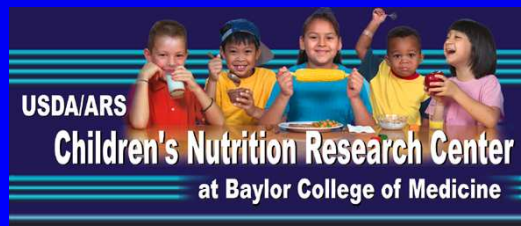


Reflujo gastroesofágico, llanto, cólicos infantiles ¿son enfermedades?

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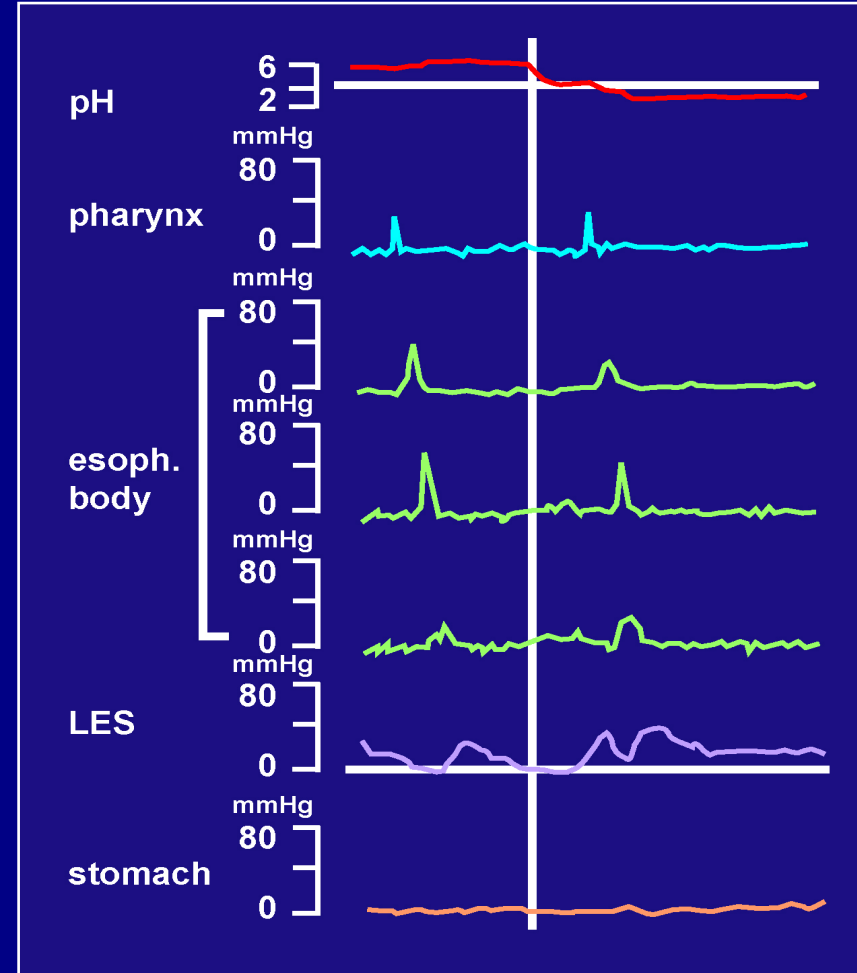
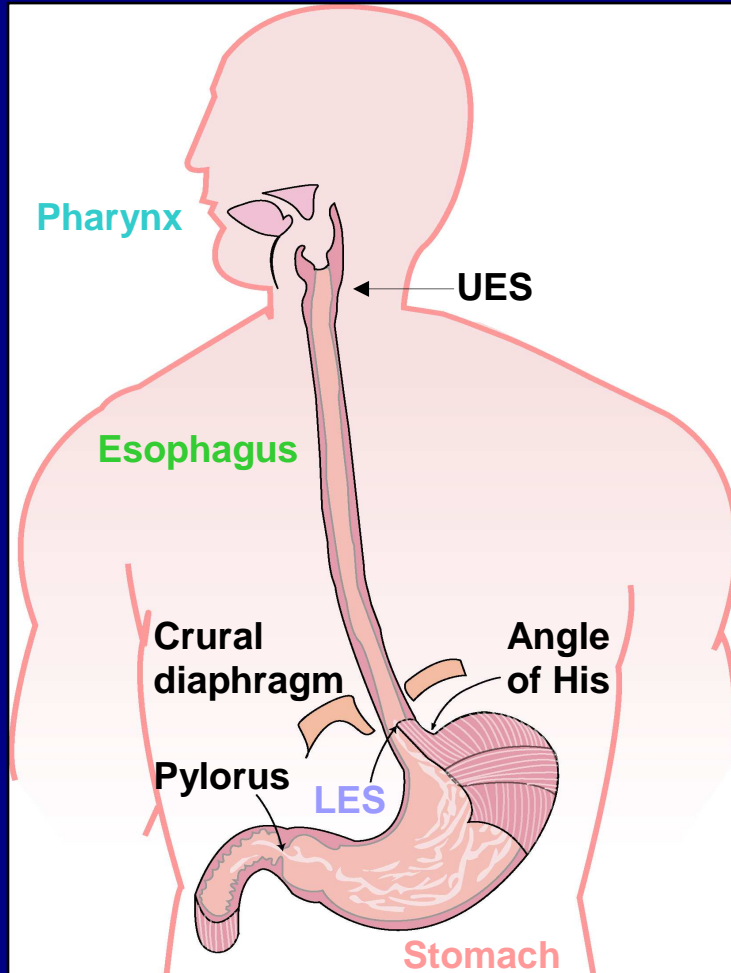
Medical Director, Europe Mead Johnson Nutritional



GER

- ❑ Effortless passage of stomach contents into the esophagus
- ❑ May or may not be symptomatic, depending on acidity of reflux
- ❑ Accounts for approximately 20% of Pedi-GI referrals
- ❑ Fundoplication is the most common major surgical procedure in children

Transient LES Relaxations



Tracings reprinted from Kawahara et al, *Gastroenterology* 1997;113:399



Normal Reflux

5 episodes/hr < 2 hr postprandial

Reflux +++ in upright in normals (sudden pH drop, stepwise return)

Rarely reflux while asleep (50% gradual drift)

Δ prone \rightarrow supine GER \uparrow x 7

Vandenplas J Ped Gas Nut 85;4:356

Functional GER ("Infantile", "Physiologic")

Begins before 3 months of age

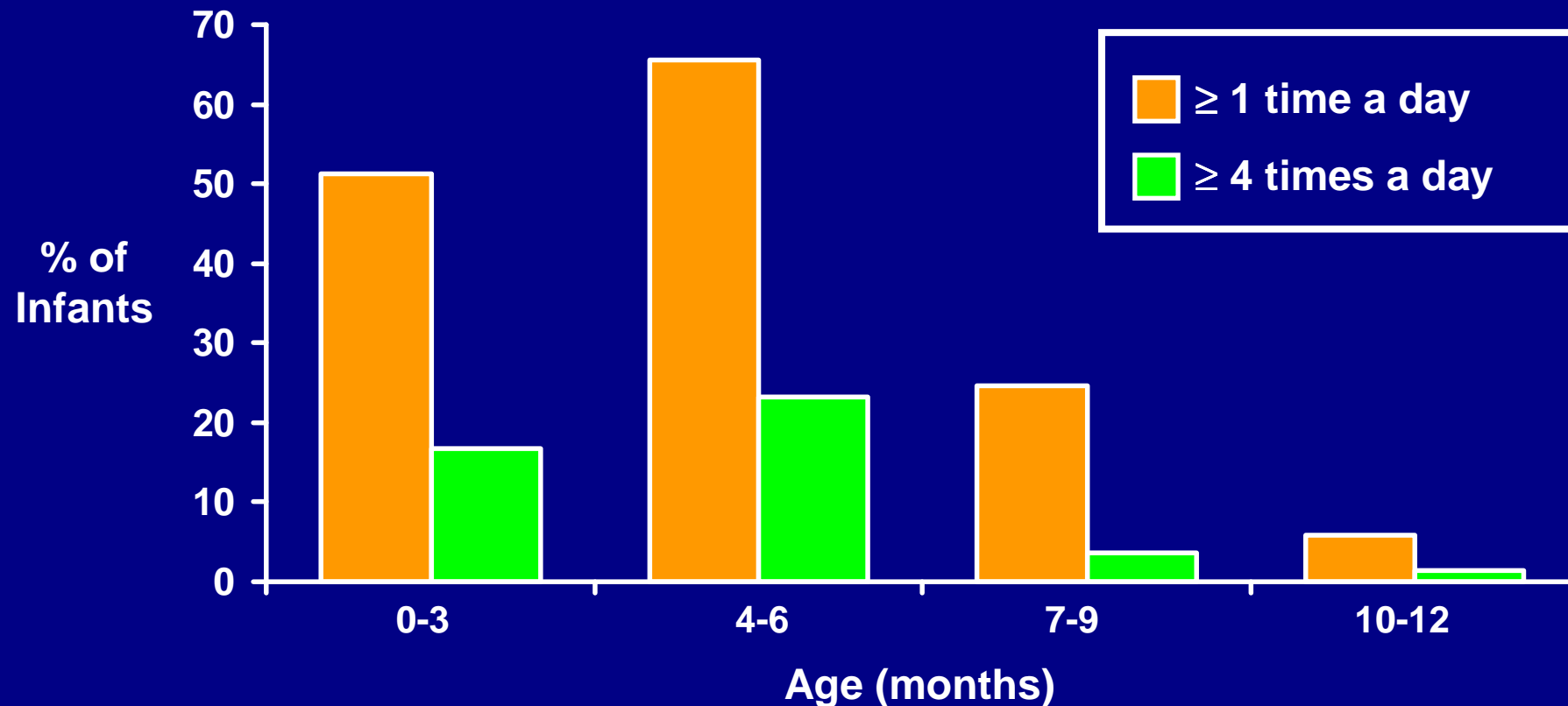
Not during sleep

Normal growth

No symptoms except effortless reflux

Improves after 6 months old

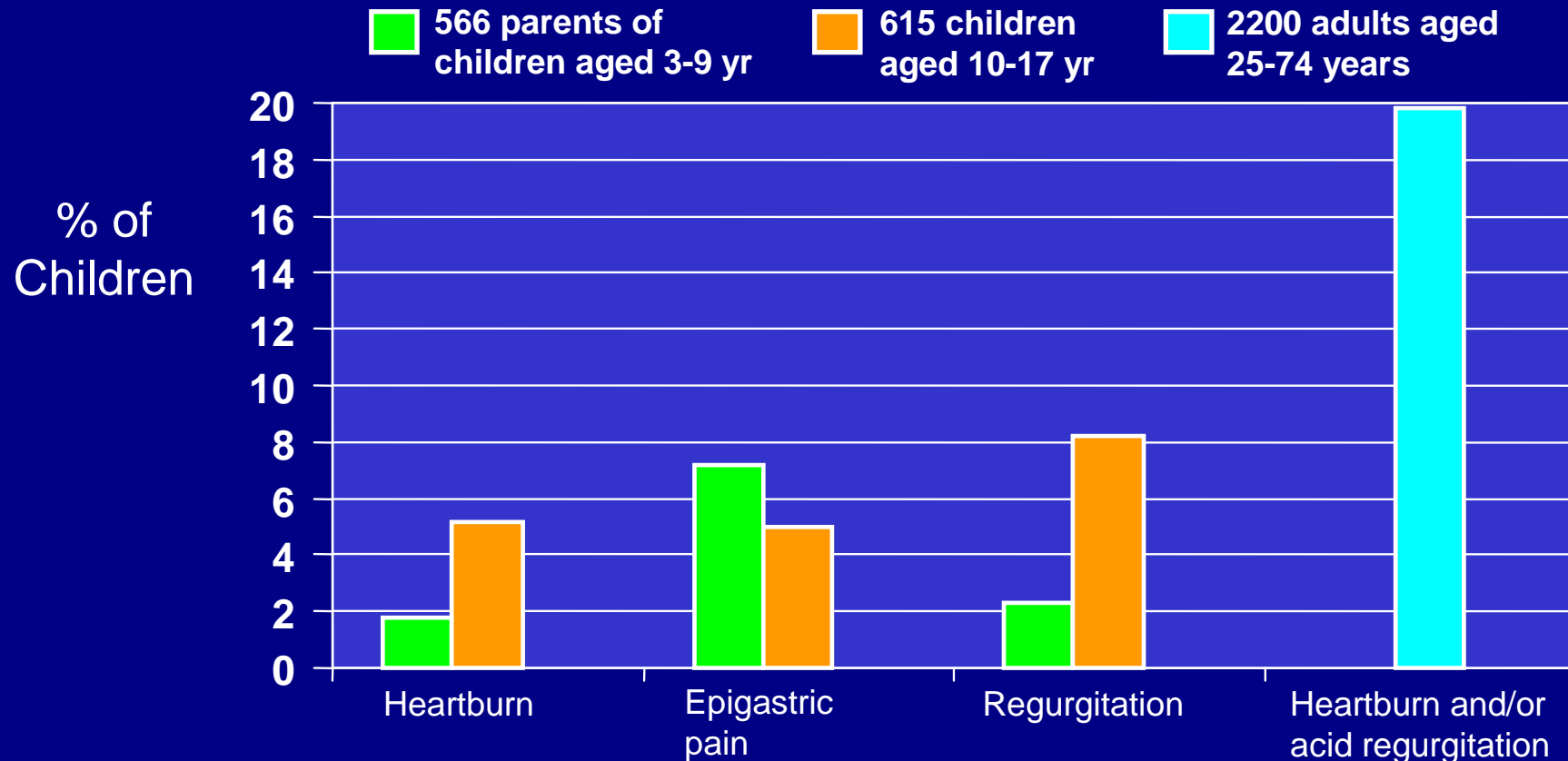
Prevalence of Regurgitation in Infancy



Adapted from Nelson et al, *Arch Pediatr Adolesc Med* 1997;151:569



Prevalence of GER Symptoms in Children

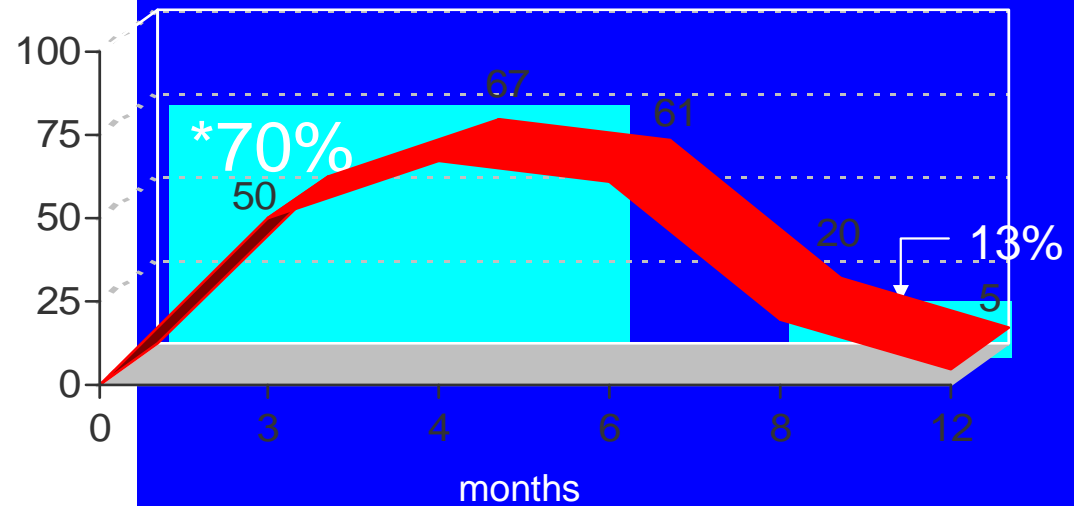


Nelson et al, *Arch Pediatr Adolesc Med* 2000;154:150 and
Locke et al, *Gastroenterology* 1997;112:1448



Prevalence

Infant

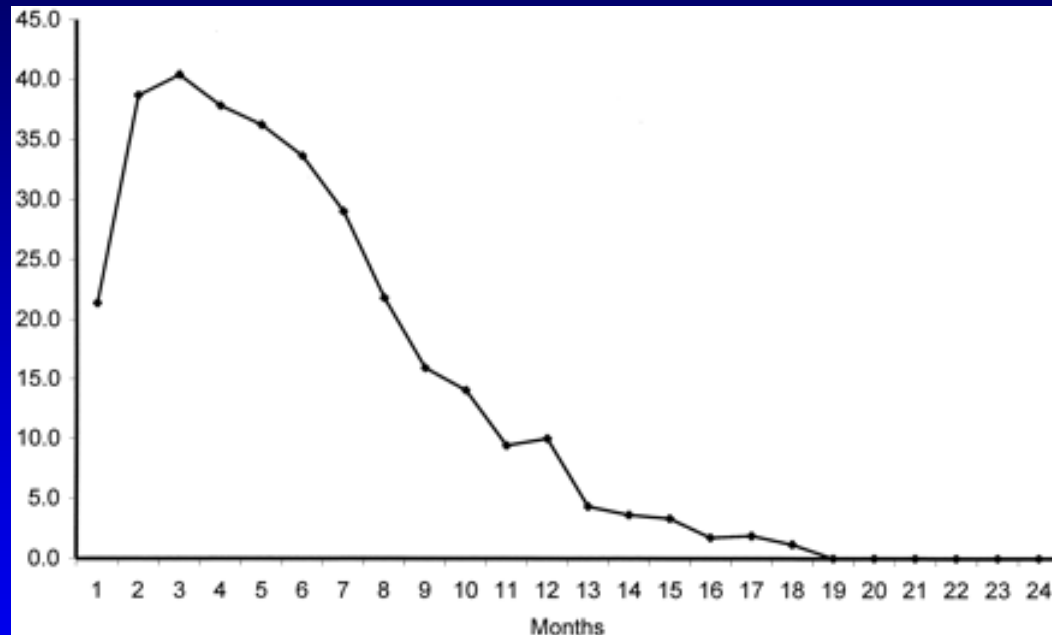


GERD <3%

VLBW, respiratory distress, neurological problems

*Vanderplas Y. Acta Ped 1998; 87:462; *Nelson SP. Arch Ped Ad Med. 1997; 151:569*

Natural History and Familial Relationships of Infant Spilling to 9 Years of Age. *James Martin A. PEDIATRICS. 2002; 109:1061*



Proportion of children with spitting up

Putative Genetic Predisposition for GERD

- Some reports of increased familial concordance for GERD symptoms, hiatal hernia, erosive esophagitis, Barrett's esophagus, and esophageal adenocarcinoma
- Proposed chromosome 13 locus (13q14) for severe pediatric GERD phenotype
- 13q14 locus excluded for infantile esophagitis phenotype
 - Chromosome 9 locus preliminarily proposed for infantile esophagitis

Gastroesophageal Reflux Disease (GERD in Toddlers)

- ❑ Poor growth or weight loss
- ❑ Abdominal pain (~ heartburn)
- ❑ Food Refusal (aversion to eating)
- ❑ Dysphagia
- ❑ “Silent” GER

Symptoms of GER

- ❑ Regurgitation: Emesis → Malnutrition
- ❑ Esophagitis:
 - ❑ Pain
 - ❑ Irritability
 - ❑ Feeding problems
 - ❑ Anemia
 - ❑ Hematemesis
 - ❑ Stricture

Symptoms of GER

- ❑ Respiratory:
 - ❑ Aspiration pneumonia
 - ❑ Wheezing
 - ❑ Apnea
 - ❑ Cyanosis
 - ❑ Cough
 - ❑ Stridor
 - ❑ Hoarseness
 - ❑ Hiccups
- ❑ Neurobehavioral “spells” Sandifer syndrome

Possible Supraesophageal Complications of GER

Dental erosion?	Present in 20/37 children
	Prevalence not increased in 53 with abnormal esophageal pH
Recurrent sinus disease?	Improvement with antireflux treatment in 15/19
	Prevalence similar in infants with and without GER
Otitis media?	Otalgia improved with GER therapy
	Prevalence not ↑ in children with GER

Dahshan et al, *J Pediatr* 2002; El-Serag et al, *Gastroenterology* 2001; Gibson et al, *Int J Pediatr Otorhinolaryngol* 1994; Nelson et al, *Pediatrics* 1998; O'Sullivan et al, *Eur J Oral Sci* 1998; Phipps et al, *Arch Otolaryngol Head Neck Surg* 2000



Physiologic Gastroesophageal Reflux (Mean upper limit of normal)

	Infants (N=509)	Children (N=48)	Adults (N=432)
No. of daily reflux episodes	73	25	45
No. of reflux episodes \geq 5 min	9.7	6.8	3.2
Reflux index (% of time pH < 4)	11.7%	5.4%	6%

GER & Allergy.

J Allergy Clin Immunol. 1996;97:822-7 Iacono G et al

- AIM: determine frequency of the association of GER with CMA in infants < 1 yr.
- METHODS: n = 204 (median age, 6.3 mo) Dx GER by 24-hr pH probe & biopsy
- RESULTS:
 - ❑ Symptoms of CMA in 19 and
 - ❑ 93 had positive test results (serum IgE anti-lactoglobulin, prick tests, circulating or fecal or nasal mucus eosinophils) but no symptoms of CMA
- CM-free diet and 2 successive blind challenges confirmed CMA in 85/204 (42%) patients with GER.
- Clinical presentations of the infants with GER alone were different, in view of the greater frequency of diarrhea ($p < 0.0001$) and atopic dermatitis ($p < 0.0002$).

Clinical and pH-metric characteristics of GER secondary to CMPA Am J Gastro. 1996;91:1215 Cavataio F et al

- N = 140, mean age 6.0 ± 2.8 mo.
- pH-metry, endoscopy and elimination diet, followed by a DB challenge,
- Patients divided into four groups:
 - ❑ Primary GER
 - ❑ GER secondary to CMPA
 - ❑ CMPA without GER and
 - ❑ Control group

Clinical and pH-metric characteristics of GER secondary to CMPA Am J Gastro. 1996;91:1215 Cavataio F et al.

- 30/72 with GER also had CMPA. No differences regarding age, sex, symptoms and clinical or family history between patients with GER only and those with GER + CMPA.
- Most useful immunological test for GER + CMPA: IgG anti-beta-lactoglobulin: positive in 27/30 with GER + CMPA and in 4/42 patients with GER only.
- Characteristic pattern of pH-probe in 26/30 pts. with GER + CMPA but in none of the 42 pts. with GER only: progressive, constant reduction in pH at the end of a feed, which continued up to the following feed, when pH rose steeply.

GER & CMA: is there a link?

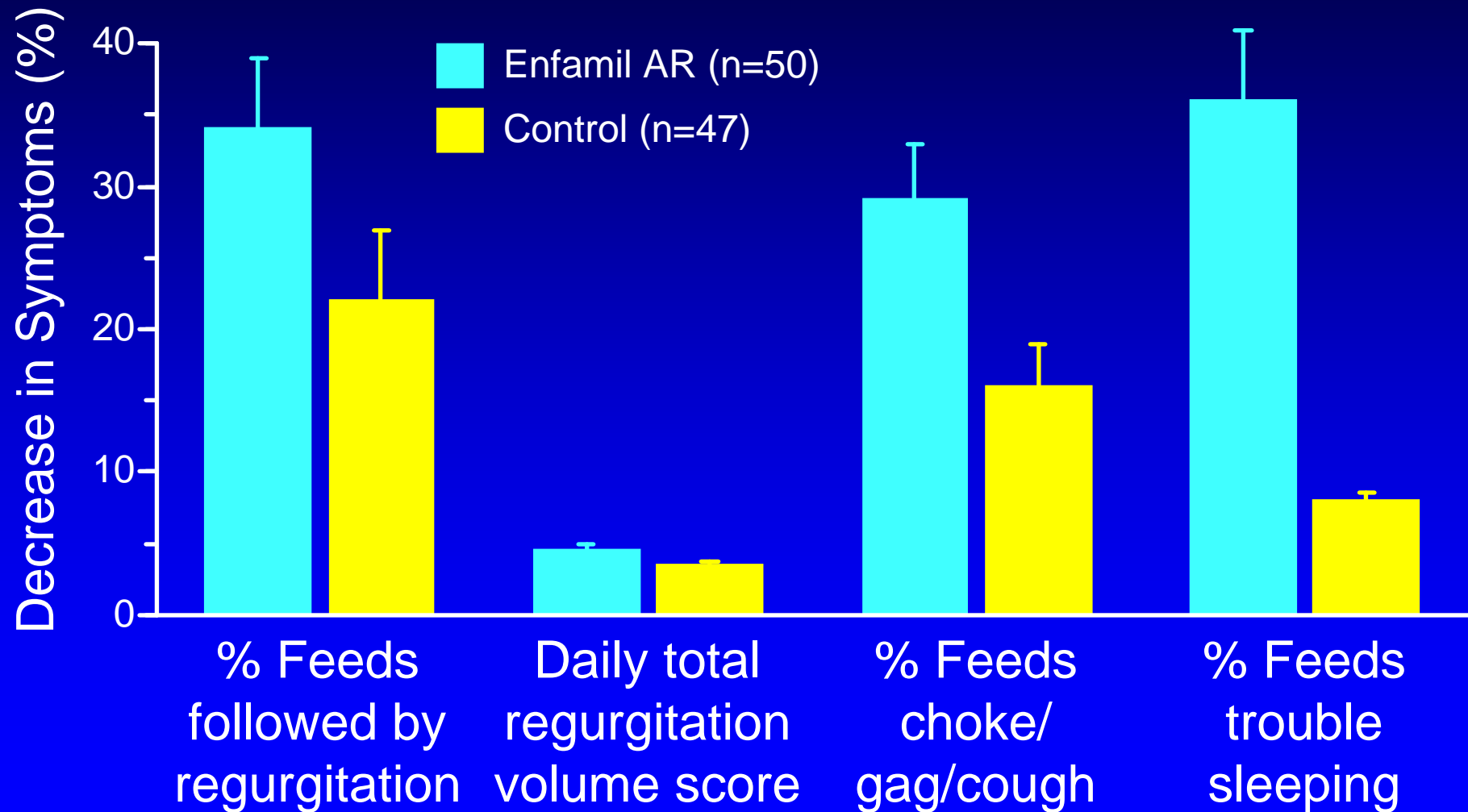
Pediatrics 2002;110:972 Salvatore S & Vandenplas Y

- In up to 50% of GER in infants < 1 yr, there may be an association with CMA
- In a high % of cases, GER is not only CMA associated but also CMA induced
- With exception of some pts. with mild typical CMA manifestations (diarrhea, dermatitis or rhinitis), symptoms of GER associated with CMA are ~ to those of observed in primary GER
- Immunologic tests and pH probe (typical pattern of progressive, slow decrease in pH between feedings)

Efficacy of a Pre-thickened Infant Formula:

Vanderhoof J et al.
Clin Pediatr 2003;42:483

Significant Changes in Symptoms



CM formula as a cause of infantile colic: a double-blind study.

Lothe L, Lindberg T, Jakobsson I. Pediatrics 1982;70:7

- N = 60 colicky infants given CM formula & soy
- Eleven (18%) free of symptoms on soy
- Symptoms of 32 (53%) unchanged or worse on CM & soy, but asymptomatic on hydrolysed casein
- Symptoms of 17 (29%) not related to diet and continued on a CM-based formula
- After 1 mo. (~ 3 mo. of age) challenge with CM: symptoms of infantile colic in 22 (36%)
- At age 6 mo., challenge with CM positive in 11 (18%) with skin and GI symptoms
- At age 12 mo. 8 (13%) and
- At age 16 mo. 5 (8%) still intolerant to CM

CM's milk proteins cause infantile colic in BF infants: a double-blind crossover study.

Jakobsson I & Lindberg T. Pediatrics 1983;71:268

- 66 mothers of 66 BF infants with colic, mothers were put on a CM free diet
 - ❑ Colic disappeared within 1-3 d in 35 (53%) &
 - ❑ Reappeared on @ least 2 challenges of CM to mother in 23 (35%)
- DB Crossover with CM whey & potato starch in 16/23 days 1 & 3
- Sequential analysis showed high correlation between infantile colic in BF-infants and their mothers' consumption of CMP.

CM's whey protein elicits symptoms of infantile colic in colicky formula-fed infants: a DBCO study
Lothe L & Lindberg T. Pediatrics. 1989;83:262.

- X age for entering study: 6.4 wk.; X age for colic 3.7 wk.
- In 24/27 symptoms disappeared on hydrolyzed formula
- These 24 entered into a DPCO study: whey protein powder or human albumin powder in identical capsules on days 6 & 10
- 18 on whey protein had colic,
- 2 on placebo had colic ($P < 0.001$)
- 4 did not react at all
- Crying for the 24: 5.6 hr/d on formula; 0.7 hr/d for CM-free ($P < 0.001$)
- Crying: 3.2 hr./d on whey protein capsules and 1 hr./d on placebo ($P < 0.001$)

Effect of low allergen maternal diet on colic in BF infants. Hill DJ et al. Pediatrics. 2005;116:709

- n = 107; BF < 6 wk. with colic; low allergen diet (CM, eggs, peanuts, tree nuts, wheat, soy & fish) (n = 53)
 - ❑ Baseline: Geometric mean crying time:
 - ❑ Tx: 690 min/48 hr. vs. C: 631 min/ 48 hr.
- Outcome @ 7 d.:
 - ❑ Tx: 74 % vs. C: 37 % cry reduction; average decrease 21%.

Breath H₂ response to milk containing lactose in colicky and noncolicky infants J Pediatr. 1988;113:979-84 Moore DJ et al.

- N= 122 healthy newborns. Studied relationship between BH production after feedings containing lactose (BM or formula) in colicky and noncolicky infants at 6 wk. and 3 mo.
- 83 infants (68%) with colic by 2.6 ± 1.8 wk. of age (mean \pm SD). Baseline BH significantly higher in colicky compared with noncolicky infants at 6 wk. (40 ± 41 vs 14 ± 32 ppm) and 3 mo. (27 ± 38 vs 8 ± 18 ppm).
- There were significantly more positive BH tests in colicky compared with noncolicky infants at 6 wk. (78% vs 36%) and 3 mo. (89% vs 45%).
- Failure to produce H₂ throughout the BH test was significantly more frequent in noncolicky compared with colicky infants at 6 wk. (50% vs 18%) and 3 mo. (43% vs 4%). These findings remained significant even when infants with mild colic (at 6 wk. and 3 mo.) were included in the noncolicky group.
- **CONCLUSIONS:** colicky infants produce more BH in the fasting state and in response to feedings containing lactose than noncolicky infants produce.

Breath hydrogen excretion in infants with colic. Miller JJ et al.

Arch Dis Child. 1989;64:725

- BH in 118 healthy infants; either BF or lactose formula, some of whom had colic.
- Infants with colic (n = 65) were selected on the basis of the mother's report of a h/o inconsolable crying lasting several hrs./d. Infants in the control group (n = 53) were not reported to cry excessively by their mothers.
- Breath samples collected using a face mask sampling device preprandially, & 90 & 150 min. after the feed.
- Normalised BH were higher in the group with colic than in the control group at each time point.
- Median maximum BH concentration in the colic group was 29 ppm, and in the control group 11 ppm.
- % of infants with incomplete lactose absorption (BH > 20 ppm) in the colic group was 62% compared with 32% in the control group.

Colonic hydrogen production in infants with colic
Hyams JS et al. J Pediatr. 1989;115:592

- N = 100 healthy babies, behavior recorded x 3 d; 31 (28%) colicky, 17/31 significant colic.
- 12/17 (8-13 wk) BHT after lactulose
- No difference between colicky and non colicky

Effects of formula change on intestinal H₂ production, crying & fussing behavior. J Dev Behav Ped. 1991;12:248 Barr RG et al

- BH excretion and behavior measured in 17 normal formula-fed infants who entered a feeding trial at 28 d. of life.
- The trial permitted two comparisons: (1) lactose and reduced lactose soy-based formulae, and (2) the infant's usual pretrial formula and the subsequent soy-based variable-carbohydrate formulae.
- Reduced lactose formula was associated with a small reduction in H₂ excretion (from a mean of 15 to 7 ppm, $p = .07$) but no difference in crying or fussing.

Effects of formula change on intestinal H₂ production, crying & fussing behavior. J Dev Behav Ped. 1991;12:248 Barr RG et al

- Change to soy-based variable-CHO formulae was associated with a substantial and sustained reduction in H₂ excretion (mean 32 to 11 ppm, $p < .03$) and a modest 21% decline in fussing (90.4 to 71.5 min/24 hr, $p < .08$).
- By 8 d after formula change, there was a 40% decline (90.4 to 53.9 min/24 hr) in fussing.
- Results suggest that, although behavioral changes due to differences in CHO content are unlikely in normal infants, formula changes involving protein and CHO can reduce colonic gas production and may have some effect on crying

Short-term effects of feed composition on sleeping and crying in newborns. Pediatrics. 1992;90:733 Oberlander TF

- To determine whether the composition of feedings would affect newborn behavior independently of the act of feeding itself, 53 2-3 d-old normal newborns were randomly assigned to receive an extra feeding of water, CHO (lactose), or balanced formula 3 hr. after their usual early morning feeding.
- Previous studies in adult humans and animals, and a single study in human newborns, have indicated that more sleep might be expected following the CHO feed compared with the water and balanced-formula feeds because of recruitment of centrally mediated serotonergic systems.
- Behavioral effects were assessed for 40 min. postfeeding by direct observation of the newborn's states (quiet, active, and indeterminate sleep; drowsiness; non-cry wakefulness; and fret/cry).

Short-term effects of feed composition on sleeping and crying in newborns. Pediatrics. 1992;90:733 Oberlander TF

- Feed composition did affect behavior, and the effects were fairly specific to particular newborn states.
- Non-cry wakefulness and drowsiness were unrelated to the presence or type of nutrients, but they tended to occur soon after the meal in all groups.
- Crying was increased in water-fed newborns relative to both carbohydrate- and formula-fed newborns.
- Sleep duration was increased in the balanced-formula group compared with the water group throughout the observation period. Contrary to the prediction, sleeping duration in CHO-fed newborns never exceeded that of formula-fed newborns; rather, it resembled that of water-fed newborns early in the postprandial period, but formula-fed newborns later.

Evaluation of the effect of a fiber-enriched formula on infant colic. J
Pediatr. 1991 Nov;119(5):695 Treem WR et al.

- N = 27 normal, term infants (aged 2 to 8 wk.) with colic.
- Infants were randomly assigned in 9-d periods to a sequence of placebo (soy) followed by fiber-supplemented formula (n = 12) or the reverse (n = 15).
- Daily diaries of crying, fussing, sleeping, formula, intake, and stooling were kept. Twenty-two infants completed three lactulose breath hydrogen tests at the end of the baseline period and after each study period.
- The crossover trial was followed by 30 to 35 days of use of the study formula chosen by the parents as most beneficial but unknown to the investigators.
- There were no significant differences in average daily time spent by the infants in fussing and crying during ingestion of the fiber-supplemented formula. However, parents of 18 of 27 infants chose fiber-supplemented formula as most beneficial in ameliorating symptoms of colic.

Crying, fussing and colic behaviour in breast- and bottle-fed infants.

Early Hum Dev. 1998;53:9- Lucas A et al.

- Used validated maternal diaries of infant behaviors, kept for 3 d at both 2 & 6 wk. of infant age, in a comparative study of 97 breast- or formula fed babies.
- The total duration of overall crying rose significantly between 2 and 6 wk. in breast-fed infants and fell in those fed formula.
- At 6 wk., breast-fed infants cried an average of almost 40 min. more per day than formula fed infants; and 31% cried for more than 3 hr./d. compared with only 12% of the formula fed group.
- At 2 wk. breast-fed infants also slept almost 80 min. less per day than the formula fed babies.
- While 6 wk. is the established peak age for infant crying, those fed formula peaked much earlier and at 2 wk. intense crying/colic behaviour occurred in 43% of formula fed babies and just 16% of those fed by breast..

Colic in breast-milk-fed infants: treatment by temporary substitution of AA infant formula. *Acta Paediatr* 2001. 90:359 Estep DC et al.

- Infant colic is a common problem characterized by excessive crying and fussing. We examined whether colic symptoms of exclusively breast-milk-fed infants would be improved by temporary substitution of Neocate, an amino acid-based infant formula, for breast milk. Six infants with colic were studied using Barr-type infant behavior diaries for a 3-5 d baseline period while they continued exclusive breast-milk-feeding, followed by a 4-8 d intervention period of exclusive Neocate feeding. All infants showed improvement in distressed behavior during intervention; five of the six improved within 1-2 d. For the period after 1 d of Neocate feeding, the total recorded crying and fussing time was reduced by an average of 42%, representing a decrease of 1.0 to 3.1 h daily. A significant difference was found between cry and fuss time at baseline versus during exclusive Neocate use. Concurrent with Neocate intervention, mothers strictly avoided all milk and dairy products. After colic symptoms improved, infants were reintroduced to breast milk, which was reasonably well tolerated in four of the six infants. Two infants had rapid recurrences of crying and fussing upon return to breastfeeding and required an additional period of Neocate feedings before subsequent reintroduction to breastfeeding. All infants exhibited colic symptoms when directly or indirectly challenged with bovine IgG (BGG), suggesting that BGG may play an etiologic role in colic. We propose that a brief intervention with Neocate, coupled with strict maternal avoidance of milk and dairy products under direct supervision of a lactation consultant, may be an effective treatment for colic in some breast-milk-fed infants.

Low plasma cholecystokinin (CCK) levels in colicky infants Huhtala V et al. **JPGN. 2003;37:42**

- Hypothesis: Colicky (COL) infants have impaired CCK secretion, which contributes to GB hypocontractility and excessive crying.
- METHODS: CCK levels of 40 COL & 37 controls (C) evaluated @ mean of age 5 wk.
- Plasma CCK measured before, immediately after, and 1 hr after a regular milk feeding. GB contraction calculated using US measurements before and 1 hr after feeding.
- RESULTS: Preprandial and 1-hr postprandial plasma levels of CCK were lower in the colicky infants than in C ($P < 0.05$).
- Immediate postprandial CCK levels were also lower in the COL, although this difference did not reach a statistical significance. The proportion of GB contractions did not differ between the study groups.
- CONCLUSIONS: low CCK levels in COL may predispose them to excessive crying in the absence of the calming effect of CCK.

Intestinal microflora in BF COL & non-COL infants

Savino F et al. Acta Paediatr. 2004;93:825

➤ METHODS:

- ❑ 71 BF 3.2 \pm 0.6 wk; 42 COL & 29 non-COL

➤ RESULTS:

- ❑ COL less frequently colonized by Lactobacillus spp., and
- ❑ more frequently by anaerobic gram-negative bacteria.

Bacterial counts of intestinal Lactobacillus species in infants with colic Savino F et al. Ped All Imm. 2005;16:72

- AIM: compare intestinal lactobacilli in BF COL and healthy infants.
- N= 56 (15-60 d); COL = 30; C = 26.
- Stool colonies counted & identified by biochemical methods
- Lactobacillus brevis (4.34×10^8 cfu/g) and L. lactis lactis (2.51×10^7 cfu/g) were found only in COL infants while L. acidophilus (2.41×10^7 cfu/g) was found only in C.

Ghrelin and motilin concentration in colicky infants.

Savino F et al. Acta Paediatr. 2006;95:738.

- Fasting blood from 18 COL & 20 non Colicky (C)
 - ❑ Ghrelin COL: 2534 ± 600 pg/ml vs. C: 2126 ± 281 pg/ml ($p = 0.011$).
- Motilin COL: 94.6 ± 23.2 pmol/l vs. C (64.1 ± 30.1 pmol/l) ($p=0.001$).
- Motilin in formula-fed COL (104.5 ± 20.4 pmol/l) vs. BF (82.2 ± 21.3 pmol/l) ($p = 0.038$).

Dietary modifications versus dicyclomine hydrochloride in the treatment of severe infantile colics.

Oggero R et al. *Acta Paediatr.* 1994;83:222.

- n = 120, 3-12 wk., with severe COL assigned to
- Group A: Diet
 - ❑ Mothers of BF received diet without CM, eggs or fish.
 - ❑ Non-BF: soy milk and if unresponsive, hydrolyzed formula;
- Group B: pharmacological treatment
 - ❑ BF and non-BF group B: dicyclomine hydrochloride 3 mg/kg/day.
- RESULTS:
 - ❑ Breastfed: no significant difference in improvement group A (62.5%) and group B (66.6%)
 - ❑ Formula-fed infants:
 - ❑ comparison of positive results using soy milk (65.9%) with positive results using dicyclomine (53.3%) was not significant;
 - ❑ positive results using soy milk and hydrolyzed milk formulas in non-responders to soy milk, provided an improvement in 95.4% of cases.
- Pharmacological treatment provided an improvement in 53.3% of cases. The difference was significant ($p < 0.01$).

Effect of a low allergen maternal diet on colic

Hill D et al. Pediatrics 2005.116:709

- N=107 BF, 90 completed (X age 5.7 wk)
- Baseline crying time:
 - ❑ low allergen (LA): 690 min/48 hr. (geometric mean)
 - ❑ Control (C): 631 min/48 hr.
- F/u assessment @ 7 & 8 d:
 - ❑ LA 74% responders vs. 37% in C
 - ❑ absolute risk reduction: 37%.
- Cry/fuss reduction in LA 21%
- Mothers' subjective evaluation of crying: no difference (5.5 hr/d vs. 4.35 hr/d)