. A plausible explanation of the small sample sizes in this review could be that performing placebo-controlled studies on infants and children is regarded to be unethical, not only by medical ethical committees but also especially by parents who often refuse to have their child participate in placebo-controlled trials because of the “risk” of being assigned to the placebo arm. Furthermore, invasive procedures such as blood-testing, combined impedance-pH measurement, and/or endoscopy are required to be part of the study protocol, and parents are often hesitant to agree to their infant enduring such procedures. Finally, placebo-controlled studies often take place in academic centers, whereas GERD-related problems are mainly treated in nonacademic centers, which makes it more difficult to include patients. Nonetheless, it is well-known that pharmacodynamics, pathophysiology, and symptom presentation might differ substantially between children and adults. For example, dosage and delivery method, the latter especially in frequently fed infants, may vary substantially. Furthermore, evidence of effectiveness of PPIs in adults cannot be extrap-
olated to children. Thus, it could be argued that it is unethical to prescribe drugs without convincing evidence for efficacy of therapy in the age group to be treated.

Another problem that influenced meaningful comparisons between studies is that the criteria used for randomization varied greatly from study to study (e.g., pH-monitoring acid-exposure criteria\textsuperscript{27} versus symptom-frequency criteria\textsuperscript{30}). In both of these cases, diagnostic criteria used to justify randomization were defined on the basis of a “best guess” rather than previous validation. More precise diagnostic testing methods such as pH-impedance monitoring are now available. These tests, in theory, offer the potential for antireflux therapy to be better targeted at patients in whom symptom episodes can be demonstrated to be caused by acid GER and/or bolus GER by using symptom-association probability.\textsuperscript{9} It is unfortunate that despite what seems to be an improvement in diagnostic methodology, there have been no published reports from studies that have randomly assigned patients on the basis of this approach; therefore, it remains to be determined if positive symptom-association criteria are truly meaningful.

The included studies had several drawbacks. First, in the infant studies, 2 of the RCTs had a crossover design,\textsuperscript{27,28} which indicates that PPI- or placebo-treated subjects acted as their own controls. Immediate withdrawal of PPIs may trigger a rebound effect of hypersecretion of gastric acid,\textsuperscript{39,40} thereby influencing study results. However, it could also be argued that the dosing period before outcome measures were recorded was sufficiently long to nullify any of the acute affects caused by acid rebound.

Second, we included 2 infant studies that implemented an open-label phase with a PPI during the study period (1 before\textsuperscript{31} and 1 after\textsuperscript{30} randomization). Despite the fact that the authors of both studies described results of the open-label phase separately, use of a PPI before randomization also could have influenced study outcome. In the study by Winter et al.,\textsuperscript{31} they observed a rapid worsening of symptoms in patients switched from a PPI directly to placebo. Acid rebound seems the likely genesis of this response. Both in the crossover studies\textsuperscript{27,28} and the open-label study\textsuperscript{31} this possible risk of a rebound effect was not discussed.

Third, in 1 of the included study reports a significant decrease in GERD symptoms was described\textsuperscript{29} compared with symptoms of those who were on hydrolyzed formula. Although the study met our inclusion criteria, the methodologic quality was relatively poor. Besides that, the study protocol lacked data with respect to follow-up. Therefore, it remains unclear whether GERD symptoms relapsed over time in the PPI and placebo groups. Another drawback of this study is that infants were included on a reflux questionnaire solely. Questionnaires represent self-reporting behavior and, in this case, the caregivers’ judgment on their infant’s condition. Using a reflux questionnaire for the inclusion of patients without other tools to diagnose GERD is questionable, because this tool may not be of good value in the prediction of severity of GERD.\textsuperscript{41} It is well known that symptoms such as crying and irritability are nonspecific, and the presence of GERD and these symptoms may not always correlate.\textsuperscript{42,43}
Fourth, the included studies that involved children and adolescents, although randomly controlled and of high methodologic quality, were not placebo-controlled, which makes the results difficult to interpret. Four of these were dose-finding studies. As previously mentioned, no differences in efficacy were found between the different dosages of PPIs at the end of the studies. However, symptom resolution was achieved more rapidly in the higher-dosage groups in 2 studies (20 and 40 mg compared with 10 mg and 40 mg compared with 20 mg). In another study that evaluated maintenance therapy, both study groups were treated with a PPI before random assignment during 3 months, which also could have influenced the study results. The studies that used ranitidine and alginates as a control group revealed reduction in GERD symptoms in all studied groups compared with baseline. However, 1 study used 3 different treatment arms and compared the effect of the alginate and PPI alone or in combination. It is interesting to note that this study found a statistically significant difference between the combination arm and single-treatment arms. Finally, in the 3 studies from which histologic alterations and endoscopic scores were described, healing was seen in subjects in all study groups compared with baseline. However, a clear description of the biopsy analysis was lacking, and no data were provided regarding the place and the number of biopsies taken. The use of an international classification of esophagitis would make results easier to interpret. Also, the data described in 2 study reports were not supported by statistical analysis, which makes interpretation difficult. Overall, the role of histology as an outcome measure is under debate. A recent natural history study by Orenstein et al. identified infants with GERD and esophagitis who showed complete or nearly complete symptom resolution without pharmacotherapy, and there was a remarkable finding of no histologic alterations.

A decrease in GERD symptoms was described for the majority of patients in both treatment arms. Because a placebo group was lacking in 58% of the studies, the value of this outcome is questionable. It is well known that resolution of symptoms could be a result of spontaneous symptom resolution over time, the symptoms reported simply not being associated with GERD but being the result of other reasons, or a high placebo effect. It is interesting to note that studies that involved adults with GERD have revealed the effectiveness of PPIs in the decrease of GERD symptoms. Discrepancy between the findings in infants and adults could be a result of the fact that symptoms in adults are more distinct and better expressed than in infants. Because PPIs act solely as acid inhibitors, whereas in milk-fed infants gastric contents are non-acidic during a large part of the day, the poor effect of PPIs in this age group on GERD symptoms might be predicted.

Although GERD symptoms in children and adolescents resemble those in adults, PPIs in these age groups are equally effective compared with their controls (alginates, ranitidine, or different dosages of PPIs). Why these results deviate from those of adult studies might be a result of the lack of placebo-controlled studies and the possibility that young children and their parents are less accurate when reporting symptoms. Furthermore, in adults, esophagitis is more likely to exist than in children and adolescents, possibly because of long-term esophageal acid exposure.
Orenstein et al.\textsuperscript{30} found significantly more serious AEs in the PPI group compared with the placebo group. These differences, however, were judged by the clinicians treating the individual subjects and seemed not to be treatment related. When addressing AEs, as reported for the 2 adolescent studies, we noted a remarkable difference between the reported AEs in both studies (e.g., headache, 35\%\textsuperscript{37} compared with 8\%\textsuperscript{38}). A possible explanation for this difference could be the intraobserver variability of the caregiver when judging an AE as being treatment related. With respect to short-term and long-term use of PPIs, we included studies from which only short-term AEs were reported. In this review, sample sizes were small, and the methodologic quality of the exploration of AEs and TRAEs was sparse and poorly described. We found 1 study for which long-term use of PPIs was described\textsuperscript{17} but it was a retrospective study and, therefore, excluded from our evaluation.

**CONCLUSIONS**

If the primary aim is to treat GERD symptoms in infants, PPIs should not be prescribed. Despite PPIs seeming to be well tolerated in the short-term, there is insufficient evidence to support the effectiveness and safety of PPIs in the treatment of GERD in children and adolescents. Therefore, physicians should be careful when prescribing PPIs, medications that are not approved for infants and have potential adverse effects, unless there is documented disease or with careful monitoring. 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. Furthermore, we recommend more pathophysiological research on symptom genesis to be able to clearly define homogeneous patient groups and to enable the development of a therapy to tackle this growing health care problem.

**ACKNOWLEDGMENTS**

The authors would like to thank Arnold Leenders for all his effort in conducting the search strategy.
Figure 1. Flowchart of search strategy (SR=Systematic Review).

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<thead>
<tr>
<th>Study population</th>
<th>Blinding</th>
<th>Analysis</th>
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<tr>
<td>Was a method of randomization performed?</td>
<td>Was the outcome assessor blinded?</td>
<td>Were point estimates and measures of variability presented for the primary outcome measures?</td>
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<td>Was the allocation of treatment concealed?</td>
<td>Was the care provider blinded?</td>
<td>Did the analysis include an intention-to-treat analysis?</td>
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<td>Were the groups similar at baseline regarding the most important prognostic indicators (age, sex, disease duration, disease severity)?</td>
<td>Was the patient blinded?</td>
<td>Is the withdrawal/drop-out rate &lt;20% and equally distributed?</td>
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<td>Were both inclusion and exclusion criteria specified?</td>
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Table 1. The Delphi list
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<tr>
<th>Author (quality) [REF#]</th>
<th>Setting, participants, diagnosis</th>
<th>Intervention (number of participants, age [mean±SD])</th>
<th>Control intervention (number of participants, age [mean±SD])</th>
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<tbody>
<tr>
<td>Infants</td>
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</table>
| Moore et al. '03 HQ (9)  | Pediatric gastroenterology clinic. Irritable/ crying/ spilling infants (3-12 months) with a reflux index (RI) >5% on pH-monitoring and/or abnormal esophageal endoscopy/histology. | Lansoprazole (Lan)  
(n=52, months: 5.15 ± 2.81)  
< 10 kg: 0.2-0.3 mg/kg/d  
> 10 kg: 1.0-1.5 mg/kg/d | Placebo (P)  
(n=15, NS per group, months: 5.1 ± 2.1) |
| Orenstein et al. '09 HQ (9.5) | General pediatric clinic. Infants (4-51 months) with symptomatic GERD, 3 times i-GERQ-MH screening (score not stated). Crying/ fussing/irritability 1 hour after >25% of feeds. No response to conservative therapy. | Double-blind period:  
Lansoprazole (Lan)  
(n=52, months: 5.15 ± 2.81)  
< 10 wks: 0.2-0.3 mg/kg/d  
> 10 wks: 1.0-1.5 mg/kg/d | Double-blind period:  
Pantoprazole (Pan)  
(n=54, months: 5.04 ± 2.81)  
1.2 mg/kg/d |
| Winter et al. '10 HQ (8) | General pediatric clinic. Post-term infants (≥12 days < 12 months), preterm infants (corrected age: 44 weeks < 12 months) with GSQ-I score >16. Clinical diagnosis of suspected, symptomatic or endoscopic GERD. | Double-blind period:  
Pantoprazole (Pan)  
(n=52, months: 5.15 ± 2.81)  
1.2 mg/kg/d | Double-blind period:  
Pantoprazole (Pan)  
(n=54, months: 5.04 ± 2.81)  
1.2 mg/kg/d |
| Omari et al. '07 HQ (7)  | General pediatric (inpatient) department. Preterm infants (34-40 weeks PMA) with reflux symptoms. Reflux index >5% on pH-monitoring. | Omeprazole (O)  
(n=10, 34-40 wks PMA, 36.1 ± 0.7 wks)  
0.7 mg/kg/d | Placebo (P)  
(n=10, 34-40 wks PMA, 36.1 ± 0.7 wks) |
| Khoshoo et al. '08 HQ (6) | Pediatric gastroenterology clinic. Infants (3-7 months) with a I-GERQ-R scores >16 over a 1-week period. | Lan 15 mg/d (Lan1)  
(n=15, months: 4.8 ± 1.8)  
Lan 2 x 7.5 mg/d (Lan2)  
(n=15, months: 4.3 ± 1.0) | Hydrolyzed formula (HF) |

Table 2. Results of included studies (AI=alginate, AE=adverse event, CPK=creatinine phosphokinase, CSS=composite symptom score score, Eso=esomeprazole, GAS=global assessment score, GASP-Q=gastroesophageal reflux assessment of symptoms in pediatrics questionnaire, I-GERQ-R=infant gastroesophageal reflux questionnaire revised, ISS=individual symptom score, Lan=lansoprazole, NS=not stated, O=omeprazole, Pan=pantoprazole, PGA=physician global assessment, P=placebo, PMA=post-menstrual age, R=ranitidine, SD=standard deviation, TRAE=treatment related adverse event, URI=upper respiratory infection, UTI=urinary tract infection, VA=visual analog, WGSS=weakly GERD symptom scores).
<table>
<thead>
<tr>
<th>Follow-up (loss to follow up%)</th>
<th>Outcome measures</th>
<th>Results</th>
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<td><strong>infant</strong></td>
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| 4 weeks                         | Reduction in RI; | O: \(-8.9 \pm 5.6, P; -19 \pm 20 (p < 0.001)\)  
|                                | change in cry/fuss score; | O: \(191 \pm 120, P; 201 \pm 00 (p=0.4)\)  
|                                | change in visual analog (VA) score of infant irritability. | O: \(5.0 \pm 3.1, P; 5.9 \pm 2.1 (p=0.214)\)  
|                                |                  | Baseline vs period 2 (P&O): baseline; \(6.8 \pm 1.6, period 2; 4.8 \pm 2.9 (p=0.008)\). |
| LFU: 4/34 (6%)                  |                  |         |
| Pre: 1-2 wks                    | Responder status: >50% reduction from baseline in feeding-related crying; | L: 54 %, P: 54 % (not sign.) |
| Double-blind:                   | Changes in GERD symptoms; | L: 20, P: 20 (not sign.) |
| 1-4 wks                         | Improvement of GAS; | GAS: L: 56%, P: 51% (not sign.) |
| Open-label:                     | Reported adverse events (AEs) and treatment related AEs (TRAEs). | AEs: mild/moderate: Lan; 62 %, P: 46 % (p=0.058), most frequent; upper respiratory tract infection; Lan; 22 %, P: 21 %, serious: Lan; 12 %, P: 2 % (p=0.032), most frequent: lower respiratory tract infection, Lan; 12 %, P: 2 %. TRAEs: mild/moderate: Lan; 15%, P: 16% (not sign.) |
| 2-4 wks                         | Withdrawal rate; | Pan; 6, P: 6 (not sign.) |
| Post-treatment: 30 days         | Change in weekly GERD symptom scores (WGSS); | Pan; -2.39±2.47 (p<0.001), Placebo; -2.52±2.7 (p<0.001), no significant changes between groups. AEs: mild/moderate: most common: upper respiratory infection (URI); Pan; 13%, P: 13% (not sign.) TRAEs: NS |
| LFU: 2/162 (1.2%)               | Reported AEs & TRAEs. |         |
| Pre: 2-4 wks                    |                  |         |
| Open-label: 4 wks               | Withdrawal rate; | Pan; 6, P: 6 (not sign.) |
| Double-blind: 4 wks             | Change in weekly GERD symptom scores (WGSS); | Pan; -2.39±2.47 (p<0.001), Placebo; -2.52±2.7 (p<0.001), no significant changes between groups. AEs: mild/moderate: most common: upper respiratory infection (URI); Pan; 13%, P: 13% (not sign.) TRAEs: NS |
| LFU: 0/106 (0%)                 | Reported AEs & TRAEs. |         |
| 2 weeks                         | Change in gastric acidity; | O: \(13.9 \pm 51, P; 53.8 \pm 6.8 (p < 0.0005)\)  
| LFU: not stated                 | Esophageal acid exposure; | O: \(19.0 \pm 4.5, P; 4.9 \pm 3.4 (p < 0.01)\)  
|                                | Acid GER episodes; | O: \(59.6 \pm 26.7, P; 119.4 \pm 20.9 (p < 0.05)\)  
|                                | Change of GER symptom assessment charts. | Symptom assessment score: no significant changes Blood chemistry or complete blood picture (no significant alteration) |
|                                | Blood samples on day 6 and 13. |         |
| 2 weeks                         | Improvement > 30% in I-GERQ-R scores. | Lan: pre; 26.6 ± 2.8, post: 20.6 ± 4.2  
| LFU: 0/ 45 (0%)                 | | Lan2: pre; 26.9 ± 3.7, post: 20.0 ± 3.3  
|                                | | HF: pre; 25.9 ± 3.3, post: 25.8 ± 3.2  
|                                | | HF vs Lan1 or Lan2: p < 0.05 |
### Table 2 (continued). Results of included studies (AI=alginate, AE=adverse event, CPK=creatinine phosphokinase, CSS=composite symptom score, Eso=esomeprazole, GAS=global assessment scores, GASO=gastroesophageal reflux assessment of symptoms in pediatric questionnaire, I=GERQ-R=infant gastroesophageal reflux questionnaire revised, ISS=individual symptom score, Lan=lansoprazole, NS=not stated, O=omeprazole, Pan=pantoprazole, PGA=physician global assessment, P=placebo, PMA=post-menstrual age, R=ranitidine, SD=standard deviation, TRAE=treatment related adverse event, URI=upper respiratory infection, UTI=urinary tract infection, VA=visual analog, WGSS=weakly GERD symptom scores).

<table>
<thead>
<tr>
<th>Author (quality) [REF#]</th>
<th>Setting, participants, diagnosis</th>
<th>Intervention (number of participants, age (mean±SD))</th>
<th>Control intervention (number of participants, age (mean±SD))</th>
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</thead>
<tbody>
<tr>
<td><strong>Children</strong></td>
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<tr>
<td>Tolia et al. '06</td>
<td>General pediatric practice. Children (5-11 yrs). Endoscopic proven GERD with a CSS &gt;16 on the GASP-Q.</td>
<td>Pan 10 mg/d (n=19, yrs: 8.5 ± 1.65)</td>
<td>Pan 20 mg/d (20 mg/d: n=18 yrs: 8.2 ± 1.48; 40 mg/d: n=16 yrs: 7.6 ± 1.89)</td>
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<tr>
<td>HQ (8.5)</td>
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<tr>
<td>Gilger et al. '08</td>
<td>General pediatric practice. Children (1-11 yrs) with endoscopic or histologic confirmed reflux esophagitis.</td>
<td>Esomeprazole (Eso) &lt;20 kg: 5 mg/d &gt;20 kg: 10 mg/d</td>
<td>Eso &lt;20 kg: 10 mg/d &gt;20 kg: 20 mg/d</td>
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<tr>
<td>HQ (7.5)</td>
<td></td>
<td>(n=10, mean: NS)</td>
<td>(&lt;10 mg/d: n=23, mean: NS, 20 mg/d: n=29, mean: NS)</td>
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<tr>
<td>Boccia et al. '07</td>
<td>General pediatric practice. Children (3-170 months) with GERD and reflux esophagitis in endoscopic remission treated with omeprazole (1.4 mg/kg/d) for 3 months.</td>
<td>Omeprazole 50% of starting dose (1.4 mg/kg/d)</td>
<td>Ranitidine (R) 10 mg/kg/d</td>
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<tr>
<td>HQ (7.5)</td>
<td></td>
<td>(n=16, months: 86 ± NS)</td>
<td>No treatment (No)</td>
</tr>
<tr>
<td>Borreli et al. '02</td>
<td>General pediatric practice. Children (1-12 yrs) with GERD symptoms combined with results of pH monitoring and/or moderate esophagitis on endoscopy.</td>
<td>Lan (Lan) 2 x 1.5 mg/kg/d</td>
<td>Alginat (AI) 2 ml/kg/d</td>
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<tr>
<td>LQ (5)</td>
<td>Lan + Al (LanAL)</td>
<td>(Lan; n=10, mean: NS, LanAL: n=12, mean: NS)</td>
<td>(n=10, mean: NS)</td>
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<tr>
<td>Cuccchiara et al. '93</td>
<td>General pediatric practice. Children (6 months-13.4 yrs) with GER esophagitis based on pH-monitoring, endoscopy and histology. Unresponsive to ranitidine (2 x 8 mg/kg/d) and cisapride (3 x 0.8 mg/kg/d).</td>
<td>Omeprazole (O) 40 mg/d/1.73m² body surface area</td>
<td>Ranitidine (R) 20 mg/kg/d</td>
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<tr>
<td>LQ (5.5)</td>
<td>(n=16, mean: NS)</td>
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<td>(n=16, mean: NS)</td>
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<td><strong>Adolescents</strong></td>
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<tr>
<td>Tsou et al. '06</td>
<td>General pediatric practice. Adolescents (12-16 yrs) with a CSS &gt;16 on the GASP-Q, clinical diagnosis of suspected symptomatic or endoscopic proven GERD.</td>
<td>Pan 20 mg/d (n=68, yrs: 13.9 ± 1.37)</td>
<td>Pan 40 mg/d (n=68, yrs: 14.1 ± 1.37)</td>
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<td>HQ (9)</td>
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<tr>
<td>Gold et al. '07</td>
<td>General pediatric practice. Adolescents (12-17 yrs) with clinical diagnosis of GERD based on: medical history, physical examination, pH monitoring and/or endoscopy and biopsy.</td>
<td>Eso 20 mg/d (n=76, mean: NS)</td>
<td>Eso 40 mg/d (n=73, mean: NS)</td>
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<td>HQ (8.5)</td>
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<tr>
<td>Follow-up (loss to follow up(%))</td>
<td>Outcome measures</td>
<td>Results</td>
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<td><strong>Pre: 2 wks Treatment:</strong> 8 wks Post: 2 wks LFU: 1/53 (2%)</td>
<td>Change in GASP-Q in mean CSS; individual symptom score (ISS); physician global assessment (PGA); Reported AEs &amp; TRAEs.</td>
<td>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 &lt; 0.001) All 3 doses: belly pain, difficulty swallowing, nausea, pain after eating (all p &lt;0.001), chest pain (p=0.006) Disease improvement in all 3 doses (p &lt; 0.001) CSS, ISS and PGA: differences in mean score between groups; not sign. AE: NS Mild or moderate TRAEs: most common; 10mg/d: headache (3), 20 mg/d: Abdominal pain (1), increased appetite (1), 40mg/d: headache (1). Differences between groups; not sign.</td>
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<td><strong>8 weeks LFU: 0/109</strong></td>
<td>Reported AEs &amp; TRAEs; Change in symptoms by PGA Assessment by parents.</td>
<td>AE: n=82 TRAEs: most common; diarrhea (3), headache (2), somnolence (2) Differences between groups; not sign. PGA vs baseline: p &lt; 0.005 (all groups) Parents scores vs baseline: p &lt; 0.01 (all groups) sign differences between groups: NS</td>
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<td>Open label: 3 months Double-blind: 6 months Follow-up: 33 months LFU: 2/48 (4%)</td>
<td>Change in endoscopic healing and symptom score (daily dairy parents and at each clinical visit).</td>
<td>No statistically significant difference between groups. Significant reduction in histological (p=0.02), endoscopic (p=0.01), and symptomatic scores (p=0.004) in all study groups compared to baseline.</td>
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<tr>
<td><strong>8 weeks LFU: 4/36 (11%)</strong></td>
<td>Change in clinical symptom scores; Reduction in esophageal acid exposure time; Intra-gastric acidity; Endoscopic healing;</td>
<td>AI: 4.2 ± 0.9, Lan: 4.3 ± 1.2, LanAI: 3.0 ± 1.1 LanAI vs AI and Lan: p &lt; 0.05, AI/Lan/LanAI vs baseline: p &lt; 0.01 AI: 6.1 ± 1.9, Lan: 5.5 ± 1.5, LanAI: 3.8 ± 0.7 LanAI vs AI and Lan: p &lt; 0.05, AI/Lan/LanAI vs baseline: p &lt; 0.01. AI 2.5± 0.6, Lan: 3.9 ± 0.3, LanAI 4.2 ± 0.8. Lan and LanAI vs baseline: p &lt; 0.01, AI vs baseline: p=0.08. all groups (significance NS).</td>
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<td><strong>8 weeks LFU: 2/32 (6%)</strong></td>
<td>Reduction in median gastric pH; Change in symptom score; Change in esophagitis score (by endoscopy + histology);</td>
<td>O: 60.1 (9.3-81), R: 37.4 (0-56.7) (p &lt; 0.05) O: 9.0 (0-18), p=0.01; R: 9.0 (6-12) (p &lt; 0.001) sign difference between groups: NS</td>
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<tr>
<td><strong>Adolescents</strong></td>
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<tr>
<td><strong>8 weeks LFU: 6/136 (4%)</strong></td>
<td>Change in GASP-Q in mean CSS; Reported AEs &amp; TRAEs;</td>
<td>CSS: 20 mg/d: 177.7 vs 67.2 (p &lt; 0.001), 40 mg/d:174.1 vs 58.2 (p &lt; 0.001) No significant changes between study groups AE: NS (no serious AE) TRAEs (mild/moderate); 20 mg/d: 59 (87%), 40 mg/d: 53 (78%). Most common: headache (35%), infection (23%), pharyngitis (19%). No significant differences between groups.</td>
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<tr>
<td>Reported AEs &amp; TRAEs; Reduction of GERD symptoms by PGA;</td>
<td>AE: 113 TRAEs: 14.9% of patients, most common: headache (8%), abdominal pain (3%), diarrhea (2%). No significant differences between groups. PGA: No significant changes between groups. Symptoms significantly reduced compared to baseline (p &lt; 0.0001).</td>
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</tbody>
</table>
REFERENCES


Chapter 8

Contributors’ statement

Marije Smits and Rachel van der Pol: conceptualized and designed the study, scored all abstracts and full text articles, drafted the initial manuscript, and approved the final manuscript as published. RvP and MS contributed equally to the manuscript.

Michiel van Wijk, Taher Omari and Merit Tabbers: reviewed and revised the manuscript, and approved the final manuscript as submitted.

Marc Benninga: was deciding rater of full text articles for systematic review, senior author, reviewed and revised the manuscript, and approved the final manuscript as submitted.