4.1. Uitgangsvraag 2 – Niet-farmacologische therapie

4.1.1. – 4.1.3 Voedingsinterventies

Quality assessment						Summary of findings				Importance
						No of patients				
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Thickened feeds	Standard formula	Effect	Quality	
I-GERQ-R questionnaire (total score 0-42)										
1	RCT; parallel	Serious [1]	N/A	Not serious	Very serious [2]	25	25	Median symptom score, range (intervention vs control group): Baseline: 13 (8-19) vs 13 (7-19) Wk 4: 10 (5-16) vs 12 (7-14) Wk 8: 5 (0-15) vs 8 (2-14) Median I-GERQ-R scores significantly lower in intervention (p<0.038) and control (p<0.03) group at week 8 compared to baseline. No comparison between groups at week 8. Median I-GERQ-R scores more significantly reduced in intervention group vs control group (p<0.001).[3] (1)	Very low	Critical
Crying/distress (various definitions)										
2	RCT; parallel	Serious [1]	Serious [4]	Serious [5]	Serious [6]	225	199	1. Infants in intervention group are significantly more likely to be in good mood at day 14 (p=0.007) and day 34 vs day 0 (p=0.044) (parent-reported) compared to control group. No significant difference in sudden fits of crying (p=0.055) nor crying episodes >30min (p=0.092) at day 14 vs day 0 between both groups.[7] (2) 2. Crying (number of children, intervention vs control group) Baseline: 4/41 vs 5/40 Wk 4: 1/41 vs 3/40 Wk 8: 1/41 vs 2/40 At wk 8: RR = 0.49 (95% CI 0.05-5.17)	Very low	Critical

								Irritability (number of children, intervention vs control group) Baseline: 12/41 vs 12/40 Wk 4: 4/41 vs 10/40 Wk 8: 1/41 vs 8/40 At wk 8: RR = 0.12 (0.02-0.93)[8] (3) 3. No difference in sleeping disturbance. No data.[9] (4) 4. Significant decrease in feedings followed by trouble sleeping (p=0.030). No differences in fussiness. No data.[10] (5)		
Visible regurgitation/vomiting: episodes of regurgitation per day										
3	RCT; parallel	Serious [1, 11]	Serious [12]	Not serious [13]	Serious [6]	145	145	Pooled estimated effect end of study periods (4 weeks): MD: -1.18 (95% CI -1.69 - -0.66) FEM: I^2 = 85%, p = 0.002 (2, 6, 7)	Very low	Critical
1	RCT; cross-over[14]	Serious [1]	N/A	Not serious	Serious [6]	27	27	Intervention vs control mean ± SD during treatment with both formulas (1wk) HL-350 vs standard (n=13): 12.9 ± 3.5 vs 22.6 ± 3.9 HL-450 vs standard (n=14): 12.8 ± 3.0 vs 29.8 ± 3.6# (8)	Low	Critical
Visible regurgitation/vomiting: episodes of vomiting per day										
2	RCT; parallel	Serious [1, 11]	Not serious	Not serious	Serious [6]	79	77	Pooled estimated effect end of study periods (4 weeks): MD: -0.93 (-1.31 - -0.55) FEM: I^2 = 55%, p =0.13 (6, 7)	Low	Critical
Visible regurgitation/vomiting: episodes of regurgitation per day (change at 1 and 5 weeks)										
1	RCT; parallel	Serious [1,15]	N/A	Not serious	Serious [6]	55	49	Regurgitation frequency per day, intervention vs control group: Baseline: 13 ± 1 vs 11 ± 1 Change from baseline at 1 week: -6 ± 1 vs -6 ± 1 Change from baseline at 5 weeks: -7 ± 1 vs -5 ± 1[15] (5)	Low	Critical
Visible regurgitation/vomiting: frequency of regurgitation per day (median, IQR)										
2	RCT; cross-over[14]	Serious [1]	Not serious	Not serious	Serious [6]	47	47	Intervention vs control, median (IQR) during treatment (1wk): HL-450 vs standard (n=16): 1.6 (IQR 0.8 - 2.0) vs 3.5 (IQR 2.3 - 4.9)# (9) HL-350 vs standard (n=31): 1.3 (IQR 0.6 - 2.3) vs 2.9 (IQR 2.0 - 3.2)# (9) 2.3 (IQR 1.6 - 3.6) vs 5.2 (IQR 3.7 - 7.8)# (10)	Low	Critical
Visible regurgitation/vomiting: percentage of feeds with regurgitation										
1	RCT; parallel	Serious [1]	N/A	Not serious [13]	Serious [6]	66	67	Intervention vs control, % of feeds associated with regurgitation: Baseline = 50.9 ± 28.9 vs 48.6 ± 28.5 Day 7 = 31.0 ± 22.4 vs 48.3 ± 38.7	Low	Critical

Appendix 5 – Evidence tabellen

								Day 28 = 28.8 ± 31.1 vs 36.0 ± 34.1, p = 0.015[*,16] MD day 7: -17.30 (95% CI -26.78 - -7.82) MD day 28: -7.20 (95% CI -18.30 - 3.90) (2)		
Visible regurgitation/vomiting: percentage of feeds with regurgitation (change at 1 week)										
1	RCT; parallel	Serious [1]	N/A	Not serious	Serious [6]	55	49	% of feeds with regurgitation, intervention vs control group: Baseline: 87 ± 2 vs 85 ± 2 Change from baseline at 1 week: -34 ± 5 vs -22 ± 5 Change from baseline at 5 weeks: -38 ± 5 vs -24 ± 5[15] (5)		Critical
Visible regurgitation/vomiting: number of infants with regurgitation (1 week and 4 weeks)										
1	RCT; parallel	Serious [1]	N/A	Not serious [13]	Serious [6]	66	67	RR at 1 week: 0.99 (95%CI 0.96 – 1.02) RR at 4 weeks: 0.88 (95%CI 0.78 – 0.99) (2)	Low	Critical
Visible regurgitation/vomiting: number of infants with regurgitation and/or vomiting (4 week and 8 weeks)										
1	RCT; parallel	Serious [1]	N/A	Not serious	Very serious [2]	25	25	RR at 4 weeks = not estimable (25/25 vs 17/17) RR at 8 weeks: 0.17 (95% CI 0.03 – 0.94) (1)	Very low	Critical
Visible regurgitation/vomiting: grade of severity of regurgitations (symptom score, 0-6, 6=most severe)[17]										
1	RCT; parallel	Serious [18]	N/A	Serious [18]	Serious [6]	10	10	Regurgitation severity score, intervention vs control group, mean +/- SD: Before: 4.60 ± 0.84 vs 4.40 ± 0.84 During (1wk): 2.20 ± 1.92 vs 3.30 ± 1.16 MD: -1.10 (95%CI -2.49 – 0.29) (11)	Low	Critical
Visible regurgitation/vomiting: episodes of emesis over 90 mins time-period										
1	RCT; cross-over	Serious [20]	N/A	Serious [21]	Serious [6]	10	10	Episodes in 90 minutes, mean (SD), intervention vs control group: 1.2 ± 0.7 vs 3.9 ± 0.9 (p=0.015)[*] (12)	Low	Critical
Side effects: diarrhea, aspect of stools (diary-based)										
2	*RCT; parallel*	*Serious [1]*	*Serious [4]*	*Very serious [22]*	*Serious [6]*	*106*	*101*	*No data provided.* (4, 5)	*Very low*	*Critical*
Side effects: diarrhea, occurrence of diarrhea (number of patients, parent-reported/diary-based)										
3	RCT; parallel	Serious [1]	Serious [23]	Serious [24]	Serious [6]	16/113	4/116	RR = 3.44 (95%CI 0.04 – 318.38) REM, I^2 = 87%, p = 0.005[25, 26](3, 13, 14)	Very low	Critical
1	RCT; cross-over	Serious [1]	N/A	Not serious	Serious [6]	3/27	0/27	RR = 7.00 (95%CI 0.38 – 129.34)[#] (8)	Low	Critical

Appendix 5 – Evidence tabellen

Side effects: diarrhea, number of stools per day (parent-reported/diary-based)										
1	RCT; parallel	Serious [17]	N/A	Not serious	Serious [6]	51	45	Mean ± SD, intervention vs control group: Baseline: 3.80 ± 2.34 vs 2.62 ± 0.77, (p=0.05) 4 wk: 3.54 ± 2.03 vs 2.60 ± 0.81, (p=0.08) MD = 0.94 (95% CI 0.33 – 1.55) MD_{change} = -0.24 (95% CI -2.06 – 1.58) (7)	Low	Critical
Side effects: diarrhea, number of stools per day (parent-reported/diary-based; median, IQR)										
1	RCT; cross-over[14]	Serious [1]	Not serious	Not serious	Serious [6]	47	47	Intervention vs control group, median (IQR) during treatment (1wk): HL-450 vs control group: 1.4 (1.0-1.5) vs 1.4 (1.1-1.6), (p 0.48)* HL-350 vs control group: 1.8 (1.2 to 2.4) vs 1.2 (0.9 to 1.6), (p<0.01)*# (10) 1.4 (0.8-1.6) vs 1.6 (1.1-2.3), (p=0.02)*,#,27 (9)	Low	Critical
Side effects: SAE's (number of events)										
3	RCT; parallel	Serious [1]	Not serious [28]	Not serious [29]	Serious [6]	6/169	3/164	RR= 1.92 (95% CI 0.50 – 7.40)[30] FEM, I^2 = 56%, p = 0.13 (1, 2, 5)	Low	Critical
Side effects: discontinuation rates due to intolerability[31]										
5	RCT; parallel	Serious [1]	Not serious [32]	Not serious [33]	Serious [6]	49/308	35/300	RR = 1.37 (95% CI 0.93 – 2.03)[34] FEM, I^2 = 63%, p = 0.05 (2, 5, 7, 13, 14)	Low	Critical
1	RCT; cross-over	Serious [1]	N/A	Not serious	Serious [6]	3/27	0/27	RR = 7.00 (95% CI 0.38 – 129.34)# (9)	Low	Critical

* As reported by authors, #It is unclear how these studies are linked. Numbers in each arm differ.

RCT = randomized controlled trial; SD = standard deviation; MD = mean difference at end of study period; MD_{change} = MD in change from baseline to end of study period; RR = relative risk; 95% CI = 95% confidence interval; NS = not significant; N/A = not applicable; FEM = fixed effects model; REM = random effects model; SAE = serious adverse event.

1. Allocation concealment and/or randomization process unclear. Not clear if personnel and participants were blinded. High loss to follow up due to discontinuation. High chance of bias due to selective reporting.
2. Limited number of patients and events.
3. No sub-scores on different domains of I-GERQ-R questionnaire provided.
4. Results are not uniformly pointing in the same direction across studies (i.e. neutral, positive or negative result of intervention)
5. *Intervention*: One study recorded symptoms for 3 days at baseline and for 7 days during study period. This may mask a natural decrease in symptoms with time. Interventions not directly comparable due to differences in treatment regimen. One study compared soy formula with soy fiber with standard formula (not soy-based), thereby assessing two interventions. *Comparison*: In one study the control group received 25% thickened formula. *Outcome*: Heterogeneity between definitions of outcome measures between studies. In none of the studies a further specification or cut-off for definition of the outcome measures has been provided.
6. Limited number of patients and events.
7. Parent reported on 5-point frequency scale, reported after 7 days with intervention. No absolute numbers provided.

8. Clinical parameters recorded by parents, no further specification when a parameter was considered positive in an infant. Parameters expressed as means. Authors report a significant decrease in the whole set of clinical regurgitation symptoms in the intervention group, significance of individual items not reported, no p-value provided.
9. Only baseline data provided, no further data provided. Not clear at what time-points analysis was performed.
10. Only baseline data provided, no further data provided. Unclear what presented figures represent.
11. In the study of Moukarzel et al, 14 infants were excluded from the study after being randomized (n=6 normal milk, n=8 thickened milk) because they needed medical therapy for GERD due to symptom development.
12. Heterogeneity between studies, however results pointing into same direction and confidence intervals are overlapping. Therefore we decided not to downgrade for inconsistency.
13. *Intervention:* Study compared soy formula with soy fiber with standard formula (not soy-based), thereby assessing two interventions. We decided not to downgrade for this.
14. Study in a cross-over setting, no interim analysis at cross-over point. Therefore results cannot be pooled with data from the parallel studies.
15. Children assessed at 1 week and some given further treatment. Results as reported in study, no mean data provided at week 1 and week 5.
16. Children assessed at 1 week and some given further treatment. At day 7, n=87 patients in intervention and n=85 patients in control group included for analysis. At day 28, n=66 patients in intervention and n=67 patients in control group included for analysis.
17. Symptom score based on both the frequency and volume of regurgitation.
18. Randomization and allocation concealment process unclear.
19. Not clear at what time point the 'before' treatment scores were assessed. Prospective diary of 3 (2-4) days, not clear at what days of the intervention this diary was taken.
20. Allocation concealment and/or randomization process unclear. Not clear if personnel and participants were blinded.
21. *Patients:* No information on patient characteristics provided. *Intervention:* Only a single feed for each arm.
22. *Outcome:* Visible emesis during pH-metry. Scintigraphy performed as well, methods of monitoring invasive. *Patients*: In one study infants with excessive crying, when not present at baseline, were excluded. *Intervention:* One study compared soy formula with soy fiber with standard formula (not soy-based), thereby assessing two interventions. *Comparison:* In one study the control group received 25% thickened formula. In one study the control group received positioning therapy.
23. Results are not uniformly pointing in the same direction across studies , and I^2 = 56%. However, 95CI% intervals are overlapping. We therefore decided to downgrade the level of evidence with one step.
24. *Comparison:* The control group received positioning therapy. We hypothesized that this would not influence the outcome of diarrhoea and therefore decided not to downgrade the level of evidence.
25. In one study not clear in what study arm diarrhoea occurred (Chao, 2007[a]), so calculations based on n=3 studies.
26. Random effects model used to better take into account the sources of error in the estimation of the distribution of effects.
27. No baseline data provided.
28. Results are not uniformly pointing in the same direction across studies , however 95% confidence intervals are overlapping and I^2 = 56%. Therefore we decided not to downgrade for inconsistency.
29. *Intervention:* One study compared soy formula with soy fiber with standard formula (not soy-based), thereby assessing two interventions. We hypothesized that this would not influence the occurrence of SAEs and therefore chose not to downgrade the level of evidence.
30. In one study (Ummarino, 2015) there were no SAEs in the intervention nor in the control group. This study was therefore not used in the relative risk calculation.
31. We chose to define discontinuation due to intolerability as: development of diarrhea, serious enteritis or (upper) airway infection.
32. Results are not uniformly pointing in the same direction across studies , however study deviating the most from others is the study with lowest weight, furthermore 95% confidence intervals are overlapping and I^2 = 59%. Therefore we decided not to downgrade for inconsistency.
33. *Intervention:* One study compared soy formula with soy fiber with standard formula (not soy-based), thereby assessing two interventions. *Comparison:* The control group received positioning therapy. We hypothesized that these factors would not influence the discontinuation rates and therefore decided not to downgrade the level of evidence.
34. One study (Chao, 2007[a]) did not specify discontinuation rates to treatment or intervention group. This study was therefore not included in the analysis.

Appendix 5 – Evidence tabellen

4.1.4. Houdingsadviezen

Quality assessment						Summary of findings[1]				Importance
						No of patients				
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Positioning therapy (LLP)	Control group (HE)	Effect	Quality	
Crying (total crying time, min)										
1	RCT; parallel	Serious[2]	N/A	Very serious[3]	Very serious[4]	12	14	Mean ± SD[5], intervention vs control group: Baseline: 92 ± 34.6 vs 71 ± 41.2 2 wk: 92 ± 34.6 vs 81 ± 37.4 MD = 11.00 (95% CI -16.7 – 38.70) MD_{change} = -10.00 (95% CI -32.34 – 12.34)	Very low	Critical
Crying (number of cries)										
1	RCT; parallel	Serious[2]	N/A	Very serious[3]	Very serious[4]	12	14	Mean ± SD[5], intervention vs control group: Baseline: 48 ± 31.2 vs 30 ± 26.2 2 wk: 48 ± 27.7 vs 49 ± 26.2 MD = -1.00 (95% CI -21.83 – 19.83) MD_{change} = -12.00 (95% CI -33.90 – 9.90)	Very low	Critical
Side effects (SAEs, number of events)										
1	RCT; parallel	Serious[2]	N/A	Very serious[3]	Very serious[4]	0/12	2/14	RR = 0.23 (95% CI 0.01 – 4.38)[6]	Very low	Critical

RCT = randomized controlled trial; LLP = left lateral position; HE = head elevation; SD = standard deviation; MD = mean difference end of study period; MD_{change} = MD in change from baseline to end of study period; RR = relative risk; 95% CI = 95% confidence interval; N/A = not applicable.

1. Study in infants treated with esomeprazole.
2. Allocation concealment process unclear. No blinding for outcome, blinding for intervention not clear. High loss to follow up due to discontinuation. High chance of bias due to selective reporting.
3. *Population:* all infants were treated with a proton pump inhibitor during study time
   Comparison: all infants in the control group were positioned with the head of cot in 20 degrees elevation
   Outcome: duration of study limited to two weeks.
4. Limited number of patients and events.
5. Standard deviations, mean differences and mean differences in change calculated manually from standard error of mean and number of study subjects.
6. None of the adverse events were considered to be treatment-related by the treating physicians, i.e. one patient admitted to the hospital with reduced oral intake and weight loss and one patient with rotavirus infection.

Appendix 5 – Evidence tabellen

Quality assessment						Summary of findings[1]				
						No of patients				
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Positioning therapy (LLP)	Control group (HE)	Effect	Quality	Importance
Crying (total crying time, min)										
1	RCT; parallel	Serious [2]	N/A	Very serious [3]	Very serious [4]	13	12	Mean ± SD[4,] intervention vs control group: Baseline: 106 ± 68.5 vs 74 ±69.3 2 wk: 88 ± 36.1 vs 66 ± 45.0 MD = 22.00 (95% CI -10.15 – 54.15) MD_{change} = -9.00 (95% CI -52.51 – 34.51)	Very low	Critical
Crying (number of cries)										
1	RCT; parallel	Serious [2]	N/A	Very serious [3]	Very serious [4]	13	12	Mean ± SD[5,] intervention vs control group: Baseline: 60 ± 43.3 vs 38 ± 34.6 2 wk: 54 ± 32.5 vs 35 ± 24.2 MD = 19.00 (95% CI -3.35 – 41.35) MD_{change} = -2.00 (95% CI -34.14 – 30.14)	Very low	Critical
Side effects (SAEs)										
1	RCT; parallel	Serious [2]	N/A	Very serious [3]	Very serious [4]	0/13	0/12	RR = not estimable.[6]	Very low	Critical

RCT = randomized controlled trial; LLP = left lateral position; HE = head elevation; SD = standard deviation; MD = mean difference end of study period; MD_{change} = MD in change from baseline to end of study period; RR = relative risk; 95% CI = 95% confidence interval; N/A = not applicable.

1. Results in infants treated with Mylanta, antacid containing the following active agents per 5ml: 200mg aluminium hydroxide, 200mg magnesium hydroxide and 20 mg simethicone.
2. Allocation concealment process unclear. No blinding for outcome, blinding for intervention not clear. High loss to follow up due to discontinuation. High chance of bias due to selective reporting.
3. *Population:* all infants were treated with an antacid during study time
   Comparison: all infants in the control group were positioned with the head of cot in 20 degrees elevation
   Outcome: duration of study limited to two weeks.
4. Limited number of patients and events.
5. Standard deviations calculated manually from standard error of mean and number of study subjects.
6. Relative risk not estimable due to n=0 events in both of the treatment arms.

Appendix 5 – Evidence tabellen

4.1.4. Leefstijladviezen

Quality assessment						Summary of findings				Importance
						No of patients				
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Massage therapy	Non-massage therapy	Effect	Quality	
I-GERQ-R questionnaire (total score 0-42)										
1	RCT; parallel	Not serious	N/A	Serious [2]	Very serious [1]	18	18	Mean scores ± SD; intervention vs control Baseline: 22.0 ± 4 vs 23.5 ± 4 Wk 4: 15.0 ± 4 vs 15.1 ± 5 Wk 6: 14.4 ± 4 vs 13.7 ± 6 MD = 0.70 (95%CI -2.63 – 4.03)[3]	Very low	Critical
Crying time (categorized, number of infants crying <10min, 10min-1h, 1h-3h and >3h)										
1	RCT; parallel	Not serious	N/A	Serious [2]	Very serious [1]	18	18	Crying > 3 h: RR = 1.00 (95%CI 0.07 – 14.79)[4]	Very low	Critical
Distress (cortisol levels, µg/dl)										
1	RCT; parallel	Not serious	N/A	Serious [2]	Very serious [1]	18	18	Geometric mean 60% lower in intervention compared to control group after 6 weeks of treatment, adjusting for baseline (p=0.003).[5] Hodges-Lehmann point estimate of between group difference (AUC): 18µgr.hr/dl (95% CI -44 to 9µgr.hr/dl, p=0.11).[6]	Very low	Critical

RCT = randomized controlled trial; SD = standard deviation; MD = mean difference end of study period; RR = relative risk; 95% CI = 95% confidence interval; N/A = not applicable; AUC = area under the curve.

1. Limited number of patients and events.
2. *Population:* 91% of infants included in the study used some kind of proton pump inhibitor during study time.
   Comparison: Control group received sham therapy (non-massage treatment), similar to rocking and touching and holding mothers typically perform.
   Outcome: Surrogate outcome measure for distress used: cortisol levels in saliva at baseline, 4 weeks and 6 weeks.
3. Mean difference in change not calculable from provided data.
4. Data on crying time categorized into <10min, 10min-1h, 1h-3h and >3h. For clinical relevance, we provided calculations on RR for the category >3h of daily crying.
5. No absolute numbers provided at baseline.
6. Hodges-Lehman estimator to assess between-group difference in post-intervention AUC change of daily cortisol. This finding suggests that that the massage group had a greater decrease in cortisol than the non-massage group after 6 weeks of therapy.

4.2. Uitgangsvraag 4 – Farmacologische therapie

A – Antacida en alginaten

Quality assessment						Summary of findings				
						No of patients				
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Antacid	Placebo / Feed intervention	Effect	Quality	Importance
ALGINATES VS PLACEBO or NO TREATMENT*										
I-GERQ-R questionnaire (total score 0-42, 42 = most severe, ≥16 suggestive for GERD)										
1	RCT; parallel	Serious [1]	N/A	Not serious[2]	Very serious [3]	24	17	Median symptom score, range (intervention vs control group): Baseline: 15 (8-24) vs 13 (7-19) Wk 4: 7 (1-20) vs 12 (7-14) Wk 8: 1 (0-19) vs 8 (2-14) Median I-GERQ-R scores significantly lower in intervention ($p<0.002$) and control ($p<0.03$) group at week 8 compared to baseline. No comparison between groups at week 8. Median I-GERQ-R scores more significantly reduced in intervention group vs control group ($p<0.0001$) at week 8.[4] (1)	Very low	Critical
Visible regurgitation/vomiting: number of infants with regurgitation and/or vomiting (4 week and 8 weeks)										
1	RCT; parallel	Serious [1]	N/A	Not serious	Very serious [2]	25	25	RR at 4 weeks: 0.14 (95%CI 0.01 – 2.71) RR at 8 weeks: 0.04 (95% CI 0.01 – 0.25) (1)*	Very low	Critical

Appendix 5 – Evidence tabellen

Visible regurgitation/vomiting: number of vomiting/regurgitation episodes in previous 24 hours										
1	RCT; parallel	Serious [1]	N/A	Not serious[2]	Very serious [3]	42	46	Median number of episodes, range (intervention vs control group): Baseline: 8.5 (2-50) vs 7.0 (2-36) Wk 2: 3.0 (0-22) vs 5.0 (0-37), p = 0.009 (15)	Low	Critical
Visible regurgitation/vomiting: mean frequency of vomiting/regurgitation episodes after 14 days										
1	RCT; parallel	Serious [1]	N/A	Not serious[2]	Very serious [3]	42	46	Mean number of episodes, SD not reported (intervention vs control group) Baseline: 10.2 vs 10.2 Wk 2: 4.5 vs 6.2, p = 0.056 (15)	Low	Critical
Side-effects: AEs (number of infants experiencing ≥1 AE)										
2	RCT; parallel	Serious [1]	None	Not serious[2]	Serious [3]	24/66	27/63	RR : 1.30 (95%CI 0.87 – 1.93) (1, 15)[a,b]* FEM, I^2 = 0%, p=0.74.	Low	Critical
Side-effects: SAEs (number of infants experiencing ≥1 SAE)										
2	RCT; parallel	Serious [1]	N/A	Not serious[2]	Serious [3]	2/66	2/63	RR : 1.10 (95%CI 0.16 – 7.43)[5] (1, 15)*	Low	Critical
Side-effects: withdrawal of study due to AEs										
1	RCT; parallel	Serious [1]	N/A	Not serious[2]	Very serious [3]	4/42	7/46	RR : 0.63 (95%CI 0.20 – 1.99) (15)	Low	Critical

RCT = randomized controlled trial; H2RA = H2 receptor antagonist; SD = standard deviation; MD = mean difference end of study period; RR = relative risk; FEM = fixed effects model; 95% CI = 95% confidence interval; N/A = not applicable, NR = not reported in study, NS = not significant, AE = adverse event, SAE = severe AE.
*There was no placebo administered to the control group in the study of Ummarino, 2015. Both groups received conservative therapy.

a. Reported events were: functional diarrhea, teething syndrome, emesis, constipation, colic, nasopharyngitis, pyrexia.
b. One patient treated with Mg alginate plus simethicone presented with constipation.
1. Allocation concealment and/or randomization process unclear. Not clear if personnel and participants were blinded. High loss to follow up due to discontinuation. High chance of bias due to selective reporting.
2. *Patients:* Study in infants only
3. Limited number of patients and events.
4. No sub-scores on different domains of I-GERQ-R questionnaire provided.
5. In one study no events in both treatment arms, therefore RR not estimable (Ummarino, 2015).

Appendix 5 – Evidence tabellen

Quality assessment						Summary of findings				Importance
						No of patients				
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Antacid	Placebo / Feed intervention	Effect	Quality	
ALGINATES VS FEED INTERVENTION										
I-GERQ-R questionnaire (total score 0-42, 42 = most severe, ≥16 suggestive for GERD)										
1	RCT; parallel	Serious[1]	N/A	Not serious[2]	Very serious[3]	24	23	Median symptom score (antacid vs feed intervention): Baseline: 15 (8-24) vs 13 (8-19) Wk 4: 7 (1-20) vs 10 (5-16) Wk 8: 1 (0-19) vs 5 (0-15) Median I-GERQ-R scores significantly lower in antacid intervention (p<0.002) and feed intervention (p<0.038) group at week 8 compared to baseline. No comparison between groups at week 8. Median I-GERQ-R scores more significantly reduced in intervention group vs control group (p<0.002) at week 8.[4] (1)	Very low	Critical
Visible regurgitation/vomiting: number of infants with regurgitation and/or vomiting (4 week and 8 weeks)										
1	RCT; parallel	Serious[1]	N/A	Not serious	Very serious[2]	25	25	RR at 4 weeks: 0.09 (95%CI 0.00 – 1.84) RR at 8 weeks: 0.26 (95% CI 0.26 – 0.88) (1)	Very low	Critical
Side-effects: AEs (number of infants experiencing ≥1 AE)										
1	RCT; parallel	Serious[1]	N/A	Not serious[2]	Very serious[3]	1/24	0/23	RR : 2.88 (95%CI 0.12 – 67.29) (1)	Very low	Critical

Appendix 5 – Evidence tabellen

Side-effects: SAEs (number of infants experiencing ≥1 SAE)										
1	RCT; parallel	Serious[1]	N/A	Not serious[2]	Very serious[3]	0/24	0/23	RR not estimable.[5] (1)	Very low	Critical

RCT = randomized controlled trial; H2RA = H2 receptor antagonist; SD = standard deviation; MD = mean difference end of study period; RR = relative risk; FEM = fixed effects model; 95% CI = 95% confidence interval; N/A = not applicable, NR = not reported in study, NS = not significant, AE = adverse event, SAE = severe AE.

a. Reported events were: functional diarrhea, teething syndrome, emesis, constipation, colic, nasopharyngitis, pyrexia.
b. One patient treated with Mg alginate plussimethicone presented with constipation

1. Allocation concealment and/or randomization process unclear. Not clear if personnel and participants were blinded. High loss to follow up due to discontinuation. High chance of bias due to selective reporting.
2. *Patients:* Study in infants only
3. Limited number of patients and events.
4. No sub-scores on different domains of I-GERQ-R questionnaire provided.
5. In one study no events in both treatment arms, therefore RR not estimable (Ummarino, 2015).

Appendix 5 – Evidence tabellen

B - Zuurremmers

Quality assessment						Summary of findings				
						No of patients				
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	PPI	Placebo	Effect	Quality	Importance
PPI vs PLACEBO										
I-GERQ-R questionnaire (total score 0-42, 42 = most severe, ≥16 suggestive for GERD)										
1	RCT; parallel	Serious[1]	N/A	Serious[2]	Serious[3]	Rabeprazole; 178[4]	90	NR; NS[5] (16)	Very low	Critical
Crying/distress (crying time, minutes of crying per day)										
2	RCT; parallel and cross-over[6]	Serious[7, 8]	No	Serious[9, 10]	Serious[3]	Lansporazole; 81, Omeprazole; 15	96	Mean ± SD, intervention vs control group: Baseline: 47.0 ± 37.30 vs 55.4 ± 46.11 4 weeks: 22.1 ± 29.96 vs 27.6 ± 36.57 MD_{change}: 2.80 (95% CI -8.58 - 14.18) (17) Baseline: 246 ± 105 vs 287 ± 132 2 weeks: 203 ± 113 vs 204 ± 87 MD: -1.00 (95%CI -73.17 – 71.17) (18)[11] Pooled estimated effect end of study periods:[12] MD: -5.50 (95%CI -15.80 - 4.80)	Very low	Critical
Crying/distress (% of feeds)										

Appendix 5 – Evidence tabellen

1	RCT; parallel	Serious[7]	N/A	No[9]	Serious [3]	Lansoprazole; 81	81	Mean ± SD, intervention vs control group: Baseline: 51.0 ± 20.39 vs 52.4 ± 20.46 4 wk: 31.0 ± 25.41 vs 32.4 ± 28.13 Mean difference at 4 weeks: MD: -1.40 (95% CI -9.66 - 6.86) MD_{change}: 0.00 (95%CI -7.23 - 7.23) (17)	Low	Critical
Crying/distress (number of cries per day)[13]										
1	RCT-parallel	Serious[14]	N/A	No[15]	Serious [3]	Esomeprazol; 25	26	Mean ± SD, intervention vs control group: Baseline: 88.87 ± 24.71 vs 89.46 ± 22.71 2 wk: 88.83 ± 19.84 vs 88.85 ± 20.18 Mean difference at 2 weeks: MD: -0.02 (95%CI -11.00 - 10.96) MD_{change}: 0.56 (95%CI -10.53 - 11.65) (19)	q	Critical
Crying/distress (Visual Analogue Scale by parents of infants irritability, total score 0-10, 10 = most severe)										
1	RCT; cross-over[8]	Serious[8]	N/A	Serious[10]	Very serious [3]	Omeprazole; 15	15	Mean ± SD, intervention vs control group Baseline: 7.1 ± 1.4 vs 6.6 ± 1.7 2 weeks: 5.9 ± 2.6 vs 6.0 ± 2.1 Mean difference at 2 weeks: MD: -0.10 (95%CI -1.79 – 1.59) (18)	Very low	Critical
Crying/distress (crying <1h after a feed, number of cries)										

1	RCT; parallel	Serious[16]	N/A	Serious[17]	Serious [3]	Pantoprazole; 54	52	Mean ± SD, change from base line vs wk 4, intervention vs control group: -0.39 ± 0.58 (p<0.001 vs baseline) vs -0.55 ± 0.55 (p<0.001 vs baseline. Mean ± SD, change from base line vs wk 8 intervention vs control group: -0.49 ± 0.57 (p<0.001 vs baseline) vs -0.64 ± 0.72 (p<0.001 vs baseline) Change in mean difference at 4 weeks: MD_{change} : 0.16 (95%CI -0.06 – 0.38) Change in mean difference at 8 weeks: MD_{change} : 0.15 (95%CI -0.10 – 0.40) (20)[18]	Very low	Critical
Crying/distress (crying time after a feed, minutes of crying)										
1	RCT; parallel	Serious[7]	N/A	No[9]	Serious [3]	Lansoprazole; 81	81	Mean ± SD, intervention vs control group: Baseline: 7.9 ± 6.05 vs 9.0 ± 7.25 4 wk: 4.3 ± 5.52 vs 4.9 ± 6.20 Mean difference at 4 weeks: MD: -0.60 (95%CI -2.41 - 1.21) MD_{change}: 0.50 (95%CI -1.36 - 2.36) (17)	Low	Critical
Crying/distress (symptom severity score, 0-3, 3 = most severe)										
1	RCT; parallel	Serious[19]	N/A	Serious[20]	Serious [3]	Esomeprazole; 37	40	Mean ± SD, change from baseline in symptom score, intervention vs control group: 0.06 ± 0.58 vs 0.19 ± 0.59. (21)[18] Change in mean difference at 4 weeks: MD_{change}: = -0.13 (95%CI -0.39 – 0.13)	Very low	Critical
Visible regurgitation/vomiting: % of feeds with regurgitation per week										
1	RCT; parallel	Serious[7]	N/A	No[9]	Serious [3]	Lansoprazole; 81	81	Mean (ie, averaged across infants) change from pretreatment baseline, intervention vs control group: -14% vs -10% (NS)[21] (17)	Very low	Critical
Visible regurgitation/vomiting: Frequency of regurgitation										

Appendix 5 – Evidence tabellen

1	RCT; parallel	Serious[1]	N/A	Serious[2]	Serious [3]	Rabeprazole; 178[4]	90	NR; NS[24] (16)	Very low	Critical
Visible regurgitation/vomiting: Number of vomiting[15]										
1	RCT-parallel	Serious[14]	N/A	No[15]	Serious [3]	Esomeprazol; 25	26	Mean ± SD, intervention vs control group: Baseline: 5.79 ± 7.14 vs 4.17 ± 4.31 2 wk: 5.21 ± 6.75 vs 4.87 ± 5.93 Mean difference at 2 weeks: MD: 0.34 (95%CI -3.15 - 3.83) MD_{change}: -1.28 (95%CI -4.42 - 1.86) (19)	Low	Critical
Visible regurgitation/vomiting: Number of vomiting										
1	RCT; parallel	Serious[16]	N/A	Serious[17]	Serious [3]	Pantoprazole; 54	52	Mean ± SD, change from base line vs wk 4, intervention vs control group: -0.45 ± 0.68 (p<0.001 vs baseline) vs -0.41 ± 0.52 (p<0.001 vs baseline. Mean ± SD, change from base line vs wk 8 intervention vs control group: -0.62 ± 0.72 (p<0.001 vs baseline) vs -0.48 ± 0.87 (p<0.001 vs baseline) Change in mean difference at 4 weeks: MD_{change} : -0.04 (95% CI -0.27 - 0.19) Change in mean difference at 8 weeks: MD_{change} : -0.14 (95% CI -0.44 - 0.16) (20)[18]	Very low	Critical
Visible regurgitation/vomiting: severity of vomiting/regurgitation (total score 0-3, 3 = most severe)										
1	RCT; parallel	Serious[19]	N/A	Serious[20]	Serious [3]	Esomeprazole; 37	40	Mean ± SD, change from baseline in symptom score, intervention vs control group: 0.04 ± 0.56 vs 0.09 ± 0.61. (21)[18] Change in mean difference at 4 weeks: MD_{change}: = -0.13 (95%CI -0.39 – 0.13)	Very low	Critical
Side-effects: AEs (number of infants experiencing ≥1 AE)										

Appendix 5 – Evidence tabellen

2	RCT; parallel	Serious[14,19]	No	Serious[15,20]	Serious 3	Esomeprazole; 29/64	36/77	RR : 0.84 (95% CI 0.61 – 1.18) FEM, I^2 = 0%, p = 0.58 (19)[a](21)[b]	Very low	Critical
Side-effects: SAEs (number of infants experiencing ≥1 SAE)										
4	RCT; parallel	Serious,, 14,16, 19	No[2] 3	Serious[2,] 5,17,20	Serious 3	7/205[24]	13/299	RR : 0.79 (95% CI 0.32 – 1.91) FEM, I^2 = 41%, p = 0.16 (19)[c](21)[d](20)[e](16)[f]	Very low	Critical
Side-effects: TAEs (number of infants experiencing ≥1 TAE)										
4	RCT; parallel	Serious[1,] 7,14,19	No	Serious[2,] 9,15,20	Serious 3	94/234[25,26]	121/326	RR : 1.16 (95% CI 0.95 – 1.41) FEM, I^2 = 16%, p = 0.31 (19)[g](21)[h](16)[j](17)[i]	Very low	Critical
Side-effects: TSAEs (number of infants experiencing ≥1 TSAE)										
2	RCT; parallel	Serious[7]	Serious 27	Serious[9]	Serious 3	10/81	2/81	RR = 0.50 (95%CI 0.11 – 2.31) (17)[j,28]	Very low	Critical
Side-effects (not predefined)										
1	RCT; cross-over[8]	Serious[1,] 8	N/A	Serious[10]	Very serious 3	15	30	No adverse events of treatment were reported.(18)[29]	Very low	Critical

RCT = randomized controlled trial; PPI = proton pump inhibitor; H2RA = H2 receptor antagonist; SD = standard deviation; MD = mean difference between groups at end of study period; MD_{change} = MD in change from baseline to end of study period; RR = relative risk; 95% CI = 95% confidence interval; N/A = not applicable, NR = not reported in study, NS = not significant, AE = adverse event, SAE = serious adverse event, TAE = treatment emergent AE, TSAE = treatment emergent SAE.

a. The most commonly reported AEs by organ system class were gastrointestinal disorders, infections/infestations, and investigations.
b. Reported events were: upper respiratory tract infection, pyrexia, rhinitis, diarrhea, cough and nasopharyngitis
c. In placebo group only, reported events were: neonatal bradycardia, cyanosis, inappropriate device signal detection, and infantile apneic attack
d. Reported events in intervention group were: respiratory syncytial virus bronchiolitis, bronchospasm, poor peripheral circulation, gastroenteritis, apnea, and chlamydial infection. In placebo-group: urinary tract infection in 1 patient.
e. Reported events were: gastroenteritis and failure to thrive.
f. In the rabeprazole groups, 5 infection-related SAEs were reported. No infection-related SAEs were observed in the placebo group
g. Neonatal anemia.
h. Reported events were: abdominal pain, regurgitation, tachypnea, and alanine aminotransferase increase
i. Reported events were: *Infection – URI, ear, LRTI, viral, constipation, eczema, fever, respiratory tract congestion, rhinorrhea, candidiasis, diarrhea, vomiting*.
j. Reported events were: *Lower respiratory infection, diarrhea, Ileua, dehydration, otitis media, upper respiratory infection, epididymal infection, arachnoid cyst, febrile convulsion, klebsiella infection.*
1. Not clear if personnel and participants were blinded. High chance of bias due to selective reporting. No washout period between open label and blinded part of study.

2. *Patients:* Study conducted in infants only. Only included patients in whom PPIs were effective in a pre-randomization phase. Patients included if I-GERQ-R score >16 within ≤ 6 days of first dose of study drug.
   Intervention: Two different treating regimens of rabeprazole (5mg or 10mg once daily).
   Comparison: Continued use of conservative management including thickened feeds allowed. Other PPI/H2RAs discontinued, motility influencing drugs prohibited
3. Limited number of patients and events.
4. Rabeprazole 5 mg, n=90; Rabeprazole 10 mg, n =88.
5. Data on I-GERQ-R scores only provided as total scores in a figure, no further data provided, no further analysis possible.
6. Cross-over design of one study, data of period 1 (two weeks of treatment, intervention vs placebo in n=15 patients) were used.
7. Not clear if personnel and participants were blinded for the outcome. In intervention group N=32 and N=34 in control group discontinued after 1 week, no subanalysis performed to assess between group differences. Open label initial visit served as the double blind termination visit (Orenstein, 2009).
8. Allocation concealment and/or randomization process unclear. Not clear if personnel and participants were blinded. High chance of bias due to selective reporting. No wash-out period between treatments. 64 patients were assessed for inclusion, not clear why 30 patients were not eligible for the study. Patient characteristics not reported per treatment group (Moore et al, 2003).
9. *Patients:* Study conducted in infants only, in whom non-pharmacological treatment had failed. Infants with persistence of symptoms after 1 week of double-blind treatment were eligible for open-label lansoprazole.
   Intervention: Two different treating regimens according to weight, with a large spread in dose (0.2-0.3mg/kg/day for infants ≤10wks and 1.0-1.5mg/kg/day for infants > 10wks. No between group analysis made).
   Comparison: Non-pharmacological treatment was continued in both arms.
   Based on above-mentioned, no down-grading was performed.
10. *Patients:* All infants received empirical pharmacologic treatment for GER/irritability, 87% cisapride, 73% H2RA, 67% antacid, 20% thickening agents
11. MD_{change} not calculable from data provided.
12. End of treatment, evaluation at 2 and 4 weeks respectively.
13. Outcomes assessed during 8h video monitoring period. No 24h monitoring.
14. Not clear if personnel and participants were blinded. High chance of bias due to selective reporting. Groups were unbalanced at baseline (Davidson et al, 2013).
15. *Patients:* Study conducted in infants only. Number of patients who did not meet inclusion criteria not reported. Patients were included if symptoms were reproducible during an 8-hour monitoring period. No down-grading was performed.
16. Allocation concealment and/or randomization process unclear. Not clear if personnel and participants were blinded. High risk of bias due to selective reporting. No washout period be open label and blinded part of study.
17. *Patients:* Study conducted in infants only. Only included patients in whom PPIs were effective in the open-label phase. *Intervention:* Specified study calcium-containing rescue antacid (MYLANTA Supreme or local country equivalent) was allowed.
18. No base-line or end-of-treatment data provided. MD not calculable.
19. Two methods of randomization are outlined, plus stratification, it is unclear which was used. Not clear if personnel and participants were blinded. Only included patients in whom PPIs were effective in the open-label phase. Placebo not described. No washout period between open label and blinded part of study.
20. *Patients:* Study conducted in infants only, in whom non-pharmacological treatment had failed. *Intervention:* Maalox or non-bismuth containing liquid antacid was allowed as rescue medication.
21. Wilcoxon test for changes from baseline in percent of feedings with individual symptoms. Baseline data provided, but mean change from pretreatment baseline averaged across infants. Therefore no further analysis possible.
22. No data provided.
23. Results are not uniformly pointing in the same direction across studies , however 95% confidence intervals are overlapping and I^2 = 41%. Therefore we decided not to downgrade for inconsistency.
24. N=64 patients esomeprazole, n=52 patients pantoprazole, n=178 patients rabeprazole. .
25. Two different treatment regimens per group (Rabeprazole 5mg/day and Rabeprazole 10mg/day). Pooled results for total number of children in intervention group used for analysis.
26. N=64 patiens esomeprazole, n=81 patients lansoprazole, and n=178 patients rabeprazole.
27. Results are not uniformly pointing in the same direction across studies , I^2 = 78% and p=0.03. We downgraded for inconsistency.
28. In one study no events in both intervention and control group (Winter, 2012). RR therefore not estimable and not used in pooled analysis.
29. *Outcome:* Side-effects not predefined as outcome measure in methods section.

Appendix 5 – Evidence tabellen

Quality assessment						Summary of findings				
						No of patients				
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	H2RA	Placebo / Antacid	Effect	Quality	Importance
H2RA vs PLACEBO										
Crying/distress: abdominal colic (clinical score 0-3, 3 = most severe)[1,2]										
1	RCT; parallel	Serious[3]	N/A	Serious[4]	Very serious [5]	Nizatidine; 12	12	Mean ± SD, intervention vs control group: Baseline: 2.7 ± 0.5 vs 2.7 ± 0.5 4 wks: 1.4 ± 1.1 vs 2.2 ± 1.0 (p<0.01 in intervention group compared to baseline, placebo NS) 8 wks: 0.7 ± 1.2 vs 1.6 ± 1.1 (p<0.01 in intervention group compared to baseline, placebo NS)) Mean difference at 4 and 8 weeks: MD 4 wks : -0.80 (95%CI -1.64 – 0.04) MD 8 wks : -0.90 (95% CI -1.82 – 0.02) (22)	Very low	Critical
Heartburn (clinical score 0-3, 3 = most severe)[2]										
1	RCT; parallel	Serious[3]	N/A	Serious[4]	Very serious [5]	Nizatidine; 12	12	Mean ± SD, intervention vs control group: Baseline: 2.3 ± 1.2 vs 2.2 ± 0.8 4 wks: 1.7 ± 1.1 vs 1.8 ± 0.8 (p<0.01 in intervention group compared to baseline, placebo NS) 8 wks: 1.0 ± 1.7 vs1.6 ±0.9 (p<0.01 in intervention group compared to baseline, placebo NS)) Mean difference at 4 and 8 weeks: MD 4 wks : -0.10 (95%CI -0.87 – 0.67)	Very low	Critical

								MD 8 wks : -0.60 (95%CI -1.69 – 0.49) (22)		
Visible regurgitation/vomiting: severity of regurgitation (total score 0-3, 3 = most severe)										
1	RCT; parallel	Serious[3]	N/A	Serious[4]	Very serious [5]	Nizatidine; 12	12	Mean ± SD, intervention vs control group: Baseline: 2.4 ± 1.0 vs 2.5 ± 0.8 4 wks: 1.3 ± 1.1 vs 2.2 ± 1.3 (NS compared to baseline for placebo and intervention group) 8 wks: 0.3 ± 1.7 vs 1.7 ± 1.4 (p<0.01 in intervention group compared to baseline, placebo NS)) Mean difference at 4 and 8 weeks: MD 4 wks : -0.90 (95%CI -1.86 - 0.06) MD 8 wks : -1.40 (95%CI -2.29 - -0.51) (22)	Very low	Critical
Visible regurgitation/vomiting: severity of vomiting (total score 0-3, 3 = most severe)										
1	RCT; parallel	Serious[3]	N/A	Serious[4]	Very serious [5]	Nizatidine; 12	12	Mean ± SD, intervention vs control group: Baseline: 2.4 ± 0.7 vs 2.6 ± 0.5 4 wks: 0.8 ± 0.9 vs 2.1 ± 1.1 (p<0.01 in intervention group compared to baseline, placebo NS) 8 wks: 0.4 ± 0.7 vs1.6 ± 1.9 (p<0.01 in intervention and placebo group compared to baseline) Mean difference at 4 and 8 weeks: MD 4 wks : -1.30 (95%CI -2.10 - -0.50) MD 8 wks : -1.20 (95%CI -2.24 - -0.16) (22)	Very low	Critical
Endoscopy (macroscopically)healed (number of patients)										

1	RCT; parallel	Serious[3]	N/A	Serious[4]	Very serious[5]	Nizatidine; 5/12	2/12	RR : 2.50 (95%CI 0.60 – 10.46) (22)	Very low	Critical
Histology healed (number of patients)										
1	RCT; parallel	Serious[3]	N/A	Serious[4]	Very serious[5]	Nizatidine; 9/12	3/12	RR : 3.00 (95%CI 1.07 – 8.43) (22)	Very low	Critical
Histology improved (number of patients, normal, mild or moderate esophagitis)										
1	RCT; parallel	Serious[3]	N/A	Serious[4]	Very serious[5]	Nizatidine; 11/12	5/12	RR : 2.20 (95%CI 1.10 – 4.39) (22)	Very low	Critical
Esophagitis score (total score 0-9, 9 = most severe)										
1	RCT; parallel	Serious[6]	N/A	Serious[7]	Very serious[5]	Cimetidine; 17	15	Mean ± SD, intervention vs control group: Baseline: 6.35 +/- 2.78 vs 6.80 +/- 2.88 (p<0.01) 12 wks: 1.6 +/- 2.43 vs 5.43 +/- 3.81 (NS) Mean difference at 12 weeks: MD : -3.83 (95%CI -6.08 – -1.58) (23)	Very low	Critical
Esophagitis score improved (number of patients, based on category: normal, mild-moderate or severe esophagitis)										
1	RCT; parallel	Serious[6]	N/A	Serious[7]	Very serious[5]	Cimetidine; 16/17	7/15	RR : 2.02 (95%CI 1.16 – 3.51) (23)	Very low	Critical
Side-effects: AEs (number of patients with ≥ 1 event)										
1	RCT; parallel	Serious[8]	N/A	Serious[9]	Very serious[5]	Ranitidine: 12/19	0/10	RR: 13.75 (95%CI 0.90 – 210.7) (24)[a]	Very low	Critical
Side-effects: TAEs (number of patients with ≥ 1 event)										

Appendix 5 – Evidence tabellen

1	RCT; parallel	Serious[8]	N/A	Serious[9]	Very serious 5	Ranitidine: 4/19	0/10	RR: 4.95 (95%CI 0.29 – 83.68) (24)	Very low	Critical

RCT = randomized controlled trial; H2RA = H2 receptor antagonist; SD = standard deviation; MD = mean difference end of study period; MD_{change} = MD in change from baseline to end of study period; RR = relative risk; 95% CI = 95% confidence interval; N/A = not applicable, NR = not reported in study, NS = not significant, AE = adverse event, TAE = treatment emergent AE.

a. Reported events were: vomiting, nausea and abdominal pain, dizziness, intermittent headache and lightheadedness, nasal discomfort and dehydration.
1. Defined as 'abdominal pain colic (in infants)' by authors. We interpreted this as the typical colicky symptom, i.e. the presence of prolonged crying.
2. Score based on symptoms per week, symptom score ranging from 0-3. Therefore, data cannot be analyzed as a continuous variable. However, authors reported data as means ± SD, we therefore did calculate the mean differences.
3. Allocation concealment and/or randomization process unclear. Not clear if personnel and participants were blinded. High chance of bias due to selective reporting. Not clear to what group patients improved or came from, i.e. the extent of improvement not specified. High drop-out rate (26%).
4. *Patients:* Both infants and children (range 6 months – 8 years). Groups too small to perform analysis for both infants and children separately. Only included children with peptic esophagitis, > grade III or when grade I or II was seen esophagitis had to be histologically confirmed. *Intervention:* In all patients, positional therapy and dietary manipulation with thickened feeds (dry rice cereal) were recommended. *Comparison:* Placebo not further specified. Based on the abovementioned, we decided to downgrade one level for indirectness.
5. Limited number of patients and events.
6. Allocation concealment and/or randomization process unclear. Not clear if personnel and participants were blinded. High chance of bias due to selective reporting. Treatment group of patients that failed to complete the study not reported.
7. *Patients:* Both infants and children (range 1 month – 14 years), no subanalysis performed or possible from reported results. Included children with established peptic reflux esophagitis, 18-24h intraesophageal pH monitoring, a drop of the distal esophageal pH <4.00 for >20 seconds. *Intervention:* All patients received intensive postural therapy. Based on the abovementioned, we decided to downgrade one level for indirectness.
8. Allocation concealment and/or randomization process unclear. Not clear if personnel and participants were blinded. Not clear why 5 patients did not complete study. No data on individual symptoms provided. Study duration only 6h (time of pH-monitoring). End-point of assessment of AEs not specified.
9. Patients: Study in children only. Children with a history of acid reflux symptoms over the previous 3 months were included, inclusion criteria not further specified.
   Intervention: Single dose only. Intervention vs placebo in a 2:1 ratio.
   Comparison: Placebo not further specified. Based on the abovementioned, we decided to downgrade one level.

Appendix 5 – Evidence tabellen

Quality assessment						Summary of findings				
						No of patients				
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	PPI	H2RA	Effect	Quality	Importance
PPI VS H2RA										
Crying/distress (symptom severity score, 0-3)										
1	RCT; parallel	Serious[1]	N/A	Serious[2]	Very serious [3]	Omeprazole; 19	Ranitidine; 16	Mean ± SD, intervention vs control group: Baseline: 0.84 ± 2.19 vs 0.81 ± 1.77 3 mo: 0.16 ± 0.69 vs 0.25 ± 1 (p=0.6 between groups after therapy) Mean difference at 3 months: MD: -0.09 (95%CI -0.67 – 0.49) (25)	Very low	Critical
Crying/distress (symptom frequency change from baseline)										
1	RCT; parallel	Serious[4]	N/A	Serious[5]	Very Serious [3]	Omeprazole; 30	Ranitidine; 30	Frequency change from baseline, intervention vs control group: 1 wk: 7.8-12.8 vs 8.20-14.32 2 wk: 1.8-6.5 vs 2.5-6.8 (26)	Very low	Critical
Visible vomiting/regurgitation (symptom frequency change from baseline)										

Appendix 5 – Evidence tabellen

1	RCT; parallel	Serious[4]	N/A	Serious[5]	Very Serious [3]	Omperazole; 30	Ranitidine; 30	Frequency change from baseline, intervention vs control group: 1 wk: 21.74-32.21 vs 17.25-24.53 (p=0.01) 2 wk: 5.01 -11.25 vs 7.5-13.6 (26)	Very low	Critical
Chest pain (symptom severity score, 0-3)										
1	RCT; parallel	Serious[1]	N/A	Serious[2]	Very serious [3]	Omeprazole; 19	Ranitidine; 16	Mean ± SD, intervention vs control group: Baseline: 0.68 ± 20.06 vs 0.56 ± 2.25 3 mo: 0.05 ± 0.23 vs 0.56 ± 2.25 (p=0.01 between groups after therapy) Mean difference at 3 months: MD: -0.51 (95%CI -1.62 – 0.60) (25)	Very low	Critical
Side-effects (not predefined)										
2	RCT; parallel	Serious[1]	No	Serious[2, 6]	Very serious [3]	Omeprazole; 49	Ranitidine; 46	No adverse events of treatment were reported. (25, 26)	Very low	Critical
Endoscopic/histologic healing (grade 0 to 2 on histology score)										
1	RCT; parallel	Serious[7]	N/A	Serious[8]	Very serious [3]	Omeprazole, 9/13	Ranitidine; 8/12	RR : 0.92 (95% CI 0.57 – 1.50) (27)	Very low	Critical

RCT = randomized controlled trial; PPI = proton pump inhibitor; H2RA = H2 receptor antagonist; SD = standard deviation; MD = mean difference between groups at end of study period; MD_{change} = MD in change from baseline to end of study period; RR = relative risk; 95% CI = 95% confidence interval; N/A = not applicable, NR = not reported in study, NS = not significant, AE = adverse event, SAE = serious adverse event, TAE = treatment emergent AE, TSAE = treatment emergent SAE.

1. Allocation concealment and/or randomization process unclear. Not clear if personnel and participants were blinded. High chance of bias due to selective reporting. At baseline, low prevalence of pathologic symptom scores in both treatment arms.
2. *Patients:* The diagnosis of GERD was based on the impact of symptoms on the general well-being of the children and positive MII/pH monitoring (SI >50% and SAP>95% defined as pathologic). Patients had to have both esophageal and extra-esophageal symptoms. Study in infants and children (range 1-181 months), no sub analysis for age performed.
3. Limited number of patients and events.
4. Not clear if personnel and participants were blinded. High change of bias due to selective reporting.
5. Patients: Study performed in infants who had failed previous standard treatment of two weeks. Outcome: Baseline scores are not provided
6. *Outcome:* Side-effects not predefined as outcome measure in methods section.

7. Allocation concealment and/or randomization process unclear. Not clear if personnel and participants were blinded. High chance of bias due to selective reporting. High dropout rate and small sample size. Inclusion criteria not further specified.
8. *Patients:* Study performed in children who had failed previous treatment. *Outcome:* Outcome of definition of endoscopic healing nog provided.

Appendix 5 – Evidence tabellen

Quality assessment						Summary of findings				Importance
						No of patients				
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	PPI	Antacid	Effect	Quality	
PPI VS ANTACID[1]										
Crying/distress (crying time, minutes of crying)										
1	RCT; parallel	Serious[2]	N/A	No	Very serious [3]	Esomeprazole; 26[4]	Antacid; 25 [4.5]	Mean ± SD, intervention vs control group:[6] *In infants in left lateral position:* 1. Total crying time (mins) Baseline: 92 ±24.2 vs 106 ± 68.5 2 wk: 92 ± 34.6 vs 88 ± 36.1 Mean difference at 2 weeks: MD: 4.00 (95%CI -23.71 – 31.72) MD_{change}: 16.00 (95%CI -21.84 – 53.84) *In infants in head of cot elevation position:* 1. Total crying time (mins) Baseline: 71 ± 41.2 vs 74 ± 69.4 2 wk: 81 ± 37.4 vs 66 ± 45.0 Mean difference at 2 weeks: MD: 15.00 (95%CI -17.13 – 47.13) MD_{change}: 17.00 (95%CI -15.22 – 49.22) (28)	Very low	Critical
Crying/distress (number of cries)										

Appendix 5 – Evidence tabellen

1	RCT; parallel	Serious[2]	N/A	No	Very serious [3]	Esomeprazole; 26[4]	Antacid; 25 [4,5]	Mean ± SD, intervention vs control group:[6] *In infants in left lateral position:* Baseline: 48 ± 31.2 vs 60 ± 43.3 2 wk: 48 ± 27.7 vs 54 ± 32.4 Mean difference at 2 weeks: MD: -6.00 (95%CI -29.58 – 17.58) MD_{change}: 12.00 (95%CI -15.31 – 39.31) *In infants in head of cot elevation position:* Baseline: 30 ± 26.2 vs 38 ± 34.6 2 wk: 49 ± 26.2 vs 35 ± 24.2 Mean difference at 2 weeks: MD: 14.00 (95%CI -5.39 – 33.39) MD_{change}: 22.00 (95%CI -5.70 – 49.70) (28)	Very low	Critical

RCT = randomized controlled trial; PPI = proton pump inhibitor; H2RA = H2 receptor antagonist; SD = standard deviation; MD = mean difference between groups at end of study period; MD_{change} = MD in change from baseline to end of study period; RR = relative risk; 95% CI = 95% confidence interval; N/A = not applicable, NR = not reported in study, NS = not significant, AE = adverse event, SAE = serious adverse event, TAE = treatment emergent AE, TSAE = treatment emergent SAE. *As reported by study

1. This study consisted of 4 treatments arms, also assessing positioning therapy (left lateral positioning vs head of cot elevation) next to PPI vs antacid.
2. Allocation concealment process unclear. No blinding for outcome, blinding for intervention not clear. High loss to follow up due to discontinuation. High chance of bias due to selective reporting.
3. Limited number of patients and events
4. PPI and left lateral position, n=12; PPI and head of cot elevation, n=14; antacid and left lateral position, n=13; antacid and head of cot elevation, n=12.
5. Anatacid Mylanta.
6. Standard deviations calculated manually from standard error of mean and number of study subjects.

Appendix 5 – Evidence tabellen

Quality assessment						Summary of findings				
						No of patients				
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	PPI	Quince	Effect	Quality	Importance
PPI vs. Quince syrup										
Visible vomiting/regurgitation (individual symptom score)										
1	RCT; parallel	Not Serious	N/A	Serious[1]	Very serious[2]	Omeprazole; 40	Quince; 40	Mean ± SD, intervention vs control group: Infants and young children: age <60 mo. Baseline: 18.87 ± (49.50) vs. 18.33 ± (34.92) 4 wk: 6.50 ± (24.43) vs. 5.14 ± (12.81) 7 wk: 6.38 ± (24.44) vs. 2.36 ± (6.70) Children and adolescents: age 60-216 mo. Baseline: 1.95 ± (3.90) vs. 1.77 ± (3.20) 4 wk: 0.67 ± (1.71) vs. 3.06 ± (11.48) 7 wk: 2.04 ± (10.00) vs. 0.02 ± (0.09) (29)	Low	Critical
Heartburn (individual symptom score)										
1	RCT; parallel	Not Serious	N/A	Serious[1]	Very Serious[2]	Omeprazole; 24/40[3]	Quince; 18/40[3]	Mean ± SD, intervention vs control group: Children and adolescents[3] Baseline: 4.30 ± (6.96) vs. 21.94 ± (35.92) 4 wk: 1.81 ± (7.08) vs. 3.15 ± (8.25) 7 wk: 5.87 ± (22.80) vs. 3.49 ± (7.07) (29)	Low	Critical

Appendix 5 – Evidence tabellen

Side-effects: AEs (not pre-defined)										
1	RCT; parallel	Not serious	N/A	Serious	Very Serious	Omeprazole; 40	Quince; 40	No adverse events of treatment were reported (29)	Low	Critical

RCT = randomized controlled trial; PPI = proton pump inhibitor; H2RA = H2 receptor antagonist; SD = standard deviation; MD = mean difference between groups at end of study period; MD_{change} = MD in change from baseline to end of study period; RR = relative risk; 95% CI = 95% confidence interval; N/A = not applicable, NR = not reported in study, NS = not significant, AE = adverse event, SAE = serious adverse event, TAE = treatment emergent AE, TSAE = treatment emergent SAE. *As reported by study

1. Two different groups were made (<60 months and 60-216 months) and no subanalysis for each group was performed
2. Limited number of patients and events
3. The outcome measure heartburn was only investigated in the group of children and adolescents (age 60-216 months)

Appendix 5 – Evidence tabellen

Quality assessment						Summary of findings				
						No of patients				
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	H2RA	Placebo / Antacid	Effect	Quality	Importance
H2RA VS ANTACID										
Esophagitis score (total score 0-12, three category scale, 12 = most severe)										
1	RCT; parallel	Serious[1]	N/A	No[2]	Very serious [3]	Cimetidine: 14	Antacid[4]: 15	Mean ± SD, H2RA vs antacid: Baseline: 8.14 ± 2.17 vs 8.2 ± 2.39 12 wks: 3.21 ± 3.80 vs 3.4 ± 3.18 (wk 12 vs baseline in both groups p<0.01) Mean difference at 12 weeks: MD: -0.19 (95%CI -2.75 – 2.37) (30)	Very low	Critical
Endoscopy (macroscopically) healed (total score 0-3, 3 = most severe)										
1	RCT; parallel	Serious[5]	N/A	No[6]	Very serious [3]	Famotidine: 10/24	Alginate antacid[7]: 10/23	RR: 0.96 (95%CI 0.49 – 1.86) (31)	Very low	Critical
Endoscopy (macroscopically) improved (total score 0-3, 3 = most severe)										
1	RCT; parallel	Serious[5]	N/A	No[6]	Very serious [3]	Famotidine: 18/24	Alginate antacid: 13/23	RR: 1.33 (95%CI 0.87 – 2.03) (31)	Very low	Critical
Histology healed (no esophagitis, mild or severe esophagitis)										

Appendix 5 – Evidence tabellen

1	RCT; parallel	Serious[5]	N/A	No[6]	Very serious [3]	Famotidine: 17/24	Alginate antacid: 12/23	RR: 1.36 (95%CI 0.85 – 2.17) (31)	Very low	Critical
Histology improved (no esophagitis, mild or severe esophagitis)										
	RCT; parallel	Serious[5]	N/A	No[6]	Very serious [3]	Famotidine: 19/24	Alginate antacid: 18/23	RR: 1.01 (95%CI 0.75 – 1.36) (31)	Very low	Critical

RCT = randomized controlled trial; H2RA = H2 receptor antagonist; SD = standard deviation; MD = mean difference end of study period; MD_{change} = MD in change from baseline to end of study period; RR = relative risk; 95% CI = 95% confidence interval; N/A = not applicable, NR = not reported in study, NS = not significant, AE = adverse event, TAE = treatment emergent AE.

1. Allocation concealment and/or randomization process unclear. Not clear if personnel and participants were blinded. High chance of bias due to selective reporting. Data on laboratory measurements not provided, therefore incompleteness of data regarding safety management. Authors mention that symptom score was increased with 3 points in presence of hiatal hernia. Not clear if this was also applied for individual score for endoscopy findings or only in total scoring system. Only improvement of score provided, not clear how many patients healed or improved.
2. *Patients*: Both infants and children (range 2 – 42 months). No subanalysis performed or possible from results provided. Infants included with a history suggesting GER, shown by radiology (positive if >2 episodes of reflux at fluoroscopy) and acid reflux test (Tuttle test, pH drop <4 for >20 sec).
   Intervention: All children underwent positional therapy and received fractionated feeds. In infants, formula milk was thickened by adding cereals or Nestargel (1%). Based on the abovementioned, we decided not to downgrade for indirectness.
3. Limited number of patients and events.
4. Antacid: liquid magnesium hydroxide and aluminum hydroxide.
5. Allocation concealment and/or randomization process unclear. Not clear if personnel and participants were blinded. Baseline imbalance between groups.
6. *Patients:* Study in children only. Included only children with peptic esophagitis, > grade III or when grade I or II was seen esophagitis had to be histologically confirmed. No downgrading.
7. Alginate-antacid: 0.5g alginic acid, 0.1g aluminum hydroxide, 0.025g magnesium trisilicate and 0.17g sodium bicarbonate.

Appendix 5 – Evidence tabellen

Quality assessment						Summary of findings				Importance
						No of patients				
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	PPI	Antacid	Effect	Quality	
PPI VS FEED INTERVENTION										
I-GERQ-R questionnaire (total score 0-42, 42 = most severe, ≥16 suggestive for GERD)										
1	RCT; parallel	Serious[1]	N/A	Serious[2]	Very serious [3]	Lansoprazole; 30[4]	15	Mean ± SD, lansoprazole 15mg/day (A) vs lansoprazole 7.5mg/2xday (B) vs hydrolyzed formula (C) Baseline: 26.6 ± 2.8 vs 26.9 ± 3.7 vs 25.9 ± 3.3 2 weeks: 20.6 ± 4.2 vs 20.0 ± 3.3 vs 25.8 ± 3.2 Mean difference at 2 weeks: MD = 0.60 (95% CI -2.10 – 3.30, A vs B) MD = -5.20 (95% CI -7.98 – -2.53, A vs C) MD = -5.80 (95% CI -5.80 – -3.47, B vs C) (32)	Very low	Critical
Crying/distress (number of cries)										
1	RCT; parallel	Serious[1]	N/A	Serious[2]	Very serious [3]	30	15	No adverse events of treatment were reported. (32)	Very low	Critical

RCT = randomized controlled trial; PPI = proton pump inhibitor; H2RA = H2 receptor antagonist; SD = standard deviation; MD = mean difference between groups at end of study period; MD_{change} = MD in change from baseline to end of study period; RR = relative risk; 95% CI = 95% confidence interval; N/A = not applicable, NR = not reported in study, NS = not significant, AE = adverse event, SAE = serious adverse event, TAE = treatment emergent AE, TSAE = treatment emergent SAE.

1. Not clear if personnel and participants were blinded. High chance of bias due to selective reporting. No washout period between open label and blinded part of study.
2. *Patients:* Study conducted in infants only. N=68 patients were screened for inclusion to provide the 30 consecutive patients for the study, not clear why 38 patients did not fulfill inclusion criteria and were not randomized. Mothers of all included patients had to have high school or higher education. Patients included if I-GERQ-R score ≥ 16 over 1-week period.
   Intervention: Two different treating regimens of lansoprazole (15mg once or 7.5mg twice daily).

Comparison: Control group (C) used a extensively hydrolyzed formula. No formula or feeding schedules were made in groups A and B.

3. Limited number of patients and events.
4. Lansoprazole 15mg once daily, n=15; Lansoprazole 7.5mg twice daily, n=15.

Appendix 5 – Evidence tabellen

Quality assessment						Summary of findings				
						No of patients				
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	H2RA	Sucralfate	Effect	Quality	Importance
H2RA VS SUCRALFATE										
Endoscopy (macroscopically) healed (definition NFS)										
1	RCT; parallel	Serious[1]	N/A	No[2]	Very serious [3]	Cimetidine 14/25	Sucralfate tablets: 14/25 Sucralfate suspension: 15/25	RR: 1.00 (95%CI 0.61 – 1.63) (33) RR: 0.93 (95%CI 0.58 – 1.50) (33)	Very low	Critical
Endoscopy (macroscopically) improved (definition NFS)										
1	RCT; parallel	Serious[1]	N/A	No[2]	Very serious [3]	Cimetidine 7/25	Sucralfate tablets: 7/25 Sucralfate suspension: 7/25	RR: 1.00 (95%CI 0.61 – 1.63) (33)	Very low	Critical
Side-effects (AE, NFS)										
1	RCT; parallel	Serious[1]	N/A	No[2]	Very serious [3]	0/25	Sucralfate tablets: 0/25 Sucralfate suspension: 0/25	No adverse events of treatment were reported.(33)[4]	Very low	Critical

Appendix 5 – Evidence tabellen

RCT = randomized controlled trial; H2RA = H2 receptor antagonist; RR = relative risk; 95% CI = 95% confidence interval; NFS = not further specified, AE = adverse event

1. Allocation concealment and/or randomization process unclear. Not clear if personnel and participants were blinded. High chance of bias due to selective reporting.
2. *Patients:* all included patients had an endoscopic diagnosis of reflux esophagitis. Patients with gastroduodenal ulcer, kidney disease and those who had taken H2RAs, antacids, sucralfate, ulcer agents or antirheumatic drugs were excluded. Study in children only. *Outcome:* Side-effects not predefined as outcome measure in methods section.
3. Limited number of patients and events.
4. RR therefore not estimable and not used in pooled analysis.

Appendix 5 – Evidence tabellen

Quality assessment						Summary of findings				
						No of patients				
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	H2RA	Hypoallergenic diet	Effect	Quality	Importance
H2RA vs. feeding intervention										
Visible vomiting/regurgitation: % of patients vomiting at end of treatment										
1	RCT	Serious[1]	N/A	Serious[2]	Very serious [3]	25	25	Frequency (%), intervention vs control group: Baseline: 25 (100) vs 25 (100) 2 wks: 19 (76) vs 19 (76) (P=0.01)(34)	Very low	Critical
Crying/irritability: % of patients with irritability at end of treatment										
1	RCT	Serious	N/A	Serious	Very serious	25	25	Frequency (%), intervention vs control group: Baseline: 23 (93) vs 18(72) 2 wks: 21(84) vs 15(60) P <0.05 between groups(34)	Very low	Critical

RCT = randomized controlled trial; N/A = not applicable, AE = adverse event.
1. Randomization process and allocation concealment unclear. Not clear if personnel or patients were blinded.
2. Patients: Inclusion via I-GERQ-R, this Is not a good diagnostic test. Outcome: percentages in frequency table are not well calculated.
3. Limited number of patients and events

C – Prokinetica

Quality assessment						Summary of findings				
						No of patients				
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Baclofen	Placebo	Effect	Quality	Importance
BACLOFEN vs PLACEBO										
Side-effects: AEs (number of adverse events)										
1	RCT; parallel	Serious[1]	N/A	Serious[2]	Very serious [3]	15	15	Intervention vs placebo, total number of AEs: 5 vs 4.(35)[a, 4,5]	Very low	Critical

RCT = randomized controlled trial; N/A = not applicable, AE = adverse event.

a. Reported events were: breathlessness , tiredness, nausea, sore nostril/throat.

1. Allocation concealment and/or randomization process unclear. Not clear if personnel and participants were blinded. Measurement of symptoms up to 48h after each visit (in total n = 2 visits), but total duration of study not clear and not clear from what time-point the 48h were measured.
2. *Patients:* Study in children only. Children with severe GERD were included, children were referred for further investigation who failed to improve after routine therapeutic measures (ie, parental reassurance, postural advice, feed thickeners, antacids, H2-antagonists, and proton pump inhibitors [PPIs]). Inclusion criteria not further specified.*Intervention:* One test dose of baclofen was given to assess toleration, second session performed > 72h after safety session. Study assesses only 2 doses of Baclofen. *Outcome:* methods and definitions of measurement of adverse events not predefined in methods section.
3. Limited number of patients and events.
4. Measured during and up to 48 hours after second visit. Symptoms after first visit not split out for intervention or placebo.
5. Only total number of AEs reported, no data on number of AEs per patient.

Appendix 5 – Evidence tabellen

Quality assessment						Summary of findings				
						No of patients				
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Domperidone	Placebo	Effect	Quality	Importance
DOMPERIDONE VS PLACEBO										
Visible regurgitation/vomiting: % of patients vomiting at end of treatment										
1	RCT; parallel	Very serious[1]	N/A	Not serious[2]	Very serious[3]	15	15	Data only provided in figure, no raw data provided. Authors report significant improvement of %patients vomiting in the domperidone vs placebo group (p<0.001). (36)*	Very low	Critical
Side-effects: number of patients with AEs										
2	RCT; parallel	Very serious[1,4]	No	Not serious[5]	Very serious[3]	0/35	0/35	RR = not estimable.(36)[6](34)	Very low	Critical

RCT = randomized controlled trial; RR = relative risk.
*As reported by study

1. Allocation concealment and/or randomization process unclear. Not clear if personnel and participants were blinded. High chance of bias due to selective reporting. Groups not comparable at baseline.
2. *Patients:* Study conducted in infants and children, no subanalysis performed according to age.
3. Limited number of patients and events.
4. In one study stratified and successive block randomization of patients. Therefore constrained randomization.
5. *Patients:* Study conducted in infants and children, no subanalysis performed according to age. *Intervention:* All infants received additional treatments: fractionated feeding, thickened milk formulas for unweaned infants and positional management. All infants were treated with another dose of placebo administered 1 and 3 h after meals alongside domperidone and first dose of placebo. No downgrading was performed.
6. RR not estimable as there were no events in both treatment arms.

Appendix 5 – Evidence tabellen

Quality assessment						Summary of findings				
						No of patients				
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Metoclopramide	Placebo	Effect	Quality	Importance
METOCLOPRAMIDE VS PLACEBO										
Visible regurgitation/vomiting: % of patients vomiting at end of treatment										
1	RCT; parallel	Very serious[1]	N/A	Not serious[2]	Very serious[3]	17	15	Data only provided in figure, no raw data provided. Authors report significant improvement of %patients vomiting in the metoclopramide vs placebo group (p<0.001).(36)*	Very low	Critical
Side-effects: number of patients with AEs										
2	RCT; cross-over	Very serious[4]	N/A	Not serious[5]	Very serious[3]	0/15	0/15	RR = not estimable.(37)[6]	Very low	Critical
1	RCT; parallel	Very serious[1]	N/A	Not serious[2]	Very serious[3]	0/17	0/15	RR = not estimable.(36)[6]	Very low	Critical
Side-effects: any AE leading to discontinuation										
1	RCT; parallel	Very serious[1]	N/A	Not serious[8]	Very serious[3]	3/19	1/20	RR = 3.16 (95%CI = 0.36 - 27.78) (38)	Very low	Critical

RCT = randomized controlled trial; SD = standard deviation; RR = relative risk; 95% CI = 95% confidence interval; N/A = not applicable.
*As reported by study
1. Allocation concealment and/or randomization process unclear. Not clear if personnel and participants were blinded. High chance of bias due to selective reporting.

2. *Patients:* Study conducted in infants and children, no subanalysis performed according to age.
3. Limited number of patients and events.
4. Allocation concealment and/or randomization process unclear. Not clear if personnel was blinded for outcome of investigations. High chance of bias due to selective reporting.
5. No washout period between cross-over. Individual periods not reported so reanalysis could not be undertaken. No complete overview of baseline characteristics provided.
6. *Patients:* Study conducted in infants and children, no subanalysis performed according to age. *Intervention.* Positioning or thickening of feeding, were kept constant during the pretreatment and both feeding periods. Not clear how many infants received conservative treatment. No downgrading was performed.
7. RR not estimable as there were no events in both treatment arms.
8. *Patients:* Study conducted in infants and children, no subanalysis performed according to age. *Intervention.* All patients received positional therapy. No other treatments for GERD allowed. No downgrading was performed. *Outcome:* 'Triangular test' (statistical approach) used on main endpoint, but no further specification provided on what authors define as the main endpoint.

Appendix 5 – Evidence tabellen

Quality assessment						Summary of findings				
						No of patients				
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Domperidone	Metoclopramide	Effect	Quality	Importance
DOMPERIDONE VS METOCLOPRAMIDE										
Visible regurgitation/vomiting: % of patients vomiting at end of treatment										
1	RCT; parallel	Very serious[1]	N/A	Not serious[2]	Very serious[3]	15	17	Data only provided in figure, no raw data provided. Authors report significant improvement of %patients vomiting in the domperidone vs metoclopramide group ($p<0.05$).(36)*	Very low	Critical
Side-effects: number of patients with AEs										
1	RCT; parallel	Very serious[1]	N/A	Not serious[2]	Very serious[3]	0/15	0/17	RR = not estimable.(36)[4]	Very low	Critical

RCT = randomized controlled trial; RR = relative risk.
*As reported by study
1. Allocation concealment and/or randomization process unclear. Not clear if personnel and participants were blinded. High chance of bias due to selective reporting.
2. *Patients:* Study conducted in infants and children, no subanalysis performed according to age.
3. Limited number of patients and events.
4. RR not estimable as there were no events in both treatment arms.

Appendix 5 – Evidence tabellen

Referenties

1. Ummarino D, Miele E, Martinelli M, Scarpato E, Crocetto F, Sciorio E, et al. Effect of magnesium alginate plus simethicone on gastroesophageal reflux in infants. Journal of pediatric gastroenterology and nutrition. 2015;60(2):230-5.
2. Ostrom KM, Jacobs JR, Merritt RJ, Murray RD. Decreased regurgitation with a soy formula containing added soy fiber. Clinical pediatrics. 2006;45(1):29-36.
3. Chao HC, Vandenplas Y. Comparison of the effect of a cornstarch thickened formula and strengthened regular formula on regurgitation, gastric emptying and weight gain in infantile regurgitation. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus / ISDE. 2007;20(2):155-60.
4. Hegar B, Rantos R, Firmansyah A, De Schepper J, Vandenplas Y. Natural evolution of infantile regurgitation versus the efficacy of thickened formula. Journal of pediatric gastroenterology and nutrition. 2008;47(1):26-30.
5. Vanderhoof JA, Moran JR, Harris CL, Merkel KL, Orenstein SR. Efficacy of a pre-thickened infant formula: a multicenter, double-blind, randomized, placebo-controlled parallel group trial in 104 infants with symptomatic gastroesophageal reflux. Clinical pediatrics. 2003;42(6):483-95.
6. Moukarzel AA, Abdelnour H, Akatcherian C. Effects of a prethickened formula on esophageal pH and gastric emptying of infants with GER. J Clin Gastroenterol. 2007;41(9):823-9.
7. Xinias I, Mouane N, Le Luyer B, Spiroglou K, Demertzidou V, Hauser B, et al. Cornstarch thickened formula reduces oesophageal acid exposure time in infants. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver. 2005;37(1):23-7.
8. Miyazawa R, Tomomasa T, Kaneko H, Morikawa A. Effect of formula thickened with locust bean gum on gastric emptying in infants. Journal of paediatrics and child health. 2006;42(12):808-12.
9. Miyazawa R, Tomomasa T, Kaneko H, Morikawa A. Effect of locust bean gum in anti-regurgitant milk on the regurgitation in uncomplicated gastroesophageal reflux. Journal of pediatric gastroenterology and nutrition. 2004;38(5):479-83.
10. Miyazawa R, Tomomasa T, Kaneko H, Arakawa H, Morikawa A. Effect of formula thickened with reduced concentration of locust bean gum on gastroesophageal reflux. Acta paediatrica (Oslo, Norway : 1992). 2007;96(6):910-4.
11. Vandenplas Y, Hachimi-Idrissi S, Casteels A, Mahler T, Loeb H. A clinical trial with an "anti-regurgitation" formula. European journal of pediatrics. 1994;153(6):419-23.
12. Orenstein SR, Magill HL, Brooks P. Thickening of infant feedings for therapy of gastroesophageal reflux. The Journal of pediatrics. 1987;110(2):181-6.
13. Chao HC, Vandenplas Y. Effect of cereal-thickened formula and upright positioning on regurgitation, gastric emptying, and weight gain in infants with regurgitation. Nutrition (Burbank, Los Angeles County, Calif). 2007;23(1):23-8.
14. Iacono G, Carroccio A, Cavataio F, Montalto G, Bragion E, Lorello D, et al. Severe gastroesophageal reflux in children: Effectiveness of different combinations of drugs. Current Therapeutic Research - Clinical and Experimental. 1991;50(4):474-81.
15. Miller S. Comparison of the efficacy and safety of a new aluminium-free paediatric alginate preparation and placebo in infants with recurrent gastro-oesophageal reflux. Current medical research and opinion. 1999;15(3):160-8.
16. Hussain S, Kierkus J, Hu P, Hoffman D, Lekich R, Sloan S, et al. Safety and efficacy of delayed release rabeprazole in 1- to 11-month-old infants with symptomatic GERD. Journal of pediatric gastroenterology and nutrition. 2014;58(2):226-36.
17. Orenstein SR, Hassall E, Furmaga-Jablonska W, Atkinson S, Raanan M. Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. The Journal of pediatrics. 2009;154(4):514-20.e4.
18. Moore DJ, Tao BS, Lines DR, Hirte C, Heddle ML, Davidson GP. Double-blind placebo-controlled trial of omeprazole in irritable infants with gastroesophageal reflux. The Journal of pediatrics. 2003;143(2):219-23.
19. Davidson G, Wenzl TG, Thomson M, Omari T, Barker P, Lundborg P, et al. Efficacy and safety of once-daily esomeprazole for the treatment of gastroesophageal reflux disease in neonatal patients. The Journal of pediatrics. 2013;163(3):692-8.e1-2.
20. Winter H, Kum-Nji P, Mahomedy SH, Kierkus J, Hinz M, Li H, et al. Efficacy and safety of pantoprazole delayed-release granules for oral suspension in a placebo-controlled treatment-withdrawal study in infants 1-11 months old with symptomatic GERD. Journal of pediatric gastroenterology and nutrition. 2010;50(6):609-18.
21. Winter H, Gunasekaran T, Tolia V, Gottrand F, Barker PN, Illueca M. Esomeprazole for the treatment of GERD in infants ages 1-11 months. Journal of pediatric gastroenterology and nutrition. 2012;55(1):14-20.

22. Simeone D, Caria MC, Miele E, Staiano A. Treatment of childhood peptic esophagitis: a double-blind placebo-controlled trial of nizatidine. Journal of pediatric gastroenterology and nutrition. 1997;25(1):51-5.
23. Cucchiara S, Gobio-Casali L, Balli F, Magazzu G, Staiano A, Astolfi R, et al. Cimetidine treatment of reflux esophagitis in children: an Italian multicentric study. Journal of pediatric gastroenterology and nutrition. 1989;8(2):150-6.
24. Orenstein SR, Blumer JL, Faessel HM, McGuire JA, Fung K, Li BU, et al. Ranitidine, 75 mg, over-the-counter dose: pharmacokinetic and pharmacodynamic effects in children with symptoms of gastro-oesophageal reflux. Alimentary pharmacology & therapeutics. 2002;16(5):899-907.
25. Ummarino D, Miele E, Masi P, Tramontano A, Staiano A, Vandenplas Y. Impact of antisecretory treatment on respiratory symptoms of gastroesophageal reflux disease in children. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus. 2012;25(8):671-7.
26. Azizollahi HR, Rafeey M. Efficacy of proton pump inhibitors and H2 blocker in the treatment of symptomatic gastroesophageal reflux disease in infants. Korean journal of pediatrics. 2016;59(5):226-30.
27. Cucchiara S, Minella R, Iervolino C, Franco MT, Campanozzi A, Franceschi M, et al. Omeprazole and high dose ranitidine in the treatment of refractory reflux oesophagitis. Archives of disease in childhood. 1993;69(6):655-9.
28. Loots C, Kritas S, van Wijk M, McCall L, Peeters L, Lewindon P, et al. Body positioning and medical therapy for infantile gastroesophageal reflux symptoms. Journal of pediatric gastroenterology and nutrition. 2014;59(2):237-43.
29. Zohalinezhad ME, Imanieh MH, Samani SM, Mohagheghzadeh A, Dehghani SM, Haghighat M, et al. Effects of Quince syrup on clinical symptoms of children with symptomatic gastroesophageal reflux disease: A double-blind randomized controlled clinical trial. Complementary therapies in clinical practice. 2015;21(4):268-76.
30. Cucchiara S, Staiano A, Romaniello G, Capobianco S, Auricchio S. Antacids and cimetidine treatment for gastro-oesophageal reflux and peptic oesophagitis. Archives of disease in childhood. 1984;59(9):842-7.
31. Oderda G, Dell'Olio D, Forni M, Farina L, Tavassoli K, Ansaldi N. Treatment of childhood peptic oesophagitis with famotidine or alginate-antacid. The Italian journal of gastroenterology. 1990;22(6):346-9.
32. Khoshoo V, Dhume P. Clinical response to 2 dosing regimens of lansoprazole in infants with gastroesophageal reflux. Journal of pediatric gastroenterology and nutrition. 2008;46(3):352-4.
33. Arguelles-Martin F, Gonzalez-Fernandez F, Gentles MG. Sucralfate versus cimetidine in the treatment of reflux esophagitis in children. The American journal of medicine. 1989;86(6a):73-6.
34. Famouri F, Zibanejad N, Kabiri P, Kelishadi R. Comparison of Hypoallergenic Diet vs. Ranitidine in Treatment of Gastroesophageal Reflux Disease of Infants: A Randomized Clinical Trial. Iranian Journal of Pediatrics. 2017;27(4):e5343.
35. Omari TI, Benninga MA, Sansom L, Butler RN, Dent J, Davidson GP. Effect of baclofen on esophagogastric motility and gastroesophageal reflux in children with gastroesophageal reflux disease: a randomized controlled trial. The Journal of pediatrics. 2006;149(4):468-74.
36. De Loore I, Van Ravensteyn H, Ameryckx L. Domperidone drops in the symptomatic treatment of chronic paediatric vomiting and regurgitation. A comparison with metoclopramide. Postgraduate medical journal. 1979;55 Suppl 1:40-2.
37. Tolia V, Calhoun J, Kuhns L, Kauffman RE. Randomized, prospective double-blind trial of metoclopramide and placebo for gastroesophageal reflux in infants. The Journal of pediatrics. 1989;115(1):141-5.
38. Bellissant E, Duhamel JF, Guillot M, Pariente-Khayat A, Olive G, Pons G. The triangular test to assess the efficacy of metoclopramide in gastroesophageal reflux. Clinical pharmacology and therapeutics. 1997;61(3):377-84.