



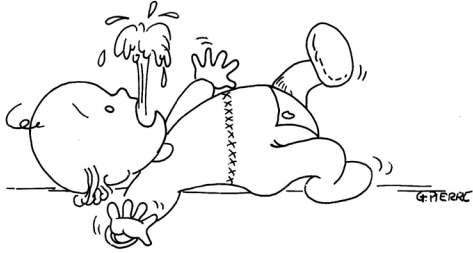
# What can we learn from the clinical studies in infants (*on thickeners*)?

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Member of the FAF WG "Re-evaluation of FA in foods for infants below 16 weeks of age"

FA Stakeholders Workshop 30 November 2018

# Natural history of regurgitations in infants



« All babies spit up »



< 3 mo  
50%

4 mo  
67%

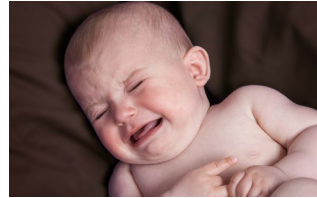
6 mo  
61%

10-12 mo  
5%

Nelson *et al.* Arch Pediatr Adolesc Med 1997; 151: 569-72

# Gastroesophageal reflux (GER) and GER disease (GERD)

- **GER:** the passage of gastric contents into the oesophagus with or without regurgitation and/or vomiting
- **GERD:** when GER leads to troublesome symptoms and/or complications and therefore needs medical advice
- In clinical practice, it may be difficult to differentiate GER from GERD in infants
- The degree of concern of parents is often the factor driving the need for a diagnosis



## 2018 ESPGHAN-NASPGHAN Guidelines

# Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition

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*J Pediatr Gastroenterol Nutr 2018; 66: 516-64*

### **REASSURANCE FIRST**

« The WG suggests to use thickened feedings for treating visible regurgitation/vomiting in infants with GERD. »

# UK Guidelines 2015

**NICE** National Institute for  
Health and Care Excellence

Gastro-oesophageal reflux disease in  
children and young people: diagnosis and  
management

## ***REASSURANCE FIRST***

« In formula-fed infants with frequent regurgitation associated with marked distress, use the following stepped-care approach:

- Review the feeding history, ***then***
- Reduce the feed volumes only if excessive for the infant's weight, ***then***
- Offer a trial of smaller, more frequent feeds (while maintaining an appropriate total daily amount of milk) unless the feeds are already small and frequent, ***then***
- Offer a trial of thickened formula (for example, containing rice starch, cornstarch, locust bean gum) »

# Pathophysiology of GER/GERD and use of thickeners

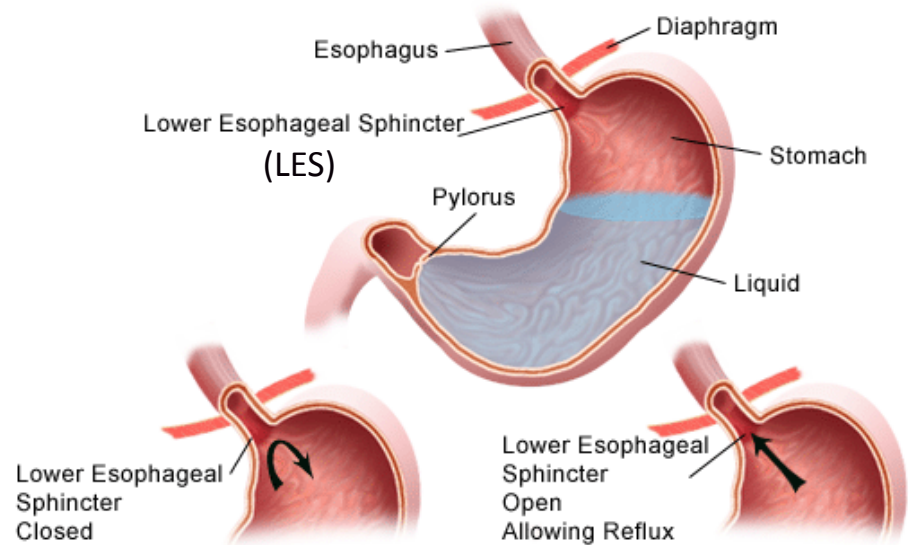
- **Pathophysiology of GER/GERD**

- Transient inappropriate relaxation of LES
- Delayed gastric emptying

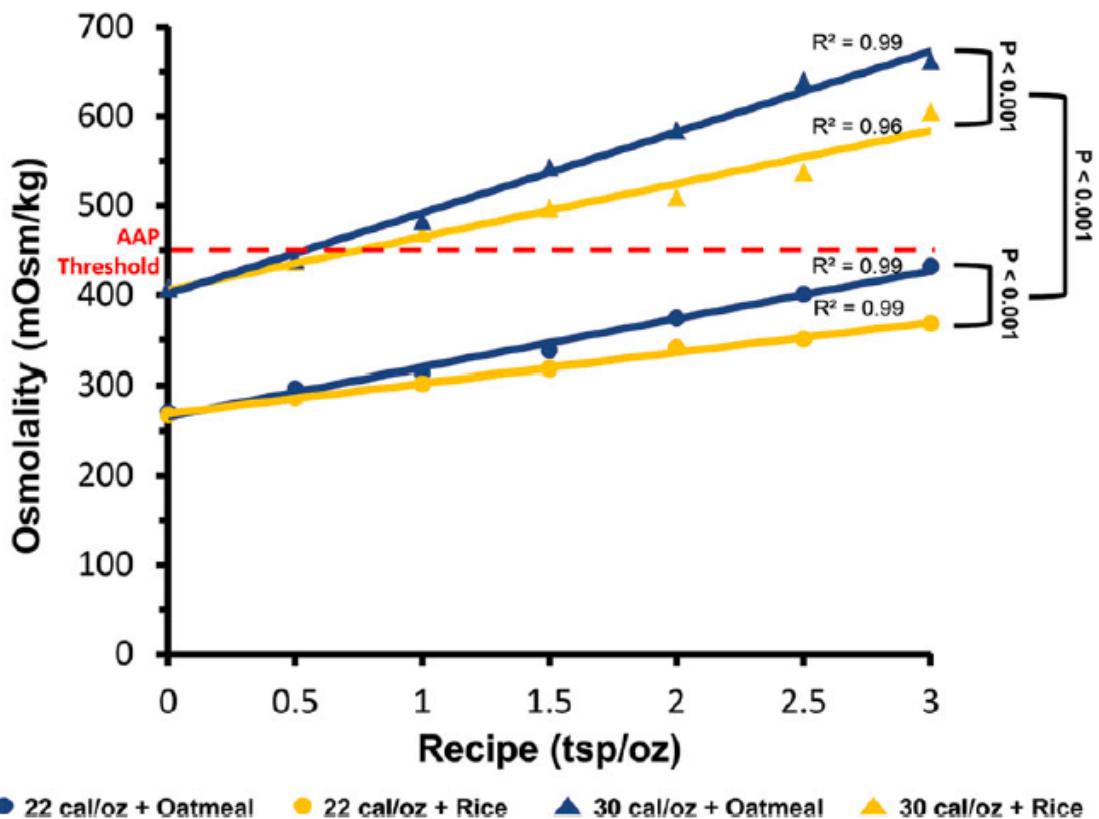
- **Thickeners**

- Increase the viscosity of the liquid content
- May increase energy density (starch) & osmolality
- May secondarily increase the frequency of relaxation of the LES and delay gastric emptying, thus worsening GER

## Gastroesophageal Reflux



# Effects of thickening agent and amount on osmolality



# Effect of thickening agent on gastric emptying

- **Locust bean gum (LBG)**

see

Miyazawa *et al.* *J Paediatr Child Health* 2006; 42: 808-12



# Most randomized clinical studies have limitations

Double-blind comparative trial with 2 antiregurgitation formulae  
Vandenplas *et al.* *J Pediatr Gastroenterol Nutr* 2013; 57: 389-93

- 2 AR formulae thickened with locust bean gum +/- starch
- 1 month double-blind, randomized cross-over trial, 115 infants (2 wk - 5 mo)
- Data on safety:
  - « The number of adverse events related to the dietary intervention was low in both groups. »
  - « The reasons for dropping out (*eg.* diarrhoea, colic, fuzziness) were comparable in both groups. »

# Most randomized clinical studies have limitations

Clinical trial with thickened feeding for treatment of regurgitation in infants  
*Iacono et al. Digest Liver Dis 2002; 34: 532-3*

- 8 weeks-randomized study of 2 formulae thickened (AR) or not with locust bean gum
- 166 bottle-fed infants under 4 months of age with frequent regurgitation or vomiting due to uncomplicated GER
- Data on safety:
  - « In 14 infants in the thickened formula group treatment was suspended due to the onset of diarrhoea during the first 2 weeks of the study. » (***No definition of diarrhea***)
  - « Weight/height ratio was similar in both groups, at all times. »

## And also reviews...



ELSEVIER

Contents lists available at [ScienceDirect](#)

### Regulatory Toxicology and Pharmacology

journal homepage: [www.elsevier.com/locate/yrtph](http://www.elsevier.com/locate/yrtph)



Locust bean gum safety in neonates and young infants: An integrated review of the toxicological database and clinical evidence

*Meunier et al. Regul Toxicol Pharmacol* 2014; 70: 155-69

- Narrative review on 13 studies investigating the effect of LBG on regurgitation
- About 400 infants, most of them included at an age < 12 weeks
- No safety concern including food intake, vomiting, growth, stool pattern... ..  
***as the authors did not report any adverse effects in the exposed infants***

# Cochrane Database System Reviews

Feed thickener for infants up to six months of age with gastro-oesophageal reflux  
Kwok TC, Ojha S, Dorling J. *Cochrane Database Syst Rev* 2017; 12: CD003211

- Eight randomised clinical trials analysing the impact of feed thickener in 637 healthy term formula fed infants up to 6 months of age with symptoms
- Locust bean gum; rice cereal; cornstarch; alginate over a 1-8 weeks period
- Trials of variable methodological quality
- Thickeners reduced significantly the number of regurgitations by nearly 2 episodes per day (mean difference (MD)-1.97, 95%CI -2.32 to -1.61, 6 studies, 442 infants)
- Insufficient evidence to recommend the use of one form of feed thickener over the other
- ***No significant side effects were identified***
- ***The effects of feed thickeners on diarrhea was variable but studies were not powered to measure side effects and only reported short term follow-up outcomes***

## Safety in preterm infants - Allergy

- Cases (n=2) of necrotizing enterocolitis in preterms receiving a locust bean gum thickener (2 deaths)
  - Clarke & Robinson. *Arch Dis Child Fetal Neonatal Ed* 2004; 889: F280
- Cases (n=22) of necrotizing enterocolitis in preterms receiving a xanthan gum thickener (7 deaths)
  - Warning of the FDA (2011)
  - Beal *et al. J Pediatr* 2012; 161: 354-6
- Cases (n=6) of diarrhea, hypokaliemia and metabolic acidosis related to the use of locust bean gum supplemented formula
  - Sievers & Schaub. *J Pediatr Gastroenterol Nutr* 2003; 36: 418
- Allergy to locust bean gum in a 5-month old infant with vomiting and urticaria
  - Savino *et al. J Pediatr Gastroenterol Nutr* 1999; 29: 475-6

# Main questions for clinical studies on thickeners

Is the use of specific thickener accompanied with an increase of adverse events ?  
 Study type, pre-specified endpoints, duration, number of participants?

Study type	Control	Blinding	Pre-specified endpoints	Duration	Number of participants
<b>RCT</b>	Unthickened infant formula	Might be difficult because of the difference in viscosity	Stool pattern (number/ consistency of stools, diarrhoea, bowel obstruction) "Colic" (crying time) Acute respiratory events	Not <8 wk	To detect a clinically meaningful difference
<b>Observational studies</b>	No additional treatment for regurgitations		Mineral availability Growth pattern Stool pattern (number/ consistency of stools, diarrhoea, bowel obstruction) "Colic" (crying time) Acute respiratory events	Not <12 wk	Smaller studies may provide data for systematic review/meta-analysis of trials addressing the question ( <i>data reuse</i> )

# Conclusion

- More clinical data are needed on the safety of use of food additives (*thickeners*) in infants
- Focusing on:
  - Diarrhoea
  - Other gastrointestinal outcomes
  - Mineral availability of infant formula
  - Growth pattern

***Thank you for your attention***