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3.1. Uitgangsvraag 1 – Diagnostiek

Study	Population				Index test	Index test cut-off/positivity	Sensitivity (%)	Specificity (%)	PPV	NPV	Remarks
	Subjects	Age	N	Patients/controls *(reference standard)*							
pH-METRY											
Boix-Ochoa (1980)(1)	*Patients*	2 – 18 mo	44	History of recurrent GER, and/or failure to thrive, and/or weight loss and/or feeding difficulties (not further specified)	**8h pH-metry** – glass probe, position manometrically determined (electrode 2.5cm above LES), supine, prone and semi-seated position, symptoms recorded.	pH in distal esophagus <4. Overall score computed from seven components, 1SD from score of each component in controls used as 1 scoring unit, final score total of all single score components: 1) the percent time pH<4 in 24h (RI, for each position); 2) total number of single refluxes pH <4; 3) number of refluxes longer than 5 minutes; 4) duration of longest episode.	Not calculable: no p-values or cut-off values for test-positivity provided. Final score calculated based on data of controls.* Final score was highest in patient group (27,4 ± 9,2 vs 7,39 ± 4,6).				Definition of GER(D) not further specified. Older children included in control group compared to patient group. No maximal value nor unit of measurement provided for the final score
	Controls	2 mo – 3 yrs	20	No history of GER (not further specified)							
Da Dalt (1989)(2)	*Patients*	9.3 mo (1 mo – 13.5 yrs)	111	Admitted patients with signs and symptoms typical of GER (vomiting (n=69), failure to thrive (n=29), feeding difficulties (n=20), hematemesis (n=15), recurrent wheezing (n=12)	**24h pH-metry** – glass probe, position determined by formula of Strobel (tip of catheter 87% of the distance from nares to upper limit of LES. Normal feeding and daily activities were remained.	Drop in esophageal pH <4 for >8 seconds. Percent time pH<4 in 24h (RI), total number of reflux in 24h, number of refluxes longer than 5 minutes, duration of longest	**Reflux time and two other measurements abnormal:** 41 (45/111)	Not calculable: values of controls used as normal values.			For this population, nu cut-off values have been established nor validated for pH-metry. Cut-off value for test-positivity therefore arbitrarily.

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				chronic cough (n=11), apnea (n=11), iron deficiency anemia (n=10), epigastric pain (n=10), irritability (n=7)		episode, mean duration of all reflux episode. Upper limit of normal based on 2SD from score of each component in controls. Measurement abnormal if percentage of reflux time and two other measurements abnormal.					This study includes children with recurrent or persistent wheezing (>3 attacks requiring hospital visit or almost daily wheezing for >4 wks). Within this specific patient group, a division between children with and without a history suggestive or reflux is made. Therefore this study was included, but results should be interpreted in the light of the patient group (wheezers and not the general pediatric population) the study focuses on.
	Controls	12.5 mo (3 – 68 mo)	14	No history or symptoms suggestive of GER							
Cucchiara (1990)(3)	*Patients*	GERD: 26.6 mo (2 mo – 10 yrs). GERD and esophagitis: 41.3 mo (1 mo – 12 yrs)	114	Infants and children referred for symptoms suggestive of GE, all with well-documented history of vomiting/regurgitation, some with additional complications (weight failure (n=45), hematemesis (n=17), chronic respiratory	**24h pH-metry** – glass probe, position determined by manometry or formula of Strobel (tip of catheter 87% of the distance from nares to upper limit of LES. Position confirmed by fluoroscopy. Normal feeding and daily activities were remained. Variables evaluated for entire period, wakefulness, sleep and postprandial.	Distal esophageal pH <4 for >20 seconds, or additional decrease of >1 pH unit during period of pH <4. Percent time pH<4 in 24h (RI), total number of reflux in 24h, number of refluxes longer than 5 minutes, duration of longest episode, mean duration of all	**RI:** 81 (92/114) **Number of refluxes > 5 min:** 70 (80/114) (data on other parameters not provided)	Not calculable: values of controls used as normal values.			Definition of GER(D) not further specified. In this study, infants presenting with apnea and upper respiratory infection are considered as controls, despite that these symptoms can be regarded as

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				symptoms (n=19). Based on endoscopy with biopsy: n=45 GERD only and n=69 GERD and esophagitis.		reflux episode. Normal acid exposure time/clearance time defined as <2SD from control means.					reflux-related. It remains that these control children were not admitted/referred and did not have a clinical history suggesting GERD based on the information provided in the paper.
	Controls	24.02 mo (2 mo – 12 yrs)	63	Absence of typical GER symptoms, but presenting with functional abdominal pain (n=5), functional constipation (n=9), IBS (n=11), feeding problems due to maternal inexperience/anxiety (n=19), apnea (n=10), upper respiratory infections (n=9)							
Kahn (1990)(4)	*Patients*	9 wks (4 – 25 wks)	10	(Full-term) infants that had been found apneic, pale or cyanotic, loss of tone and consciousness and had received vigorous resuscitation, with no cause of apparent life treathening event (ALTE) after diagnostic work-up.	**8.5h pH-metry** – glass probe, position radiologically confirmed (3cm above cardia).	Reflux episode if pH < 4. Total number of reflux in 8.5h, number of refluxes longer than 5 minutes, acid duration time (time spent with pH < 4).	Not calculable: no p-values or cut-off values provided.				Definition of GER(D) not further specified. This study includes children with ALTE. This study was included because ALTE was regarded by the authors as a possible presentation of GERD.
	Controls	7 (4 – 16 wks)	10	Infants with no history related to apnea or ALTE.							
pH-METRY & ENDOSCOPY											
Cucchiara (1993) (5)	*Patients*	32.9 mo (2 – 141 mo)	81	Children referred for evaluation of GERD, symptoms and signs including	**24h pH-metry** – glass probe, position determined by formula of Strobel (patients < 1 yr, tip of catheter 87%	Distal esophageal pH <4 for >20 seconds. Percent time pH<4 in 24h (RI), total number	Not calculable: no p-values or cut-off values provided. No data on number				

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				recurrent emesis/regurgitation (n=63), hematemesis (n=5), asthma (n=4), pneumonia (n=10), poor weight gain (n=23), apnea (n=2), irritability (n=13), anorexia (n=12), dysphagia (n=6), chest pain (n=5), heartburn (n=3), epigastric pain (n=17)	of the distance from nares to upper limit of LES) or position confirmed by fluoroscopy (patients >1 yr or >1meter height). Patients provided with standardized meals. **Endoscopy –** Olympus panendoscope (2.8mm diameter bioptic channel), >2 biopies taken from distal esophagus (avoiding lower 20%) performed under general anesthesia.	of reflux in 24h, number of refluxes longer than 5 minutes. Normal acid exposure time/clearance time defined as <2SD from control means. **Aberrant macroscopy:** friability, granularity, erosions, ulcerations. **Aberrant histology:** basal zone hyperplasia, papillar elongation, increased number of eosinophils and/or neutrophils, mucosal erosions.	of patients with abnormal test provided. **Macroscopy:** 33 (27/81) **Histology:** 88 (71/81)				
	Controls	7 mo (3 – 154 mo)	16	Children selected for absence of symptoms of GERD, including feeding problems due to maternal inexperience/anxiety (n=5), functional abdominal pain (n=4), previous respiratory complaints (n=4), transient decreased food intake (n=3)				**Macroscopy:** no data on controls provided. **Histology:** 100 (16/16)	**Macroscopy:** no data on controls provided. **Histology:** 100 (71/71)	**Macroscopy:** no data on controls provided. **Histology:** 62 (16/26)	In all controls, histology as defined by the authors was normal .
Ravelli (2006) (6)	*Patients*	3.95 yrs (2 mo – 11.9 yrs)	48	Patients referred for diagnostic upper gastrointestinal endoscopy for symptoms suggestive of GERD: vomiting, regurgitation, epigastric pain, heartburn and/or dysphagia (n=26), crying, fussiness, back arching at meals (n=5),	**24h pH-metry** – antimony probe, positioned confirmed between 9th and 10th dorsal vertebra by fluoroscopy. Method not further specified. **Endoscopy –** Standard videoendoscopes (outer diameters 5.3, 7.4 and 9 mm), performed under general anesthesia. 2-4 biopsies from distal	Percent time pH<4 in 24h (RI), total number of reflux in 24h, number of refluxes longer than 5 minutes, duration of longest episode. **Aberrant macroscopy:** erosive lesions. **Aberrant**	**RI:** 52 (15/29) **Macroscopy:**	No controls underwent pH-metry **Macroscopy:**	**Macroscopy:**	**Macroscopy:** no	Definition of GER(D) not further specified. Control group includes patients with potential abnormal macroscopy and/or histology. In all controls, histology as defined by the authors was normal. No

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				nocturnal cough, wheezing, recurrent pneumonia or apnea (n=17).	esophagus 3-5cm above Z-line.	**histology:** basal zone hyperplasia, papillar elongation, mucosal erosions, dilatation of interpapillary vascular spaces, increased number of neutrophils, eosinophils and lymphocytes, erosions or ulcerations and granulation tissue.	15 (7/48) **Histology:** 83 (40/48)	no data on controls provided. **Histology:** 100 (22/22)	no data on controls provided. **Histology:** 100 (40/40)	data on controls provided. **Histology:** 73 (22/30)	information on other possible detected macroscopic and/or histologic abnormalities provided by the authors.
	Controls	5.58 yrs (1 - 16.9 yrs)	22	Other manifestations, not compatible with GERD: food sensitive enterophaty (n=11), *H. pylori* infection with positive stool antigen or breath test (n=6), IBD (n=4), nonsteroidal anti-inflammatory drug gastropathy (n=1)							
pH-METRY & GE SCINTIGRAPHY											
Patra (2011)(7)	*Patients*	10.4 mo (3 -24 mo, ± 5.24)	16	Children 0-2 yrs with recurrent or persistent wheezing (>3 attacks requiring hospital visit or almost daily wheezing for >4 wks) with a history suggestive or reflux (not further specified)	**GE scintigraphy** – dose of Tc-99m by nasogastric tube, infant placed supine, low-energy high sensitivity collimator anteriorly and posteriorly **24h pH-metry** – glass probe, position radiologically confirmed, position, feeding and medication recorded (reflux medication prohibited)	Refluxing into the esophagus on both cine images and on the time activity curve, on at least two or three consecutive frames. RI > 10% in infants <1 yr and RI > 5% in children > 1 yr	69 (11/16) **RI:** 50 (8/16)	78 (28/36) **RI:** 82 (29/36)	58 (11/19) **RI:** 53 (8/15)	85 (28/33) **RI:** 78 (29/37)	Standards of interpretation of scintigraphy are poorly established. Criteria for pathologic GER defined based on studies of Patwari et al. (2002) and VandenPlas et al. (1992). For this population, nu cut-off values have been established nor validated for pH-metry. The two
	Controls		36	Children 0-2 yrs with recurrent or persistent wheezing (>3 attacks requiring hospital visit or almost daily wheezing for >4 wks) without a history suggestive or reflux (not further specified)							

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											studies referred to do not support the cut-off values used by the authors as a clinical diagnostic tool.Cut-off therefore arbitrary.
pH-METRY & UPPER GI SERIES & GE SCINTIGRAPHY & ENDOSCOPY											
Arasu (1980)(8)	*Patients*	5.3 yrs (3 mo - 17 yrs)	30	Infants/children referred with symptoms and signs suggestive of GER (not further specified)	**pH-metry** – probe not specified, position based on manometry (tip of catheter 85% of the distance from nares to upper limit of LES), 5-10 minutes in supine, left lateral and right lateral decubitus positions. Total time of measurement not clear. If no spontaneous reflux observed, manual abdominal compression was performed. Total time of measurement not clear. **Upper GI series** **F**luoroscopy after barium swallow (volume of normal feeding), EGJ evaluated with intermittent fluoroscopy while rolling the patient from side to side, encountering maximum extent of reflux. **GE scintigraphy** -	Intra-esophageal pH < 4 for >2 occasions (duration of event not specified) Test positivity not further specified	97 (29/30) Not calculable: no cut-off values for test-positivity provided.	100 (15/15)	100 (29/29)	94 (15/16)	Definition of GER(D) not further specified. Positivity of pH-metry not based on any evidence. For this population, nu cut-off values have been established nor validated for pH-metry. Cut-off therefore arbitrary. Test positivity not further specified.
	Controls	3.8 yrs (4 mo – 14 yrs)	15	Infants/children with failure to thrive (n=6), choking with feeding (n=2), pulmonary disease (n=2), vomiting from identifiable causes apart from GER (n=5), high intestinal obstructions (n=2)							

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					dose of Tc-99m by nasogastric tube, infant upright and supine position, one minute camera pictures in both positions. **Endoscopy –** Olympus panendoscope (outer diameter of 7.2mm < 4 yrs and 10 mm > 4 yrs), performed under general anesthesia.	Esophageal activity (not further specified) Friability, erosion, ulceration or thickened mucosa with fine nodularity.	Not calculable: no cut-off values for test-positivity provided. 71 (15/21)	100 (3/3)	100 (15/15)	33 (3/9)	Test positivity not further specified
SALIVARY PEPSIN											
Farhath (2013)(9)	*Patients*	GA 29 wks (24 - 35)	36	Premature infants, BW <2000g. Diagnosed with clinical GER if: (1) attending the neonatologist involved in clinical care and infants were on medication for GER at the time of sample collection or (2) presence of signs and symptoms of GER at the time of sample collection (persistent vomiting, apnea, bradycardia and desaturation attributed to GER, infant on prolonged or thickened	**Salivary pepsin** Mouth swab samples were collected from the cheek and below the tongue at one, two and three hours after feeding. Pepsin detected by an enzymatic assay and Western blot analysis for pepsin A and C. (29/36 infants were on anti-reflux medication at time of sampling)	Enzymatic assay positive for pepsin if concentration <12.5ng/ml. Test considered positive in case of >1 positive mouth swab sample.	72 (26/36)	71 (46/65)	58 (26/45)	82 (46/56)	

				feeding)							
	Controls	GA 30 wks (23 - 35)	65	Premature infants, BW <2000g, not fulfilling the above criteria for clinical GER.							

IBS = irritable bowel syndrome; IBD = inflammatory bowel disease; GER = gastroesophageal reflux; GERD = GER disease; LES = lower esophageal sphincter; EGJ = esophageal gastric junction; GE = gastro-esophageal; GI = gastrointestinal; ALTE = apparent life-threatening event; GA = gestational age, BW = birth weight; RI = reflux index, percentage of time that the esophageal pH <4; PPV = positive predictive value; NPV = negative predictive value. *As values of controls are used as normal values, specificity will always be 100%.

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3.2. Uitgangsvraag 2 – Niet-farmacologische therapie

Author	Design	Population			Cochrane Risk of Bias Tool						Dure	Intervention	Control	Outcome of interest	Outcome measures
		N	Age	Inclusion	Random sequence generation	Allocation concealment	Blinding intervention	Blinding outcome	Selective reporting	Follow-up					
FEED MODIFICATIONS															
Vander Hoof (2003) (10)	RCT; parallel	110	14 - 120 d	≥ 5 regurgitations per day for 2 days	Yes	Not Clear	Yes	Yes	Yes	81/110	5 wk	Rice starch pre-thickened formula (n=55)	Standard formula (n=49)	**Crying distress** Significant decrease in feedings followed by trouble sleeping (p=0.030). Trend towards decrease in feedings followed by pain (ns). No differences in fussiness (no data) **Visible regurgitation/vomiting:** Intervention vs control Regurgitation frequency per day Baseline: 13 ± 1 vs 11 ± 1 MD at 1 wk: -6 ± 1 vs -6 ± 1 MD at 5 wks: -7 ± 1 vs -5 ± 1 Regurgitation frequency (% of feeds) Baseline: 87 ± 2 vs 85 ± 2 MD at 1 wk: -34 ± 5 vs -22 ± 5 MD at 5 wks: -38 ± 5 vs -24 ± 5 **Side effects** Three SAEs: 1/55 vs 2/49 (intervention vs control) Discontinuation rates: 13% (7/55) intervention, 20% (10/49) control group No differences in constipation/diarrhea (reported as ns, no data)	Frequency of regurgitation based on diary Volume of regurgitation based on diary Volume of formula consumed based on diary

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Chao (2007[b]) (11)	RCT; parallel	80	2-6 mo	≥ 3 regurgitations per day	Not clear	Not clear	Not clear	No clear	Yes	63/80	8 wk	Cereal thickened formula (hydrolyzed rice > 90%, cornstarch <5%) (n=31)	Regular formula postural therapy (n=32)	**Side effects** No significant difference in stool frequency in diaries. Diarrhea >2 d: n=6 (2 in intervention, 4 in control group) N=2 with abdominal distension, N=1crying (intolerance)	Episodes of regurgitation/vomiting as reported by parent Weight gain Gastric emptying by milk scintigraphy
Hegar (2008) (12)	RCT; parallel	60	1-3 mo	≥ 4 episodes of regurgitation/ vomiting per day	Not clear	Yes	Not clear	Not clear	Yes	60/60	4 wk	Standard formula with B; 5g rice cereal/100ml (n=20) or C; bean gum (n=20) + parental reassurance	Parental reassurance + standard formula (n=20)	**Side effects – diarrhea** No statistical differences in consistency/frequency (diary based) of stools. No data. **Crying distress** No difference in sleeping disturbance. No data.	Parent reported frequency of regurgitation and symptoms Weight
Iacono (2002) (13)	RCT; parallel	166	< 4 mo (median: 1.5 mo)	Frequent regurgitation / vomiting by uncomplicated GER	Not clear	Not Clear	Not Clear	Not clear	Yes	166/166 14 drop out, not clear if excluded from analysis	8 wk	Formula thickened with carob flour (locust bean gum) (n=82)	Standard formula (n=84)	**Side effects – diarrhea** 14 patients in intervention group dropped out in first 2 wks	Frequency and entity of regurgitation + symptoms by scoring system Growth
Chao (2007[a]) (14)	RCT; parallel	100	2-4 mo	≥ 3 regurgitations per day	Not clear	Not clear	Not Clear	Not Clear	Yes	81/100	8 wk	Cornstarch thickened formula (n=41)	25% thickened formula (n=40)	**Crying distress** Crying (intervention vs control group) Baseline: 4/41 vs 5/40 Wk 4: 1/41 vs 3/ 40 Wk 8: 1/41 vs 2/40 Irritability (intervention vs control group) Baseline: 12/41 vs 12/40 Wk 4: 4/41 vs 10/40 Wk 8: 1/41 vs 8/40 Significant decrease in intervention group, no p-value provided. **Side effects – diarrhea (not further specified)** N = 8 (not specified in what arm of study)	Gastric emptying using scintigraphy Regurgitation/vomiting as reported by parents Reflux symptoms

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													19 drop-outs due to side-effects	
Miyazawa (2006) (15)	RCT; cross-over	27	<6 mo	≥ 3 regurgitations per day	Not Clear	Not Clear	Not Clear	Not Clear	Yes	24/27	1 wk	Locust bean gum 0.45g/100ml (n=14) OR 0.35g/100ml (n=13)	Standard formula (n=27)	**Visible regurgitation/vomiting:** Intervention vs control mean (SD) during treatment (1wk) HL-350 vs standard: 12.9 (3.5) vs 22.6 (3.9) HL-450 vs standard 12.8 (3.0) vs 29.8 (3.6) (no baseline scores) **Side effects – diarrhea (increase in bowel movements)** N = 3 (reported by mother) in intervention groups (no severe diarrhea)	Regurgitation episodes as reported by parent Gastric emptying measurements
Miyazawa (2004) (16)	RCT; cross-over	30	<6 mo	≥ 3 regurgitations per day	Not Clear	Not Clear	Not Clear	Not Clear	Yes	27/30	1 wk	A; Locust bean gum 0.45g/100ml (n=16) or B; 0.35g/100ml (n=11)	Standard formula (n=27)	**Side effects** No complications reported Trouble sucking the formula 11 infants **Visible vomiting/regurgitation** Intervention vs control, median (IQR) HL-450 vs standard: 1.6 (IQR 0.8 to 2.0) vs 3.5 (IQR 2.3 to 4.9) HL-350 vs standard: 1.3 (IQR 0.6 to 2.3) vs 2.9 (IQR 2.0 to 3.2) **Side effects – diarrhea (bowel movement):** Group A: SF: 1.4 (1.0-1.5) HL-450: 1.4 (1.1-1.6), p 0.48 Group B: SF: 1.4 (0.8-1.6) HL350: 1.6 (1.1-2.3), p=0.02	Episodes of regurgitation reported by parents Growth Number of stools
Ostrom (2006) (17)	RCT; parallel	179	13-32d	Regurgitation in >25% of feedings (mean 7.8 times/day)	Yes	Yes	Yes	Yes	Yes	135/179	4 wk	Soy formula with soy fiber (6g/L) (n=66/89)	Standard formula + placebo (not soy based) (n=67/90)	**Side effects** 6 SAEs, 4 in control and 1 in intervention group **Crying/distress** Parent reported on 5-point frequency	Daily incidence of regurgitation (mean average during study period based on parent reports). Mean average number of feeds associated with

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													scale. No significant differences. Crying: day 0 vs day 14 significant less likely to cry (p=0.055) and less likely to cry >30min (p=0.092) in CM group. More likely to be in good mood at day 14 (p=0.007) and day 34 (p=0.044). No absolute numbers provided. **Visible vomiting/regurgitation** Intervention vs control group mean, SD: Number of regurgitations/day: Baseline = 3.9 (1.9), 3.6 (1.9) Day 7 = 2.3 (1.9), 3.4 (1.8) Day 28 = 2.0 (1.6), 2.4 (2.4), p = 0.029 % of feeds associated with regurgitation: Baseline = 50.9 (28.9), 48.6 (28.5) Day 7 = 31.0 (22.4), 48.3 (38.7) Day 28 = 28.8 (31.1), 36.0 (34.1), p = 0.015 (SD calculated manually) Number of infants with any regurgitation: Baseline = 87/87, 90/90 Day 7 = 86/87, 85/85 Day 28 = 56/67, 63/66, p = 0.027	regurgitation. Percentage of infants with reflux not associated with feeding Percentage of subjects with any regurgitation Volume of intake Mean size of regurgitation Parent response to questionnaire on regurgitation and tolerance Infant weight.
Ummarino (2015) (18)	RCT; parallel	50	1-12 mo	Infant regurgitation according to ROME III	Yes	Not clear	Not clear	Yes	Yes	40/50	8 wk	Rice starch thickened (14.3g/100ml or 14.2g100ml for infants < 6 mo) + conservative therapy (n=25)	Conservative therapy (=life style changes + reassurance) (n=25)	**I-GERQ-R scores** Significant reduction in symptom score in intervention group (p<0.001) at wk 8 (4 vs 0 pt symptom free) (no subscores provided) **Visible regurgitation/vomiting** Number of infants with regurgitation and vomiting, intervention vs control group: Baseline = 25/25 vs 25/25 4 wk = 25/25 vs 17/17 8 wk = 13/23 vs 15/17 **Side effects (reported in diary)**	I-GERQ-R scores, <7 no clinical symptoms Side effects reported in diary

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													No SAEs reported.	
Xinias (2005) (19)	RCT; parallel	96	93 +/- 35d	Excessive regurgitation and/or vomiting (mean 5x regurgitation, 3.5x vomiting)	Not clear	Not clear	Yes	Yes	Yes	96/96	4wk	Cornstarch-thickened casein predominant formula (n=51)	Standard formula (n=45)	**Visible regurgitation/vomiting** Intervention vs control, episodes of regurgitation/day 2.57 (2.71) vs 4.31 (2.01), Intervention vs control, episodes of vomiting/day 1.45 (1.65) vs 2.74 (1.37), **Side effects – diarrhea (number of stools)** Intervention group: Baseline: 3.80 +/- 2.34 4wk: 3.54 +/- 2.03 (p=0.78) Control group: Baseline: 2.62 +/- 0.77 4wk: 2.60 +/- 0.81(p=0.82) Baseline: Intervention vs control group: p=0.05 4 wk: Intervention vs control group: p=0.08 **Side effects** No side effects due to intervention recorded	Reflux index Number of reflux episodes per hour - Number of reflux episodes > 5 minutes Duration of longest reflux episode Parent reported outcomes: regurgitation episodes, vomiting, stools, weight gain
Moukarzel (2007) (20)	RCT; parallel	74	3.24 ± 1.28 mo	Diagnosis of GER based on Orenstein criteria, cut-off not specified	Not clear	No	No	No	No	60/74	4 wk	Pre-thickened formula, not further specified, viscosity 10x that of regular formula (Wyeth Nutritional) (n=28)	Normal milk formula, not further specified (Wyeth Nutritional) (n=32)	**Visible vomiting/regurgitation** Incidence of vomiting: Regular vs Thickened; mean (SD) Baseline: 2.1 (3.0), 2.6 (2.6) 4 wks: 1.2 (1.1), 0.5 (0.8) , baseline vs 4 wks p=0.0009 in intervention group, NS in control group Incidence of regurgitation: Regular vs Thickened; mean (SD) Baseline: 6.5 (3.7), 7.1 (3.9 4 wks: 52 (3.1), 2.3 (2.0), baseline vs 4 wks p=0.0003 in intervention group, NS in control group	Outcome of pH-monitoring (longest reflux episode, number of reflux episodes >5 min, reflux index). ECG procedure outcomes
Miyazawa (2007) (21)	RCT; cross-over	20	36 ± 13 days	Infants evaluated for frequent episodes of	Not clear	Not clear	Not clear	Not clear	Yes	20/20	2 wk	Formula thickened with locust bean gum	Standard formula (n=20)	**Visible vomiting/regurgitation** Intervention vs control group, episodes of regurgitation per day: 2.3 (1.6 to 3.6) vs 5.2 (3.7 to 7.8)	

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				regurgitation or vomiting (>3 episodes per day)							0.35g/100ml (n=20)		**Side effects: diarrhea** Intervention vs control group, Bowel movements per day 1.8 (1.2 to 2.4) vs 1.2 (0.9 to 1.6) No data provided at moment of cross-over	
Vanden Plas (1994) (22)	RCT; parallel	20	1-4 mo of age	Infants presenting with frequent regurgitation (>5 times per day) and pH-monitoring results pH<4 between 10-30% of time	Not clear	Not clear	Yes	Yes	No	20/20	1 wk	Antiregurgitation formula, positional treatment and reassurance (n=10)	Standard formula, positional treatment and reassurance (n=10)	**Visible regurgitation/vomiting** 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 Difference between groups before and during treatment NS. Difference before and during treatment within groups significant (p=0.002 vs p=0.03)	pH-monitoring results: reflux index, duration of longest reflux, number of reflux episodes > 5 min, regurgitation severity score
Orenstein (1987) (23)	RCT; cross-over	21	4-34 wks	Diagnosis of GER based on symptoms and/or abnormal test results from pH monitoring or endoscopy	Not clear	Not clear	Not clear	Not clear	No	20/21	90 mins	Infants regular formula with dry rice cereal (15ml/30ml formula)	Infants regular formula	**Visible regurgitation/vomiting:** Episodes in 90 minutes, mean (SD): thickened, unthickened, 1.2 (0.7) vs 3.9 (0.9)	Frequency of emesis in 90 minutes, crying time, sleep time, gastric emptying, gastric reflux by scintigraphy
POSITIONING THERAPY														
Loots (2014) (24)	RCT; parallel	66	13.6 (2-26) wks	GERD symptoms > 5 days or increasing in frequency or severity for 3 days	Yes	Not clear	No	Not clear	Yes	51/66	2 wks	Left-side positioning with PPI (n=12) or AA (n=13)	Head of cot elevation with PPI (n=14) or AA (n=12)	**Infants with PPI** **Crying (total crying time)** 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) **Crying (number of cries)** 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)	I-GERQ-R GER monitoring (pH-MII) Gastric emptying Physiological monitoring

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														Side effects (SAE): 2 SAEs in control group. RR = 0.23 (95% CI 0.01 – 4.38) **Infants with AA** **Crying (total crying time)** 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) **Crying (number of cries)** 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) **Side-effects (SAEs)** No side effects in either of the treatment arms	
MASSAGE THERAPY															
Neu, 2014	RCT; parallel	43	4-12 wk	I-GERQ-R score ≥ 16	Yes	Yes	Yes	Yes	No	36/43	6 wk	Massage therapy (n=18)	Sham therapy (non-massage treatment)(n =18), intention to treat n=1	**I-GERQ-R scores** Intervention vs control Baseline: 22±4 vs 23.5±4 Wk 4: 15.0±4 vs 15.1±5 Wk 6: 14.4±4 vs 13.7±6 **Crying** Crying < 10 min: RR = 0.71 (95%CI 0.50-0.99) Crying < 1 h, < 3 h or > 3 h: RR = 1.00 **Distress (salivary cortisol)** Geometric mean 60% lower after 6 wks of treatment, adjusting for baseline (p=0.003). Hodges-Lehmann point estimate of	Weight Actigraphy Salivary Cortisol level (samples on 3 consecutive days at baseline and after 6 wk by mothers and at baseline, wk 4 and wk 6 by therapist) Maternal anxiety and depression

													between group difference: 18µgr.hr/dl (95% CI -44 to 9µgr.hr/dl, p=0.11)	

AA = antacid; AE = adverse event; CI = confidence interval; GER = gastroesophageal reflux; GERD = GER disease; I-GERQ-R = infant gastroesophageal reflux questionnaire revised; MD = mean difference; MD_{change} = change in mean difference; PPI = proton pump inhibitor; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event

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3.3. Uitgangsvraag 3 - Farmacologische therapie

Author	Design	Population			Cochrane Risk of Bias Tool						Dure	Intervention	Control	Outcome of interest	Outcome measures
		N	Age	Inclusion	Random sequence generation	Allocation concealment	Blinding intervention	Blinding outcome	Selective reporting	Follow-up					
ANTACID VS PLACEBO															
Miller (1999) (25)	RCT; parallel	90	4 ± 0.28 mo (3.9 ± 0.40 vs 4.1 ± 0.39)	Persistent , unmanageable vomiting/regurgitation or vomiting/regurgitation >2x day for 2 days prior to the start of the study	Not clear	Not clear	Not clear	Not clear	Yes	68/90	14 d	Sodium alginate (225mg sodium alginate and magnesium alginate 87.5mg) in a total 0.65g. One sachet/day (<4.54kg) or two sachet/day (>4.54kg) (n=42)	Matching placebo (n=48)	**Visible regurgitation/vomiting:** Number of vomiting/regurgitation episodes in 24 hours, intervention vs control (medians): Baseline; 8.5 (2-50) vs 7.0 (2-36) 14 days: 3.0 (0-22) vs 5.0 (0-37) Mean number of episodes, SD not reported (intervention vs control group) Baseline: 10.2 vs 10.6 Wk 2: 10.6 vs 6.2, p = 0.056 **Side effects - AEs** AE: 57% of patients >1 AE (55% vs 59%) . Withdrawal from study because of AE: 4/42 vs 7/46. SAE: 2/42 vs 2/46 (not related to treatment). No statistically significant differences in the incidence of these adverse events were observed between treatment groups (p>0.1 in all cases).	Frequency/cessation of regurgitation, patient reported improvement, safety analysis
ANTACID + SIMETHICONE VS NON-PHARMACOLOGICAL INTERVENTION (Feed thickeners/conservative treatment)															
Ummarino (2015) (18)	RCT; parallel	75	1-12 mo	Infant regurgitation according to ROME III	Yes	Not clear	Not clear	Yes	Yes	67/75	8 wk	Magnesium alginate aluminum-free formulation plus	Rice starch thickened (14.3g/100ml or 14.2g100ml for infants < 6 mo) + conservative	**I-GERQ-R scores** Symptom scores, A vs B vs C Baseline: 15 (8-24) vs 13 (8-19) vs 13 (7-10), p = 02 Wk 4: 7 (1-20) vs 10 (5-16) vs 12 (7-14), p = 0.2	I-GERQ-R scores, <7 no clinical symptoms Side effects reported in diary

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												simethicone, 2.5mL 3x/day (weight <5kg) or 5mL 3x/day (weight >5 kg), 10 minutes after feeding + conservative therapy (A, n=25)	therapy (A, n=25) Conservative therapy (=life style changes + reassurance) (A, n=25)	Wk 8: 1 (0-19) vs 5 (0-15) vs 8 (2-14), p =0.01 Median I-GERQ-R scores significantly lower in all groups (A p<0.002, B p<0.038, C p<0.03) 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 (A vs B p<0.002, A vs C p<0.0001). (no subscores provided) **Visible regurgitation/vomiting** Number of infants with regurgitation and vomiting, intervention vs thickened formula vs conservative treatment: Baseline = 25/25 vs 25/25 vs 25/25 4 wk = 21/25 vs 25/25 vs 17/17 8 wk = 6/24 vs 13/23 vs 15/17 **Side effects (reported in diary)** No SAEs reported. AEs: 1/25 patients in group A presented with constipation	

AE = adverse event; CI = confidence interval; GER = gastroesophageal reflux; GERD = GER disease; I-GERQ-R = infant gastroesophageal reflux questionnaire revised; MD = mean difference; MD_{change} = change in mean difference; NS = not significant; PPI = proton pump inhibitor; RCT = randomized controlled trial; RI = reflux index; RR = relative risk; SAE = serious adverse event.

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Author	Design	Population			Cochrane Risk of Bias Tool						Dure	Intervention	Control	Outcome of interest	Outcome measures
		N	Age	Inclusion	Random sequence generation	Allocation concealment	Blinding intervention	Blinding outcome	Selective reporting	Follow-up					
LANSOPRAZOLE															
Orenstein (2009) (26)	RCT; parallel	162	16, 4-51 wks	Infants with symptomatic GERD who remained symptomatic with crying, fussing or irritability during/within 1 hour after feeding despite at least 1 wk conservative non-pharmacologic management (1-2 wks before randomization)	Yes	Yes	Yes	Not clear	Yes	96/162	4 wks	Lansoprazole 0.2-0.3mg/kg day for infants ≤10 wks and 1.0-1.5mg/kg/day for infants >10 wks (n=49)	Placebo formulated identically dosed comparably (n=47)	**Side effects – (S)AEs** Intervention vs control AE: 50 (62%); (46%); p = 0.058 SAE: 10 (12%); 2 (2%); p = 0.032 **Crying/distress** Intervention vs control - Percentage of feeds Baseline: 51.0 ± 20.39 vs 52.4 ± 20.46 4 wk: 31.0 ± 25.41 vs 32.4 ± 28.13 Change: -19.9 ± 23.10 vs -19.9 ± 23.83 (p=0.794) - Mins postfeed Baseline: 7.9 ± 6.05 vs 9.0 ± 7.25 4 wk: 4.3 ± 5.52 vs 4.9 ± 6.20 Change: -3.6 ± 5.4 vs -4.1 ± 6.63 (p=0.830) Mins/ day Baseline: 47.0 ± 37.30 vs 55.4 ± 46.11 4 wk: 22.1 ± 29.96 vs 27.6 ± 36.57 Change: -25.0 ± 31.86 vs -27.8 ± 41.41 (p=0.963) **Visible regurgitation/vomiting:** % of feeds with regurgitation per wk Mean (ie, averaged across infants) change from	Primary endpoint: efficacy scores (not assessed by I-GERQ-R), total scores and individual domains

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														pretreatment baseline, intervention vs control group: -14% vs -10% (NS)	
ESOMEPRAZOLE															
Loots (2014) (27)	RCT; parallel	57	13.6 (2-26) wks	GERD symptoms > 5 days or increasing in frequency or severity for 3 days	Yes	Not clear	No	Not clear	Yes	51/57	2 wks	Esomeprazole 1mg/kg/day 1x/day 2 hrs postprandially (all infants received positioning therapy, ie LLP or head of cot elevation to 20 degrees; (HE)n=12 in LLP, n=14 in HE)	Antacid Mylanta, 1.5 (0-2mo), 3 (2-4 mo) or 6mL (4-6mo) once daily (all infants received positioning therapy, ie LLP or head of cot elevation to 20 degrees; n=13 in LLP, n=12 in HE)	**Crying/distress** <u>- In infants in LLP, PPI vs AA</u> 1. Total crying time (mins) Baseline: 92 ±24.2 vs 106 ± 68.5 2 wk: 92 ± 34.6 vs 88 ± 36.1 (difference: -1 ± 24.2 vs -17 ± 64.9) 2. No of cry Baseline: 48 ± 31.2 vs 60 ± 43.3 2 wk: 48 ± 27.7 vs 54 ± 32.4 (difference: 5 ± 17.3 vs -7 ± 46.9) <u>- In infants in HE, PPI vs AA</u> 1. Total crying time (mins) Baseline: 71 ± 41.2 vs 74 ± 69.4 2 wk: 81 ± 37.4 vs 66 ± 45.0 (difference: 9 ± 37.7 vs -8 ± 45.0) 2. No of cry Baseline: 30 ± 26.2 vs 38 ± 34.6 2 wk: 49 ± 26.2 vs 35 ± 24.2 (difference: 17 ± 37.4 vs -5 ± 34.6) **Side effects – AEs** 5 AEs (not specified what treatment arm) 2 SAEs in PPI + HE group: 1 hospital admission for rota virus 1 hospital admission for reduced oral intake + weight loss	I-GERQ-R GER monitoring (pH-MII) Gastric emptying Physiological monitoring
Davidson (2013) (28)	RCT; parallel	52	48.1 ± 29.8 vs 46.5 ± 31.2 days	Suspected of having any two of (after 8h video monitoring): apnea with or without bradycardia and with or without oxygen	Yes	Yes	Not clear	Not clear	No	51/52	2 wks	Esomeprazole 0.5mg/kg in 2ml/kg of sodium bicarbonate solution (n=25)	Placebo, not further specified, 0.5mg/kg in 2ml/kg of sodium bicarbonate solution (n=26)	**Crying/irritability** No of events, intervention vs control Baseline: 88.87 ± 24.71 vs 89.46 ± 22.71 2 wk: 88.83 ± 19.84 vs 88.85 ± 20.18 Change from baseline: -0.05 ± 17.27vs -0.61 ± 22.85 **Side effects – AEs**	Change from baseline in total GERD symptoms (video recording) and GERD-related signs (cardiorespiratory monitoring. Secondary: mean difference in change of signs and symptoms, pH-metry, adverse

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				desaturations, vomiting or gagging, and irritability or pain >1x every second feed or >2x in 8 hours									Intervention group: 6 patients experienced 10 AEs, no SAEs Placebo group: 9 patients experienced 14 AEs, 4 SAEs **Visible regurgitation/vomiting:** Number of vomiting, 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 wks: MD: 0.34 (95%CI -3.15 - 3.83) MD_{change}: -1.28 (95%CI -4.42 - 1.86)	events, laboratory assessment
Winter (2012) (29)	RCT; parallel	80	4.9 ± 2.6 vs 4.9 ± 3.2 mo	GERD suspected based on symptoms or endoscopically proven. >1 of symptoms of (extra-esophageal) GERD (vomiting/regurgitation, irritability, [cough, wheezing and/or stridor, labored breathing], respiratory symptoms triggered by feeding, feeding difficulties [food refusal, gagging/ choking, hiccups for >1 hour/day]) > 2x/wk in 4-wks	Yes	Not clear	Yes	Not clear	Yes	77/80	4 wks	Esomeprazole 2.5mg (weight 3-5kg), 5mg (weight 5-7.5kg), 10mg (weight 7.5-12kg) once a day (n= 39)	Placebo, sachets containing inactive granulate dissolved into water (n=41)	**Crying/irritability** Mean (SD) change from baseline in symptom score. Esomeprazole vs placebo: 0.06 ± 0.58 vs 0.19 ± 0.59 (no mean scores provided) **Visible regurgitation/vomiting:** Severity score (0-3, 3 = most severe). Mean ± SD, change from baseline in symptom score, intervention vs control group: 0.04 ± 0.56 vs 0.09 ± 0.61. Change in mean difference at 4 wks: MD_{change}: = -0.13 (95%CI -0.39 – 0.13) **Side effects – (S)AEs** Esomeprazol vs placebo: AE: 23/39 vs 27/41 patients, NS SAE: 4/39 vs 1/41	Time from randomization to discontinuation Treatment success Daily symptoms PGA symptom severity Safety and tolerability

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RABEPRAZOLE														
Hussain (2014) (30)	RCT; parallel	268	4.7 ± 2.54 vs 4.7 ± 2.65 mo	GERD: recurrent vomiting or regurgitation in infants unresponsive to conservative interventions, and >1 of: poor weight gain as defined by failure to thrive; irritability, excessive crying, or disturbed sleep, or refusal to eat even if hungry, or arching back at meals. During screening, score >16 on I-GERQ-R within 6 days of the first dose	Not clear	Not clear	Not clear	Not clear	Yes	231/268	5 wks	Rabeprazole 5mg/day (A, n=90) or 10mg/day (B, n=88)	Placebo (C, n=178)	**I-GERQ-R score** Data only displayed in figure, insufficient information to calculate manually. No data on subscores. **Side effects – AEs** Intervention vs control AE: no infants > 1 TEAE reported: 47% vs 47% SAE: 4.5% vs 2.2% infants SAE **Visible regurgitation/vomiting:** Frequency of regurgitation, no data reported, authors report results as non-significantly different.	- Frequency of regurgitation - Weight for age z-score - I-GERQ-R weekly score - I-GERQ-R daily score - Adverse events
OMEPRAZOL														
Zohalinezhad (2015)(25)	RCT; parallel	89	0-18 yrs 67.66 (7-216)	At least two of the following symptoms at least for one month, without improvement with routine	Yes	Yes	Yes	Yes	Yes	79/89	7 wks	Omeprazole (syrup) 1 ml/kg/day	Quince syrup 0,6 ml/kg/day	Composed clinical score (by authors). Questionnaires to assess frequency and severity of symptoms:	**Infants and young children (<60 months)** **Visible vomiting/regurgitation** Omeprazole vs

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			mo.	treatments: • vomiting • restlessness • apnea and respiratory disstress • poor weight gain • refusal to eat Also, patients with endoscopic results that proved GERD									1-11 mo. GSQ-I 1-4 yr. GSQ-YC 5-18 yr. GASP-Q Parents indicated the frequency of the symptoms and rate them from 1 (not too severe) – 7 (very severe) Safety via AEs and physical examination, laboratory determinations and vital sign measurements	Quince, individual symptom scores ± (SD) Baseline: 18.87 ± (49.50) vs 18.33 ± (34.92) 4 wks: 6.50 ± (24.43) vs 5.14 ± (12.81) 7 wks: 6.38 ± (24.44) vs 2.36 ± (6.70) **Irritability** Omeprazole vs Quince, individual symptom scores ± (SD) Baseline: 14.12 ± (19.80) vs 18.09 ± (41.10) 4 wks: 12.93 ± (24.95) vs 10.21 ± (25.70) 7 wks: 16.33 ± (38.08) vs 2.97 ± (9.59) **Older children and adolescences (60-216 mo.)**

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															Visible vomiting/regurgitation Omeprazole vs Quince, individual symptom scores ± (SD) Baseline: 1.95 ± (3.90) vs 1.77 ± (3.20) 4 wks: 0.67 ± (1.71) vs 3.06 (11.48) 7 wks: 2.04 ± (10.00) vs 0.02 ± (0.09) **Irritability** Omeprazole vs Quince, individual symptom scores ± (SD) Baseline: 27.04 ± (59.20) vs 10.05 ± (26.20) 4 wks: 9.36 ± (25.26) vs 1.04 ± (1.94) 7 wks: 0.00 vs 0.17 ± (0.53) **Chest pain/heartburn** Omeprazole vs Quince, individual symptom scores ± (SD) Baseline: 4.30 ± (6.96) vs 21.94 ± (35.92) 4 wks: 1.81 ± (7.08) vs 3.15 ± (8.25) 7 wks: 5.87 ± (22.80) vs 3.49 ± (7.07)
Moore (2003) (31)	RCT; cross-over	34	5.4 ± 2.1 mo	Significant GER, RI>5% or esophagitis	Not clear	Not clear	Yes	Not clear	Yes	30/34	4 wks	Omeprazole 10mg 1x/day (5-10kg) or 10mg 2x/day	Placebo identical appearance to omeprazole	**Crying/distress** Intervention vs control, Period 1 after 2 wks, period 2 after 4 wks (no wash-out period between	Infant behavior monitored by Barr diary and VAS

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												(>10kg)		treatments) 1. Cry/fuss mins per 24 hours - Baseline: 246 ±105 vs 287 ± 132 (p=0.481) - Period 1: 203 ± 113 vs 204 ± 87 (p=0.604) - Period 2: 179 ± 129 vs 198 ± 115 (p=0.534) Independent from treatment, baseline vs period 1, p=0.040 and vs period 2, p=0.008 2. VAS for irritability - Baseline: 7.1 ± 1.4 vs 6.6 1.7 (p=0.262) - Period 1: 5.9 ± 2.6 vs 6.0 ± 2.1 (p=0.724) - Period 2: 4.0 ± 3.3 vs 5.7 ± 2.2 (p=0.105) Independent from treatment, baseline vs period 2, p=0.008, vs period 1 p=NS) **Side effects – AEs** No AEs encountered	
PANTOPRAZOL															
Winter (2010) (32)	RCT; parallel	106	5.15 ± 2.81 vs 5.04 ± 2.81 mo	I-GERQ-R > 16 at screening and baseline and a clinical diagnosis of suspected, symptomatic or endoscopically proven GERD	Not clear	Not clear	Not clear	Not clear	Yes	86/106	4 wks	Pantoprazole 1.2mg/kg/day (5 mg/day for infants 2.5-7 kg, or 10 mg/day for infants 7-15 kg)	Placebo, not further specified	**Crying/distress** Mean (SD) change from base line vs wk 4 Intervention group 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 group vs control group -0.49 ± 0.57 (p<0.001 vs baseline) vs -0.64 ± 0.72 (p<0.001 vs baseline) (no baseline and end of treatment scores provided)	Withdrawal rate due to lack of efficacy, frequency of GERD symptoms, safety via AEs

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														Visible regurgitation/vomiting: Number of vomiting, 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 wks: MD_{change} : -0.04 (95% CI -0.27 - 0.19) Change in mean difference at 8 wks: MD_{change} : -0.14 (95% CI -0.44 - 0.16) **Side effects – (S)AEs** Data on AEs not sufficient, only AEs described reported in >3% of patients, so no total numbers provided SAE: 8 patients had 1 or 2 serious AEs during the study, of which 5 occurred during treatment with pantoprazole (all considered treatment unrelated)	
OMEPRAZOL VS RANITIDINE															
Azizollahi (2016) (28)	RCT; parallel	76	2-12 mo.	Infants with a GSQ of more than 16 at screening and baseline, and remain symptomatic after receiving 2 weeks of	Yes	Yes	Not clear	Not clear	Yes	60/76	2 wks	Omeprazole capsule 0,5 mg/kg/day (n=30)	Ranitidine syrup 2-4 mg/kg/day (n=30)	Daily form with questions completed bij parents, assessing the frequency of five key GERD symptoms: • vomting/regurgitation • irritability/fussiness • choking/gagging • arching back • refusal to feed.	**Visible vomiting/regurgitation** Omeprazole vs Ranitidine, change from baseline. 1 wk: 21.74-32.21 vs

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				standard treatment of GERD									Physical examinations at study visits Safety via AE reported by parents	17.25-24.53 2 wks: 5.01-11.15 vs 7.5-13.6 (P=0.019) No baseline scores provided. **Crying/irritability** Omeprazole vs Ranitidine, change from baseline. 1 wk: 7.8-12.8 vs 8.20-14.32 2 wks: 1.8-6.5 vs 2.5-6.8 No baseline scores provided **AE** No AEs were reported
Ummarino, 2012	RCT; parallel	35	40.6 ± 36.4 mo	GERD based on impact of symptoms on general well-being of the children and pH-MII results (SI>50% and SAP>95%); infants with manifestations	Not clear	Not clear	Not clear	Not clear	Yes	35/35	1 yr	Omeprazole 1.4mg/kg/day (n=19)	Ranitidine 15mg/kg/day (n=16)	**Crying/distress** Symptom score irritability (score 0-3, 3 = most severe) Intervention vs control 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) **Chest pain**	Remission of symptoms, not further specified in methods

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				of extra-esophageal GERD									Symptom score (score 0-3, 3 = most severe) 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 mo: MD: -0.51 (95%CI -1.62 – 0.60) **Side effects – AEs** No adverse events of treatment were reported	
Cucchiara, 1993	RCT; parallel	32	6 mo – 13.4 yrs	GOR based on 24h pH monitoring and endoscopy with histology, unresponsive to an antireflux treatment	Not clear	Not clear	Not clear	Not clear	Yes	25/32	8 wks	Omeprazole 40mg/day (n=13)	Ranitidine 20mg/kg/day (n=12)	**Endoscopy/histology:** Healing of esophagitis (score A – E; E = most severe; healing is return to score A or B) intervention vs control: 9/13 vs 9/12	Clinical score for GERD, pH-metry, endoscopy with histology
ESOMEPRAZOLE VS ANTACID															
Loots, 2014	RCT; parallel	57	13.6 (2-26) wks	GERD symptoms > 5 days or increasing in frequency or severity for 3 days	Yes	Not clear	No	Not clear	Yes	51/57	2 wks	Esomeprazole 1mg/kg/day 1x/day 2 hrs postprandially (n=12 in LLP, n=14 in HE)	Antacid, 1.5 (0-2mo), 3 (2-4 mo) or 6mL (4-6mo) once daily (n=13 in LLP, n=12 in HE)	**Crying/distress** <u>- In infants in LLP, PPI vs AA</u> 1. Total crying time (mins) Baseline: 92 ±24.2 vs 106 ± 68.5 2 wk: 92 ± 34.6 vs 88 ± 36.1 (difference: -1 ± 24.2 vs -17 ± 64.9) 2. No of cry Baseline: 48 ± 31.2 vs 60 ± 43.3 2 wk: 48 ± 27.7 vs 54 ± 32.4 (difference: 5 ± 17.3 vs -7 ± 46.9) <u>- In infants in HE, PPI vs AA</u> 1. Total crying time (mins) Baseline: 71 ± 41.2 vs 74 ± 69.4 2 wk: 81 ± 37.4 vs 66 ± 45.0 (difference: 9 ± 37.7 vs -8 ± 45.0) 2. No of cry Baseline: 30 ± 26.2 vs 38 ± 34.6	I-GERQ-R GER monitoring (pH-MII) Gastric emptying Physiological monitoring

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														2 wk: 49 ± 26.2 vs 35 ± 24.2 (difference: 17 ± 37.4 vs -5 ± 34.6) **Side effects – AEs** 5 AEs (not specified what treatment arm) 2 SAEs in PPI + HE group: 1 hospital admission for rota virus 1 hospital admission for reduced oral intake + weight loss	
LANSOPRAZOLE VS FEED INTERVENTION															
Khosho o, 2007	RCT; parallel	45	4.8 ± 1.18 vs 4.3 ± 1.01 vs 4.6 ± 0.99 mo (A vs B vs C)	Patients referred to pediatric gastroenterology clinic for evaluation and treatment of GERD, I-GERQ-R scores > 16 for 1 wk	Not clear	Not clear	No	No	Yes	45/45	2 wks	Lansoprazole 15mg once a day (A, n=15) or 7.5mg twice a day (B, n=15)	Extensively hydrolyzed formula (C, n=15), no placebo provided	**I-GERQ-R scores** Mean ± SD, Group A vs Group C Baseline: 26.6 ± 2.8 vs 25.9 ± 3.3 2 wks: 20.6 ± 4.2 vs 25.8 ± 3.2 (no subscores provided) Mean ± SD, Group B vs Group C Baseline: 26.9 ± 3.7 vs 25.9 ± 3.3 2 wks: 20.0 ± 3.3 vs 25.8 ± 3.2 **Side effects – AEs** - No clinical adverse reactions, no drop=outs	No other outcome measures assessed

AE = adverse event; CI = confidence interval; GER = gastroesophageal reflux; GERD = GER disease; HE = head elevation; I-GERQ-R = infant gastroesophageal reflux questionnaire revised; LLP = left lateral position; MD = mean difference; MD_{change} = change in mean difference; NS = not significant; PPI = proton pump inhibitor; RCT = randomized controlled trial; RI = reflux index; RR = relative risk; SAE = serious adverse event; SI = symptom index; SAP = symptom association probability; VA =visual analogue

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Author	Design	Population			Cochrane Risk of Bias Tool						Dure	Intervention	Control	Outcome of interest	Outcome measures
		N	Age	Inclusion	Random sequence generation	Allocation concealment	Blinding intervention	Blinding outcome	Selective reporting	Follow-up					
RANITIDINE															
Orenstein (2002) (33)	RCT; parallel	29	9.0 (4-11) (8.0 (4-11) vs 9.0 (7-11)) mo	Infants with a history of acid reflux symptoms over the previous 3 mo	Not clear	Not clear	Not clear	Not clear	No	29/29	6h	Ranitidine 75 mg, single dose (n=19)	Placebo, not further specified, single dose (n=10)	**Side effects – AEs** 12 patients experienced a total of 15 AEs. Ranitidine vs control: AEs: 12/19 patients vs 0/10 patients (timepoint not clear)	Pharmacokinetics and dynamics, Safety analysis
CIMETIDINE															
Cucchiara (1989) (34)	RCT; parallel	37	21.7 ± 37.65 vs 29.03 ± 39.73 mo	Established peptic reflux esophagitis, 18-24h intraesophageal pH monitoring, a drop of the distal esophageal pH <4.00 for >20 seconds	Not clear	Not clear	Yes	Not clear	Yes	32/37	12 wks	Cimetidine - 30 to 40 mg/kg/day three time a day after meals for 12 wks (n=17)	Placebo - 30 to 40 mg/kg/day three time a day after meals for 12 wks (n=15)	**Histologic/endoscopic healing** Cimetidine vs placebo Histological score (score 0-9; 9 = most severe) 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) Esophagitis (score mild-severe) Mild or moderate esophagitis: improved or healed: 9/9 vs 4/7(unchanged 3/7) Severe esophagitis: improved or healed: 7/8 vs 2/8 (unchanged or worsened 1/8 vs 6/8) **Side effects – AEs** No adverse events were reported	Clinical score, histological score, endoscopic healing
NIZATIDINE															

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Simeone (1997) (35)	RCT; parallel	26	2.08 (0.5- 12) vs 1.16 (0.5-9.5) yrs	Patients with reflux esophagitis	Not clear	Not clear	Not clear	Not clear	Yes	24/26	8 wks	Nizatidine 10mg/kg in a tablet of 150mg (n=13)	Matching placebo (n=13)	**Histologic/endoscopic healing** Esophagitis score (score 0-5; 5 = most severe) Nizatidine vs Placebo: Patients 'cured' based on endoscopy: 9/12 vs 2/13 Histologic improvement: 2/12 vs 3/13 Histologic unchanged: 1/12 vs 6/13 Histologic worsened: 0/12 vs 1/13. **Heartburn** Chest pain, pyrosis symptom score (score 0-3; 3 = most severe) intervention vs control 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)) **Visible regurgitation/vomiting:** Frequency score (score 0-3; 3 = most severe)severity of regurgitation, 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 wks: MD 4 wks : -0.90 (95%CI -1.86 - 0.06) MD 8 wks : -1.40 (95%CI -2.29 - -0.51) Severity of vomiting (score 0-3; 3 = most severe)	pH-metry, parental daily diary, endoscopy

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														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 wks: MD 4 wks : -1.30 (95%CI -2.10 - -0.50) MD 8 wks : -1.20 (95%CI -2.24 - -0.16) **Crying/distress** Abdominal colic (for infants) 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)) MD 4 wks : -0.80 (95%CI -1.64 – 0.04) MD 8 wks : -0.90 (95% CI -1.82 – 0.02)	
H2RA vs Alginate-antacid															
Oderda (1990) (36)	RCT; parallel	49	10 (2-15.5) vs 7.9 (2-15.8) yrs	Children with peptic esophagitis, > grade III or when grade I or II was seen esophagitis had to be histologically confirmed	Not clear	Not clear	Not clear	Not clear	No	47/49	6 mo	Famotidine 1mg/kg before supper at 7 or 8 pm (n= 25)	Alginate-antacid mixture, 30min after each meal and at bedtime (0.5gr alginic acid, 0.1gr allumium hydroxide, 0.025gr magnesium trisilicate and 0.17gr sodium bicarbonate)(n=2	**Histologic/endoscopic healing** Famotidine vs alginate-antacid Endoscopy (score 1-3; 3 = most severe): Healed: 10/24 vs 10/23 Improved: 8/24 vs 3/23 Unchanged: 5/24 vs 10/23 Worsened: 1/14 vs 0/23 Histology (mild – severe): Healed: 17/24 vs 12/23 (p<0.001 between groups)	Histologic/endoscopic healing, no other outcome measures

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													4)	Improved: 2/24 vs 6/23 Unchanged: 3/24 vs 3/23 Worsened: 2/24 vs 2/23	
Cucchiara (1984) (37)	RCT; parallel	33	8.9 (2-34) vs 9.4 (2-42) mo	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). GERD confirmed by endoscopy (esophagitis)	Not clear	Not clear	Not clear	Not clear	Yes	29/33	12 wks	Cimetidine syrup (20 mg/kg/day) (n=17)	liquid magnesium hydroxide and aluminum hydroxide in a dose of 700 mmol (mEq)/1 -73 ml/day, one and three hours after meals, and at bedtime. (n=16)	**Endoscopic/histologic healing** Symptom scores (score mild – severe), Cimetidine 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) (no data on	Clinical, pH-metry and endoscopic assessment
H2RA vs Sucralfate															
Martin (1989) (38)	RCT; parallel	75	6.1 ± 3.6 yrs	Gastroesophageal reflux symptoms and radiological diagnosis of reflux according to Cleveland criteria, and/or esophageal scintiscanning with a reflux index of >2.5% and endoscopic diagnosis of reflux esophagitis	Not clear	Not clear	Not clear	Not clear	Yes	75/75	8 wks	Cimetidine dissolved in water in two doses, daily dose 20mg/kg	1. Sucralfate tablets (<6 yrs: 0.5g 4x day, >6 yrs 1.0g 4x day) one half hour before meals and at bedtime 2. Sucralfate suspension (same dose and scheme)	**Endoscopic/histologic healing:** Cimetidine vs sucralfate tablets vs sucralfate suspension: Healed: 14/25 vs 14/25 vs 15/25 Improved: 7/25 vs 7/25 vs 7/25 Without change/worsened: 4/25 vs 4/25 vs 3/25. (no baseline scores provided; criteria for healing/improving not further specified) **Adverse events:** No adverse events reported by any of subjects.	Symptoms during the treatment, symptoms not further specified, no baseline data provided on symptom breakdown, no validated scoring tool used.

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H2RA vs Feed intervention														
Famouri (2017) (34)	RCT	50	< 1 yr (2.8 ± 2.5 vs. 3.4 ± 1.8 mo.)	Infants and children with suspected GERD I-GERQ-R score of >7	Not clear	Not clear	Not clear	Not clear	Yes	50/50	2 wk	Ranitidine 6 mg/kg daily in two divided doses	Hypoallergenic diet: a diet free oof milk and dairy products, cow's meat, penut, fish and soy	Symptoms were evaluated and recorded by a pediatrician at baseline and after intervention to determine the outcome of intervention. Symptoms were: • irritability • vomiting • anorexia • regurgitation • respiratory symptoms • arching	**Vomiting** Ranitidine vs. Hypoallergenic Diet. Baseline: 25/25 vs. 25/25 2 wks: 19/25 vs. 19/25 (p=0.01) **Irritability** Ranitidine vs Hypoallergenic Diet. Baseline: 23/25 vs 18/25 2 wks: 21/25 vs 15/25 (P<0.05)

AE = adverse event; CI = confidence interval; GER = gastroesophageal reflux; GERD = GER disease; I-GERQ-R = infant gastroesophageal reflux questionnaire revised; MD = mean difference; MD_{change} = change in mean difference; NS = not significant; PPI = proton pump inhibitor; RCT = randomized controlled trial; RI = reflux index; RR = relative risk; SAE = serious adverse event

Author	Design	Population	Cochrane Risk of Bias Tool	Dure	Intervention	Control	Outcome of interest	Outcome measures

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		N	Age	Inclusion	Random sequence generation	Allocation concealment	Blinding intervention	Blinding outcome	Selective reporting	Follow-up					
BACLOFEN															
Omari (2006) (39)	RCT; parallel	30	11.0 ± 1.0 vs 9.1 ± 1.1 yrs	Severe GERD, infants referred for further investigation who failed to improve after routine therapeutic measures (ie, parental reassurance, postural advice, feed thickeners, antacids, H2RAs, PPIs)	Not clear	Not clear	Not clear	Not clear	Yes	30/30	?	Baclofen 0.5 mg/kg (up to a maximum of 40 mg)	Placebo consisting of an equivalent volume of isotonic saline	**Side effects – AEs** Baclofen vs placebo Total AEs 9, 5 vs 4 breathlessness (n = 2; 1 vs 1); tiredness (n = 2; 1 vs 1), nausea (n = 1; baclofen group), sore nostril/throat (n = 4; 2 vs 2).	Gastric emptying, esophageal motility and reflux
DOMPERIDONE															
DeLoore (1997) (40)	RCT; parallel	30	Domperidone 9 mo (3wks – 4 yr); Placebo: 6 mo (1mth – 5 yr)	Clinical diagnosis of GER: pronounced vomiting after meals.	Not clear	Not clear	Not clear	Not clear	Yes	30/30	2 wks	Domperidone 0.3 mg kg^{-1} three times a day	Placebo three times a day	**Side effects** No AEs reported **Visible vomiting/regurgitation** Data only provided in figure and descriptively. No raw data provided. Authors report significant improvement of %patients vomiting in the domperidone vs placebo group (p<0.001).	Symptoms of nausea and vomiting rated by investigator. Evaluation of treatment success (excellent, good, moderate or poor; based on symptom improvement
Carroccio (1994) (41)	RCT; parallel	40	Domperidone: Age median 5 mo (range 1	GER confirmed by presence of at least 2 reflux episodes	No	Not clear	Not clear	Not clear	No	40/40	8 wks	Domperidone (0.3 mg/kg/dose 15 minutes before meal) and placebo,	two different preparations of placebo administered 1 and 3 hours after meals	**Side effects** No AEs reported	- 24-hour pH monitoring at baseline and 8 weeks (most of the children spent the monitoring period at home) - Reflux time - Number of reflux episodes

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			- 16 mo), Placebo: Age median 4 mo (range 1 - 16 mo)	during fluoroscopy and 24-hour pH monitoring (RI >5.2%)							administered 1 and 3 hours after meals (n=20)	(n=20)		- Duration of longest reflux (minutes) - Number of reflux episode > 5 minutes - Jolley score
METOCLOPRAMIDE														
Bellissant (1997) (42)	RCT; parallel	44	105 ± 74 (87 ± 67 vs 122 ± 79) days	GER determined by 24h pHmetry by percentage of time pH<4 >5% measurement	Not clear	Not clear	Not clear	Not clear	Yes	39/44	14 d	Metoclopramide 2.6mg/ml solution (0.1mg/drop), 2 drops 3x/day before a meal (n=20)	Placebo, not further specified (n=19)	**Side effects** Treatment discontinued due to side effect Metoclopramide vs placebo: 1/20 vs 3/19	pH-metry, weight, four-class qualitative evaluation of treatment efficacy by parents
DeLoore (1997) (40)	RCT; parallel	32	Metoclopramide: 6 mo (3wks – 8yr); Placebo: 6 mo (1mth – 5 yr)	Clinical diagnosis of GER: pronounced vomiting after meals.	Not clear	Not clear	Not clear	Not clear	Yes	32/32	2 wks	Metoclopramide 0.3 mg kg^{-1} three times a day	Placebo three times a day	**Side effects** No AEs reported **Visible vomiting/regurgitation** Data only provided in figure and descriptively. No raw data provided. Authors report significant improvement of %patients vomiting in the metcolopramide vs placebo group (p<0.001)	Symptoms of nausea and vomiting rated by investigator. Evaluation of treatment success (excellent, good, moderate or poor; based on symptom improvement)
Tolia (1989) (43)	RCT; cross-over	30	Median age 2 mo (range 1 – 9 mo)	pH probe confirmed GER, patients were only included if the pH result was abnormal during the initial 8 hours	Not clear	Not clear	Yes	Not clear	Yes	30/30	2 wks	Metoclopramide 0.1 mg/kg x4 per day 30 minutes before feeding for 1 week (n=15)	Identical vehicle to metoclopramide and prescribed in a volume equal to 0.1mg/kg/dose of active metoclopramide (n=15)	**Side effects** No side effects observed during either study period	RI, number of reflux episodes < 4, number of episodes > 5 minutes, daily report of all symptoms, gastric emptying rates
DOMPERIDONE VS METOCLOPRAMIDE														

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DeLoore (1997) (40)	RCT; parallel	32	Domperidone 9 mo (3wks – 4 yr); Metoclopramide: 6 mo (3wks – 8yr)	Clinical diagnosis of GER: pronounced vomiting after meals.	Not clear	Not clear	Not clear	Not clear	Yes	32/32	2 wks	Domperidone 0.3 mg kg^{-1} three times a day	Metoclopramide 0.3 mg kg^{-1} three times a day	**Side effects** No AEs reported **Visible vomiting/regurgitation** Data only provided in figure and descriptively. No raw data provided. Authors report significant improvement of %patients vomiting in the domperidone vs metoclopramide group ($p<0.05$)	Symptoms of nausea and vomiting rated by investigator. . Evaluation of treatment success (excellent, good, moderate or poor; based on symptom improvement

AE = adverse event; CI = confidence interval; GER = gastroesophageal reflux; GERD = GER disease; I-GERQ-R = infant gastroesophageal reflux questionnaire revised; MD = mean difference; MD_{change} = change in mean difference; NS = not significant; PPI = proton pump inhibitor; RCT = randomized controlled trial; RI = reflux index; RR = relative risk; SAE = serious adverse event

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REFERENTIES

1. Boix-Ochoa J, Lafuenta JM, Gil-Vernet JM. Twenty-four hour exophageal pH monitoring in gastroesophageal reflux. Journal of pediatric surgery. 1980;15(1):74-8.
2. Da Dalt L, Mazzoleni S, Montini G, Donzelli F, Zacchello F. Diagnostic accuracy of pH monitoring in gastro-oesophageal reflux. Archives of disease in childhood. 1989;64(10):1421-6.
3. Cucchiara S, Staiano A, Gobio Casali L, Boccieri A, Paone FM. Value of the 24 hour intraoesophageal pH monitoring in children. Gut. 1990;31(2):129-33.
4. Kahn A, Rebuffat E, Sottiaux M, Blum D, Yasik EA. Sleep apneas and acid esophageal reflux in control infants and in infants with an apparent life-threatening event. Biology of the neonate. 1990;57(3-4):144-9.
5. Cucchiara S, Bortolotti M, Minella R, Auricchio S. Fasting and postprandial mechanisms of gastroesophageal reflux in children with gastroesophageal reflux disease. Digestive diseases and sciences. 1993;38(1):86-92.
6. Ravelli AM, Villanacci V, Ruzzenenti N, Grigolato P, Tobanelli P, Klersy C, et al. Dilated intercellular spaces: a major morphological feature of esophagitis. Journal of pediatric gastroenterology and nutrition. 2006;42(5):510-5.
7. Patra S, Singh V, Chandra J, Kumar P, Tripathi M. Diagnostic modalities for Gastro-esophageal reflux in infantile wheezers. J Trop Pediatr. 2011;57(2):99-103.
8. Arasu TS, Wyllie R, Fitzgerald JF, Franken EA, Siddiqui AR, Lehman GA, et al. Gastroesophageal reflux in infants and children comparative accuracy of diagnostic methods. The Journal of pediatrics. 1980;96(5):798-803.
9. Farhath S, He Z, Saslow J, Soundar S, Amendolia B, Bhat V, et al. Detection of pepsin in mouth swab: correlation with clinical gastroesophageal reflux in preterm infants. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2013;26(8):819-24.
10. 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.
11. 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.
12. 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.
13. Iacono G, Vetrano S, Cataldo F, Ziino O, Russo A, Lorello D, et al. Clinical trial with thickened feeding for treatment of regurgitation in infants. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver. 2002;34(7):532-3.
14. 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.
15. 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.
16. 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.
17. 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.
18. 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.
19. 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.
20. Moukarzel AA, Abdelnour H, Akatcherian C. Effects of a prethickened formula on esophageal pH and gastric emptying of infants with GER. Journal of clinical gastroenterology. 2007;41(9):823-9.
21. 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.
22. 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.
23. Orenstein SR, Magill HL, Brooks P. Thickening of infant feedings for therapy of gastroesophageal reflux. The Journal of pediatrics. 1987;110(2):181-6.
24. 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.
25. 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.

26. 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.
27. 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.
28. 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.
29. Winter H, Gunasekaran T, Tolia V, Gottrand F, Barker PN, Illueca M. Esomeprazole for the treatment of GERD in infants ages 1-11 mo. Journal of pediatric gastroenterology and nutrition. 2012;55(1):14-20.
30. 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.
31. 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.
32. 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 mo old with symptomatic GERD. Journal of pediatric gastroenterology and nutrition. 2010;50(6):609-18.
33. 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.
34. 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.
35. 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.
36. 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.
37. 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.
38. 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.
39. 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.
40. 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.
41. Carroccio A, Iacono G, Montalto G, Cavataio F, Soresi M, Notarbartolo A. Domperidone plus magnesium hydroxide and aluminum hydroxide: a valid therapy in children with gastroesophageal reflux. A double-blind randomized study versus placebo. Scandinavian journal of gastroenterology. 1994;29(4):300-4.
42. 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.
43. 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.