

GASTRO-OESOPHAGEAL REFLUX

Supporting information

This guideline and supporting information has been prepared with reference to the following:

Anon. Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: recommendations of the North American Society for Pediatric Gastroenterology and Nutrition. *J Pediatr Gastroenterol Nutr* 2001;32(Suppl 2):S1-S31

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Does positioning have an effect on GOR?

A systematic review of randomised controlled trials (Carroll, 2002) quotes a controlled prospective study of 9 infants with GOR (Orenstein, 1983) which found that positioning at a 60 degree elevation in an infant seat increased reflux compared with the prone position. A later study by the same author (Orenstein, 1990) found no significant difference between the flat and head-elevated prone positions.

The "supine reversed-Trendelenburg sleeping position", recommended by some (Taminiau, 1997), was found to increase acid reflux parameters in all 10 consecutively investigated infants in a Belgian study (Bagucka, 1999).

A study of 18 preterm infants with GOR (Ewer, 1999) compared prone, left lateral and right lateral positions. Each position was used for 8 hours, with the order randomly assigned. The reflux index was significantly less in prone (6.3) and left lateral (11.0) positions compared to the right lateral (29.4). The left lateral position may be an acceptable alternative, in infants, to the prone position which has been associated with sudden infant death (Tobin, 1997; Vandenplas, 1997) and is recommended in US guidelines (Anon, 2001) for children older than one year. The effects of positioning have not been studied in children older than 1 year (Anon, 2001).

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Bagucka B, De Schepper J, Peelman M, et al. Acid gastro-esophageal reflux in the 10 degrees-reversed-Trendelenburg-position in supine sleeping infants. *Acta Paediatr Taiwan* 1999;40:298-301

Carroll AE, Garrison MM, Christakis DA. A systematic review of nonpharmacological and nonsurgical therapies for gastroesophageal reflux in infants. *Arch Pediatr Adolesc Med* 2002;156:109-13

Ewer AK, James ME, Tobin JM. Prone and left lateral positioning reduce gastro-oesophageal reflux in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1999;81:F201-5

Orenstein SR, Whittington PF, Orenstein DM. The infant seat as treatment for gastroesophageal reflux. *N Engl J Med* 1983;309:760-3

Orenstein SR. Prone positioning in infant gastroesophageal reflux: is elevation of the head worth the trouble? *J Pediatr* 1990;117:184-7

Taminiau JA. Gastro-oesophageal reflux in children. *Scand J Gastroenterol* 1997;2(Suppl 223):18-20

Tobin JM, McCloud P, Cameron DJ. Posture and gastro-oesophageal reflux: a case for left lateral positioning. *Arch Dis Child* 1997;76:254-8

Vandenplas Y, Belli DC, Dupont C, et al. The relation between gastro-oesophageal reflux, sleeping-position and sudden infant death and its impact on positional therapy. *Europ J Pediatr* 1997;156:104-6

Evidence Level: I (Against infant seats and head-elevation); II (for the use of the left lateral position)

Are thickened feeds of use for GOR?

Two systematic reviews of randomised controlled trials (Huang, 2004; Carroll, 2002;) found no statistically significant reduction in reflux with the use of thickened infant foods compared to placebo. One study in 24 infants (Borrelli, 1997) did, however, detect a significant benefit of formula thickened with carob bean gum compared with rice flour (pH<4 for 5% vs 8% of time). This was replicated by a later study in 14 infants (Wenzl, 2003). Another study in 19 infants (Sutphen, 1989) showed that supplementing with dextrose 5% water was associated with less reflux than dextrose 10% water.

US guidelines (Anon, 2001) note that, although thickened feeds do not improve reflux index scores, they do decrease the number of episodes of vomiting. A study in 30 formula-fed babies (Vandenplas, 1987) found little change in the reflux index (17.8% vs 18.4%) after 7-14 days of thickened feeds, but in 24 infants a decrease in the number of reflux episodes in 24 hours (15.1 vs 34.5). The duration of the longest recorded episode did, however, increase from 23.3 min to 56.6 min, leading the authors to warn against possible protracted episodes of occult GOR.

Two similar studies, in 20 (Orenstein, 1987) and 52 infants respectively (Bailey, 1987) also came to the same conclusion.

A double-blind, randomised trial in 104 infants (Vanderhoof, 2003) found that a pre-thickened formula (Enfamil AR) was associated with greater symptom reduction by one week compared to placebo: % feedings with any regurgitation (p=0.045), total regurgitation volume score (p=0.035), and % feedings with choke/gag/cough (p=0.004). Sleep was improved in those infants with most symptoms at baseline (p=0.030).

The ESPGHAN Committee on Nutrition recommends that thickened feeds should be used only in selected infants with failure to thrive caused by excessive nutrient losses associated with GOR, and also points out that antireflux milk products “usually do not meet the European Union’s compositional standards for infant formula” (Aggett, 2002).

A randomised controlled trial in 96 formula-fed infants (Xinias, 2005) compared a group given standard formula (n=45) with a group given formula thickened with cornstarch/casein (n=51) for 28 days. In the cornstarch group, the percentage of time with a pH < 4.0, number of reflux episodes > 5 min and duration of the longest reflux episode all decreased significantly whilst remaining unchanged in the standard formula group.

Aggett PJ, Agostoni C, Goulet O, et al. Antireflux or antiregurgitation milk products for infants and young children: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2002;34:496-8

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Borrelli O, Salvia G, Campanozzi A, et al. Use of a new thickened formula for treatment of symptomatic gastroesophageal reflux in infants. *Dig Liver Dis* 1997;29:237-42

Carroll AE, Garrison MM, Christakis DA. A systematic review of nonpharmacological and nonsurgical therapies for gastroesophageal reflux in infants. *Arch Pediatr Adolesc Med* 2002;156:109-13

Huang RC, Forbes DA, Davies MW. Feed thickener for newborn infants with gastro-oesophageal reflux (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.

Orenstein SR, Magill HL, Brooks P. Thickening of infant feedings for therapy of gastroesophageal reflux. *J Pediatr* 1987;110:181-6

Sutphen JL, Dillard VL. Dietary caloric density and osmolality influence gastroesophageal reflux in infants. *Gastroenterology* 1989;97:601-4

Vandenplas Y, Sacre L. Milk-thickening agents as a treatment for gastroesophageal reflux. *Clin Pediatr* 1987;26:66-8

Vanderhoof JA, Moran JR, Harris CL, et al. Efficacy of a pre-thickened infant formula: a multicenter, double-blind, randomized, placebo-controlled parallel group trial in 104 infants with symptomatic gastroesophageal reflux. *Clin Pediatr* 2003;42:483-95

Wenzl TG, Schneider S, Scheele F, et al. Effects of thickened feeding on gastroesophageal reflux in infants: a placebo-controlled crossover study using intraluminal impedance. *Pediatrics* 2003;111:e355-9

Xinias I, Mouane N, Le Luyer B, et al. Cornstarch thickened formula reduces oesophageal acid exposure time in infants. *Dig Liver Dis* 2005;37:23-7

Evidence Level: I (for reduced vomiting)

Is Gaviscon of use in GOR?

A randomised study on 20 infants and children (Buts, 1987) compared Gaviscon with placebo (10 patients in each group). After 8 days of treatment with Gaviscon, all pH monitoring variables were significantly reduced between -35% and -61% of initial recorded values. In the placebo group, mean values changed little (-9.5 - +8.2 of initial values). Reported episodes of regurgitation were also reduced in the Gaviscon group compared to no change in the placebo group.

A randomised, parallel group study conducted on 50 infants with GOR (Greally, 1992) compared Gaviscon plus Carobel (carob seed flour) with oral cisapride (0.8 mg/kg/day over one month). 14 of 26 in the cisapride group (53%) were considered "better" by their parents, compared with 19 of 24 (79%) in the Gaviscon/Carobel group. 5 of 17 pH variables improved from baseline in the cisapride group compared to 11 of 17 given Gaviscon plus Carobel. Despite this, unpaired analysis of diary and pH data showed no significant difference between the groups. The authors concluded that cisapride was no more effective than Gaviscon plus Carobel.

A third randomised study comparing gaviscon and metoclopramide (Forbes, 1986) found that neither decreased the frequency or duration of GOR. Gaviscon 100mg/20 ml feed is recommended in a review of GOR (Taminiau, 1997). A double-blind, non-randomised study in 20 infants (Del Buono, 2005) compared the effects of 6 random administrations of Gaviscon Infant (625 mg in 225 ml milk) with placebo (mannitol and Solvito N, 625 mg in 225 ml milk). There was no significant difference between Gaviscon and placebo in terms of median number or duration of reflux/acid reflux events per hour, nor in minimum distal/proximal pH or total acid clearance time per hour.

Buts JP, Barudi C, Otte JB. Double-blind controlled study on the efficacy of sodium alginate (Gaviscon) in reducing gastroesophageal reflux assessed by 24 h continuous pH monitoring in infants and children. *Europ J Pediatr* 1987;146:156-8

Del Buono R, Wenzl TG, Ball G, et al. Effect of Gaviscon Infant on gastro-oesophageal reflux in infants assessed by combined intraluminal impedance/pH. *Arch Dis Child* 2005;90:460-3

Forbes D, Hodgson M, Hill R. The effects of gaviscon and metoclopramide in gastroesophageal reflux in children. *J Pediatr Gastroenterol Nutr* 1986;5:556-9

Greally P, Hampton FJ, MacFayden UM, et al. Gaviscon and Carobel compared with cisapride in gastro-oesophageal reflux. *Arch Dis Child* 1992;67:618-21

Taminiau JA. Gastro-oesophageal reflux in children. *Scand J Gastroenterol* 1997;2(Suppl 223):18-20

Evidence Level: II

Is domperidone of use in GOR?

A double-blind, randomised, placebo-controlled study in 80 children with GOR (Carroccio, 1994) found that symptoms resolved completely in 16 of 20 receiving domperidone plus magnesium hydroxide and aluminium hydroxide. This compared with 8 of 20 given domperidone plus alginate, 9 of 20 given domperidone alone, and 7 of 20 given a placebo. Similar results were achieved in an earlier study by the same team (Iacono, 1991) which compared only the first two groups of the later study. Percentage reflux time was significantly reduced only in the first group.

A double-blind, placebo-controlled trial of domperidone in 17 children (Bines, 1992) found that treatment was necessary for 8 weeks before significant improvement occurred in measures of reflux other than number of episodes in the 2 hour postprandial period.

The efficacy of domperidone in children is currently considered to be “unproven” (Cezard, 2004; Anon, 2001; Brown 2000).

A systematic review of 4 RCTs (Pritchard, 2005) concluded that “there was no robust evidence of efficacy for the treatment of GOR with domperidone in young children. Given the usually benign nature of the condition, the widespread use of unlicensed medicines for GOR is not warranted.”

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Bines JE, Quinlan JE, Treves S, et al. Efficacy of domperidone in infants and children with gastroesophageal reflux. *J Pediatr Gastroenterol Nutr* 1992;14:400-5

Brown P. Medical management of gastroesophageal reflux. *Curr Opin Pediatr* 2000;12:247-50

Carroccio A, Iacono G, Montalto G, et al. Domperidone plus magnesium hydroxide and aluminium hydroxide: a valid therapy in children with gastroesophageal reflux. A double-blind randomized study versus placebo. *Scand J Gastroenterol* 1994;29:300-4

Cezard JP. Managing gastro-oesophageal reflux disease in children. *Digestion* 2004;69(suppl 1):3-8

Iacono G, Carroccio A, Cavataio F, et al. Severe gastroesophageal reflux in children: effectiveness of different combinations of drugs. *Curr Ther Res Clin Exp* 1991;50:474-81

Pritchard DS, Baber N, Stephenson T. Should domperidone be used for the treatment of gastro-oesophageal reflux in children? Systematic review of randomized controlled trials in children aged 1 month to 11 years old. *Br J Clin Pharmacol* 2005;59:725-9

Evidence Level: II

Is ranitidine/cimetidine plus a proton pump inhibitor of use in relieving oesophagitis caused by GOR?

A randomised, double-blind trial in 32 children with reflux oesophagitis (Cucchiara, 1989) compared cimetidine 30-40 mg/kg/day (n=17) with placebo (n=15) over a 12 week period. 12 patients in the cimetidine group were healed compared to 3 in the placebo group.

Ranitidine is considered as first-line treatment for children with severe oesophagitis and case series have shown successful healing in 75-95% of children aged 3 months to 16 years given 6-8 mg/kg/day for 8 weeks (Kelly, 1994). A dose of 2mg/kg twice daily in infants has been shown to reduce the time that gastric pH was <4 by 44% (Sutphen, 1989). With thrice daily dosing the reduction was 90%. The increased gastric pH effect has been shown to last 9-10 hours in infants (Mallet, 1989).

Although there have been no RCTs of ranitidine for oesophagitis in children, expert opinion considers it as effective as cimetidine (Anon, 2001).

A study of 15 children with severe reflux given omeprazole when H₂ antagonists and prokinetics had failed (Gunasekaran, 1993) found that doses of between 10mg and 60mg daily were needed to normalise oesophageal pH. A similar study in 12 infants (Alliet, 1998) found that omeprazole 0.5mg/kg/day for 6 weeks resulted in complete resolution in 9 and improvement in the other 3. 6 out of 10 patients who responded well to omeprazole in doses of 20-40mg/day relapsed when therapy was discontinued after 3 months, raising the possibility that long-term treatment may be necessary (De Giacomo, 1997).

Although administering H₂RAs and PPIs together can inhibit the efficacy of the latter (Anon, 2001), "step-up" therapy, in which treatment begins with an H₂RA at standard dosage, followed by a PPI at standard dosage and then a PPI at higher dosage if necessary, is effective (Gunasekaran, 1993). "Step-down" therapy, which is the reverse approach, has been recommended for adults (Dent, 1999) but the two approaches have not been compared in children.

A randomised controlled trial of famotidine in 35 infants (Orenstein, 2003) found significant improvements in regurgitation frequency (p=0.04) and volume (p=0.01), and crying time (p=0.027) when compared to placebo.

Although no randomised controlled trials on the use of PPIs in children have yet been carried out (Rudolph, 2003), a double-blind, placebo-controlled trial in 30 infants

(Moore, 2003) that did not use randomisation found that omeprazole resulted in a significant fall in the reflux index (-8.9% +/- 5.6% vs -1.9% +/-2.0, p<.001).

Alliet P, Raes M, Bruneel E, et al. Omeprazole in infants with cimetidine-resistant peptic esophagitis. *J Pediatr* 1998;132:352-4

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De Giacomo C, Bawa P, Franceschi M, et al. Omeprazole for severe reflux esophagitis in children. *J Pediatr Gastroenterol Nutr* 1997;24:528-32

Dent J, Brun J, Fendrick AM, et al. An evidence-based appraisal of reflux disease management: the Genval Workshop report. *Gut* 1999;44(Suppl 2):S1-S16

Gunasekaran TS, Hassall EG. Efficacy and safety of omeprazole for severe gastroesophageal reflux in children. *J Pediatr* 1993;123:148-54

Kelly DA. Do H2 receptor antagonists have a therapeutic role in childhood? *J Pediatr Gastroenterol Nutr* 1994;19:270-6

Mallet E, Mouterde O, Dubois F, et al. Use of ranitidine in young infants with gastro-oesophageal reflux. *Eur J Clin Pharmacol* 1989;36:641-2

Moore DJ, Tao BS, Lines DR, et al. Double-blind placebo-controlled trial of omeprazole in irritable infants with gastroesophageal reflux. *J Pediatr* 2003;143:219-23

Orenstein SR, Shalaby TM, Devandry SN, et al. Famotidine for infant gastro-oesophageal reflux: a multi-centre, randomized, placebo-controlled, withdrawal trial. *Aliment Pharmacol Ther* 2003;17:1097-107

Rudolph CD. Are proton pump inhibitors indicated for the treatment of gastroesophageal reflux in infants and children? *J Pediatr Gastroenterol Nutr* 2003;37(Suppl 1):S60-S64

Sutphen JL, Dillard VL. Effect of ranitidine on twenty-four-hour gastric acidity in infants. *J Pediatr* 1989;114:472-4

Evidence Level: II

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