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Review

Thickened infant formula: What to know

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ABSTRACT

Objectives: This study aimed to provide an overview of the characteristics of thickened formulas to aid health care providers manage infants with regurgitations.
Methods: The indications, properties, and efficacy of different thickening agents and thickened formulas on regurgitation and gastroesophageal reflux in infants were reviewed. PubMed and the Cochrane database were searched up to December 2016.
Results: Based on the literature review, thickened formulas reduce regurgitation, may improve reflux-associated symptoms, and increase weight gain. However, clinical efficacy is related to the characteristics of the formula and of the infant. Commercial thickened formulas are preferred over the supplementation of standard formulas with thickener because of the better viscosity, digestibility, and nutritional balance. Rice and corn starch, carob bean gum, and soy bean polysaccharides are available as thickening agents. Hydrolyzed formulas have recently shown promising additional benefit.
Conclusions: Thickened formulas reduce the frequency and severity of regurgitation and are indicated in formula-fed infants with persisting symptoms despite reassurance and appropriate feeding volume intake.

Introduction

Infantile regurgitation is a common, physiological, transient manifestation of gastroesophageal reflux (GER) that does not require treatment but only parental reassurance and dietary management [1–4]. Thickened formulas (TFs) are indicated in infants who are formula-fed and have persistent regurgitation and poor weight gain [1,3] or marked distress [4] instead of overprescribed acid inhibitors [5–7].

Different antiregurgitation formulas (AR-F) are available on the market [8] and frequently used [9]. However, the advantages and disadvantages with regard to cost as well as nutritional and gastrointestinal effects should be carefully balanced [10]. The aim of this narrative review was to provide an updated overview of the rationale for and characteristics of AR-F to aid health care providers manage infants with regurgitation.

Conflicts of interest: S.S. has participated as a consultant and/or speaker for Danone-Nutricia, Deca, IMS-Health, Menarini, Nestlè. F.S. has participated as a consultant and/or speaker for Menarini, Danone, Nutricia, HiPP GmbH, Nestlè, and BioGaia. A.S. has participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for D.M.G., Valeas, Angelini, Miltè Menarini, Danone, Nestle'. M.A.B. has participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Astrazeneca, Norgine, Coloplast, Zeria, Sucampo, Shire, Mead Johnson, Danone, Abbott, Frieslandcampina, Novalac, and Sensus. Y.V. has participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Abbott Nutrition, Biogaia, Biocodex, Danone, Hero, Nestle Nutrition Institute, Nutricia, Mead Johnson, Merck, Orafti, Phacobel, Sari Husada, United Pharmaceuticals, Wyeth, and Yakult. The other authors did not report any conflicts of interest. All the referenced manufacturers and companies had no input or involvement in any aspect of this review or any other previous reviews carried out by the authors. There are no other interests to declare.

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Materials and methods

We searched PubMed up to December 2016 using the following keywords: "antiregurgitation" OR "thickened formula" OR "thickening agents" AND "regurgitation" OR "gastro (o) esophageal reflux" OR "GER" OR "GOR" and restricted the search to publications on humans and infants. Intervention trials, reviews, guidelines, meta-analyses, and reference lists of these studies were considered.

Results

Rationale for antiregurgitation formulas

Despite the spontaneous remission in most infants, voluminous and persistent regurgitation is a frequent reason for parental concern, formula changes, and feeding distress [9,11–15]. The rationale for AR-F is based on the addition of a thickening agent (e.g., cereal starch or carob/locust bean gum flours) to increases its viscosity [8,10,16].

Viscosity and digestibility of antiregurgitation formulas

In vitro models have demonstrated that carob seed flour is the thickening agent with the highest viscosity and particularly in predominant casein formula [17,18]. The digestibility of carbohydrates that are added to infant formula has long been a matter of concern [19–22]. To convert starch to glucose, six enzymes (two salivary and pancreatic alpha-amylases, sucrase-isomaltases, and maltase-glucoamylases) are involved [23]. Sucrase-isomaltases and maltase-glucoamylases are the key enzymes that digest starch in young infants before pancreatic alpha-amylase secretion matures [24].

The starch digestion rate is correlated to its chemical structure and determined by the different botanic sources, concentrations, food processing techniques, and the age of the infant [23,25]. The crystalline structures that are observed in x-ray diffractions classify starch granules into Type A (e.g., wheat, normal maize, and rice), B (e.g., potato and green banana), and C (e.g., beans and seeds) on the basis of high, low, or intermediate susceptibility to hydrolysis [23]. The increasing resistance to hydrolysis from waxy maize to tapioca, sorghum, ordinary corn, wheat, rice, potato, and high-amylose corn has been attributed to both the ratio of amylose and the surface pores that facilitate the access of enzymes [25]. However, cooking and gelatinization change the granular structure of the native starch and decrease the resistance to enzymatic attack and the differences between the varieties [22–24].

In infants, wheat, tapioca, corn, rice, or potato starch that is cooked for 10 min in water are all digested and efficiently (>98%) absorbed when the concentration is 1.6 g to 1.9 g/100 mL at 1 mo and 3.1 g to 3.5 g/100 mL at 3 mo of age. However, at 5 g to 6 g/100 mL, fermentative diarrhea has been reported in 2 of 5 infants who were tested [24]. An expert group from the European Society for Paediatric Gastroenterology Hepatology and Nutrition recommended that (precooked or gelatinized) starches be added to the infant formula up to 2 g/100 mL [26].

Locust bean gum is a different thickening agent that is obtained from the endosperm seed of the locust/carob tree (Ceratonia siliqua [L.] Taub) of the plant family of Leguminosae, which consists of high molecular weight polysaccharides (50 000–3 000 000 dalton) of which at least 75% are galactomannans. Locust bean gum is coded as INS/E 410 in accordance with food additive numbering and commonly used in various food items for thickening, stabilizing, emulsifying, or gelling properties. Locust bean gum is resistant to human digestive enzymes and excreted unchanged in the feces or fermented by the gut microbiota [27].

(Home) thickening compared with antiregurgitation formulas

Many parents use AR-F or add thickening agents to standard formula (SF) to reduce infants' regurgitation and/or vomiting, improve night sleep, and decrease failure to thrive [9]. Commercial AR-F has a controlled composition with thickening components less than 2 g/100 mL for starch and 1 g/100 mL for carob bean gum, and a caloric content that is similar to SF. Moreover, pretreated (e.g., gelatinized) starch presents a low viscosity that allows for an easy flow through a standard nipple and thickens only in the stomach when in contact with acid potential hydrogen (pH) [28]. In contrast, carob bean gum maintains a constant viscosity because it is not split by salivary amylase and not influenced by pH.

Home-brewed thickened SF are often prepared by parents because of the limited availability or higher (1.5–2 times) cost of AR-F but the effects of home-thickened feeding may differ from AR-F due to a heterogeneous composition. One study reported that a heaping tablespoon added a quantity of starch between 3.6 g and 4.6 g [29], which was well above the regulatory limit for starch (2 g/100 mL) in AR-F [26,30], increased the osmolarity of the formula, and provided an extra caloric intake of 20 calories per 100 mL. Moreover, overthickening of formula results in a higher viscosity that needs an increased sucking effort and/or a crosscut nipple to flow through [17,18,31–34]. Hence, parents should receive clear advice about thickening modalities in case of home-brewed TFs.

In a prospective, case-controlled study of 100 infants, regurgitation disappeared after 3 mo in a slightly higher percentage of infants (52% vs. 40%) who were fed AR-F versus a home-made, cornstarch TF [35].

Clinical effects of antiregurgitation formulas

Gastric emptying

A thickening agent (particularly a fiber) may delay gastric emptying and potentially worsen postprandial GER and symptoms but its effect depends on viscosity and concentration [36] as well as protein content. Antral cross-sectional areas that were measured by ultrasound were not significantly different in 47, 20, and 20 infants who frequently regurgitated and were fed a locust bean gum AR-F or SF (0.35 g/100 mL; 0.4 g/100 mL; and 0.6 g/100 mL, respectively). However, antral cross-sectional areas were greater in another trial that used a different formula (HL-450) in 39 infants [37–40].

In 63 of 81 infants who regurgitated, corn starch AR-F had a gastric emptying time as measured by technetium 99 m milk scintigraphy that was similar to SF [41] and faster than a 25% strengthened formula [42].

In 90 healthy infants, the gastric residual content 2 h after feeding was the smallest with whey-hydrolyzed formula (HF) and breast milk and progressively higher with acidified, whey-predominant, casein, follow-up formula and whole cow's milk [43]. In 28 infants with GER, scintigraphy showed that gastric emptying significantly increased after feeding infants the same volume and calories of a casein-predominant, soy, or whey-partial HF (pHF) [44].

In a crossover, randomized, controlled trial (RCT) that performed 13 C-octanoic acid breath tests in 20 healthy newborns, extensive HF (eHF) significantly accelerated the gastric emptying compared with pHF and intact proteins SF [45].

In a 2-wk, crossover, double-blind trial, 12 infants who frequently cried and regurgitated showed significantly reduced symptoms and gastric emptying time (as assessed by 13-C acetate

Table 1
Summary of trials that report the effect, expressed as (mean) episodes of regurgitation, with thickened formulas

Reference	At inclusion	With AR-formula (after 1–4 wk)	Thickening agent
Miyazawa et al. [38] (7 d)	22.6 ± 3.9 29.8 ± 3.6	12.9 ± 3.5 12.8 ± 3.0	Carob
Overall recalculated per d	3.74	1.84	
(HL 350)	3.2 ± 0.6	1.85 ± 0.5	
(HL 450)	4.2 ± 0.5	1.8 ± 0.4	
Miyazawa et al. [39]	5.2	3.2	Carob
Vivatkavin et al. [40]	5.7 ± 2.13	2.25 ± 1.45	Carob
Vandenplas et al. [50]	8.25	2.32 or 1.89	Carob
Wenzl et al. [51] (n = episodes GER on MII-pH over 342 h)	68	15	Carob
Recalculated per d	4.77	1.05	
Chao et al. [41]	3.71 ± 0.69	2.39 ± 0.86	Corn
Chao et al. [42]	4.19 ± 1.71	0.93 ± 0.42	Corn
Hegar et al. [13]	5.9 ± 1.7	3.3 ± 2.3	Carob
Xinias et al. [52]	5.60 ± 4.15	2.57 ± 2.71	Corn
Moukarzel et al. [53]	5.2 ± 3.1	2.3 ± 2	Corn
Moya et al. [54]	4.5 ± 2.1	2.9 ± 1.6 (with corn) 2.2 ± 1 (with carob)	Corn
Vanderhoof et al. [28]	13 ± 1	6 ± 1	Rice
Khoshoo et al. [29]	4.33 ± 0.51	2.83 ± 0.40	Rice
Mean number of regurgitations per d (all studies)	5.43	2.50	

AR, antiregurgitation; GER, gastroesophageal reflux; MII-pH, multichannel intraluminal impedance and potential hydrogen.

breath test) when they were fed a whey-pHF with a combination of thickeners (bean gum and processed tapioca starch) compared with an intact-protein casein-predominant (single) TF [46].

Regurgitation

In 1987, Orenstein et al. first reported that a 4% rice starch TF decreased regurgitation and crying and increased sleeping time in 20 infants despite an unchanged number of reflux episodes that was documented by scintigraphy [47]. In the same year, Vandenplas and Sacre showed a decrease of GER symptoms in 25 of 30 infants who were fed with a carob bean gum (1 g/115 mL) TF with a normalization of all reflux parameters as measured by pH-monitoring in six infants [48]. In 2002, a Cochrane systematic review on thickeners for infants with GER did not find any studies that fulfilled the requirements for inclusion [49]. Since then, several RCTs have reported a reduction in the daily number of episodes of regurgitation from a mean of 5.4 episodes per day to 2.5 episodes per day over a period of 1 to 4 wk (Table 1) in infants who were fed rice [28,29,41], corn [42,52–54], and locust bean gum [13,14,39,40,46,50,51,55] AR-F. However, the design of each study largely differed in inclusion criteria, research methods, duration of intervention, and formula and/or thickener tested, making the figure of a 50% in reduction only indicative. The overall characteristics and effects of thickener agents are summarized in Table 2.

In 2008, a meta-analysis including 14 RCTs with different thickening agents added to SF or AR-F concluded that TFs decreased the number of episodes of regurgitation and vomiting, significantly increased the percentage of infants without regurgitation, and increased weight gain [16]. No particular thickening agent was shown to be more effective than another. In the pooled analysis of six studies and 369 infants, the decrease in regurgitation ranged from 0.6 to 1.8 episodes per day on the basis of different statistical (fixed or random-effects) models that were

Table 2
Summary of characteristics and effects of different thickeners

a. Clinical effect

Thickener agent	Viscosity	Ref.	Digestion	Ref.	Gastric emptying	Ref.	Regurgitation	Ref.	GER/pH results	Ref
Carob/ locust bean gum	↑↑	[17,18]	No	[27]	↓ = =	[38–40]	↓	[13,14,38–40, 46,48,50,51,55]	↓n ↑longest episode ↓RI% =	[48] [48] [33,51,55]
Corn starch	↑		=	[23–25]	=	[41]	↓	[31,42] [52–54]	↓all ↓RI%	[52] [31,53]
Rice starch	↑		=		Unknown	None	↓	[28,29,31,41,47]	↓n =RI% =	[29] [29] [31]

b. Regulation and adverse effects

Thickener agent	Concentration (max limit)	Ref.	Adverse effect	Ref
Carob/locust bean gum	1 g/100 mL	[19,20]	Diarrhea	[14,38,39]
Corn starch	2 g/100 mL	[30]	–	–
Rice starch	2 g/100 mL	[30]	Cough Constipation Arsenic load	[32] [31,56] [57]

GER, gastroesophageal reflux; pH, potential hydrogen; Ref, reference; RI, reflux index; ↑, increased; No, Undigested; =, normal or no change; ↓, decreased.

used. Thickened or AR-F was associated with a statistically significant increase in weight gain (3.5–3.7 g/d) compared with SF according to four RCTs that enrolled 265 infants [16]. Only one study evaluated the efficacy of a soy-fiber (6 g/L) TF in 66 newborns with a small reduction (–0.4) in the number of episodes of regurgitation/vomiting per day after 4 wk of intervention compared with 89 infants who were fed SF [58].

Recently, an RCT of 77 infants with GER symptoms compared the effect of a highly concentrated rice starch (14.3 g/100 mL) TF with an SF in addition to parental reassurance and with treatment with alginate and simethicone [59]. After 2 mo of intervention, all three groups showed a significant reduction in symptoms with a slightly better score in the alginate group [59].

Thus, AR-F decreased visual regurgitation and may reinforce the effects of parental reassurance. Additional effects such as improved sleeping and decreased irritability, cough, and choking also have been reported [28,42] but not reputed relevant [8].

Discussion

Comparison of antiregurgitation formulas

There are limited comparative studies. According to two trials of 24 and 60 infants, carob antiregurgitation reduced regurgitation better than a rice flour (5 g/100 mL) TF [13,55] and parental reassurance plus SF [13]. In 52 infants, a casein-predominant AR-F with pregelatinized cornstarch but not whey-based 5% rice TF reduced vomiting [31].

In another study, 168 infants who were fed cereals that were thickened with whey pHF showed significantly reduced regurgitation by 1.1 and 1.3 episodes per day after 7 and 14 d compared with a SF [60]. Yet another study of 115 infants who were fed a double (i.e., treated starch and locust bean gum) AR pHF showed decreased regurgitation better than a locust bean gum AR-F [50]. A rice-thickened eHF decreased GER symptoms in 40 infants [61]. Thickened (with a specific starch complex at 1 g/100 mL and 3.6 g/100 g of mainly pectin fibers) and nonthickened casein eHF reduced GER symptoms in infants with both negative and positive cow's milk allergy [62,63].

Preterm infants

In preterm infants with GER symptoms a casein eHF significantly reduced the reflux index and number of acid episodes compared with preterm SF [34]. In 28 preterm newborns, amyl pectin TFs reduced the number of acid reflux episodes as detected by pH-monitoring but not reflux index, acid, nonacid, and proximal GER as detected by esophageal impedance [64].

Reflux parameters

Eight studies analyzed the effect of AR-F/TF on reflux parameters (Table 2).

Carob/locust bean gum

In 1987, Vandenplas and Sacre reported a normalization of all pH-monitoring parameters in 6 of 30 infants who were fed a carob bean gum (1 g/115 mL) TF. In the remaining 24 infants, the total number of reflux episodes significantly decreased, acid exposure (reflux index) and long reflux episodes were similar, and the longest reflux episode significantly increased [48]. A significant decrease of the reflux index was detected in two other studies [33,55].

In the only study that used intraluminal impedance pH, a slight but not significant decrease in proximal reflux and total number of reflux episodes was noted in 14 infants who were fed carob (0.4 g/100 mL) AR-F compared with SF [51].

Corn starch

In two studies, a casein dominant cornstarch AR-F reduced all pH-metric parameters in 51 and 52 infants, respectively [31,52]. In another RCT, a pregelatinized cornstarch AR-F decreased the reflux index in 87% of infants with a significant difference compared with a SF [53].

Rice

In six infants, a significant reduction in the total number of (acid) reflux episodes was observed but not in the reflux index with rice TF [29]. However, no improvement of reflux parameters was reported in a comparative study that enrolled 52 infants who were fed whey-based 5% rice TFs [31].

In a meta-analysis of AR formula [16], only four studies (using rice [65], corn [52,53], or carob bean gum [33] as a thickening agent) and overall 107 infants were analyzed in terms of reflux parameters measured by pH-monitoring but no statistical effect in the pooled results were observed.

Adverse effects of antiregurgitation formula?

European legislation allows for the supplementation of formula with modified starches up to either 30% of total carbohydrate or 2.0 g/100 mL [30] while the maximum accepted level of locust bean gum is 1 g/100 mL, which requires medical supervision to treat GER (Table 2) [19,20].

Caloric intake

The increased caloric density of thickened formula may benefit only infants who fail to thrive because of regurgitation, vomiting, or inadequate intake. Locust bean gum has no caloric content and is not absorbed; therefore, caloric intake does not increase [27].

Mineral absorption

According to an in vitro study, the absorption of nutrients and mineral bioavailability in infant formula could be impaired by nondigestible carbohydrates [66]. The in vitro model showed that the solubility and dialyzability (measured by atomic absorption spectrophotometer) of calcium was negatively affected by locust bean gum (significantly higher) and modified (pregelatinized) corn and rice starch when added in concentrations >50% of the maximum legal limit. Only locust bean gum (at concentrations of ≥0.5 g/100 mL) had a negative effect on the solubility and dialyzability of iron and zinc [18].

These effects can be related to the higher amount of phytic acid (myoinositol hexaphosphoric acid) in locust bean gum (47 mg/100 g) compared with modified starch (19 mg/100 g in corn; 17 mg/100 g in rice), the gel-forming capacities, and presence of ionizable groups that bind locust bean gum with calcium, iron, and zinc to form unabsorbable complexes and decrease mineral availability [18]. However, an in vivo trial that tested a casein-predominant locust bean gum (0.4 g/100 mL) AR-F in 20 healthy infants from birth to 3 mo of age reported normal growth as well as blood nutritional and mineral parameters that were similar to a whey predominant SF [67]. No difference in blood cholesterol and triacylglycerol levels were observed in 25 infants who were fed for 6 wk with locust bean gum AR-F compared with SF [68].

In all clinical studies with locust bean gum AR-F, neither specific adverse or negative effects on growth were reported [13,33,38,39,46,48,50,51,55]. Currently, locust AR-F contains ≤0.5 g/100 mL of bean gum to confer a protective margin of safety in (term) infants but a combination of thickening agents have been proposed [18,27]. The addition of rice cereal to formula at a (high) concentration of 6.5 g/100 mL still resulted in normal bioavailability of calcium and iron in 1 to 3 mo old infants [69]. To compensate the (theoretical) risk of (in vivo) malabsorption, many AR-F also present a higher mineral content compared with SF.

Arsenic load

On the basis of current literature, a risk assessment of the daily intake of rice cereal was conducted by the U.S. Food and Drug Administration in infants and toddlers [57]. Although the hazard quotients for acute intake were consistently below 1.0, the ones for chronic intake exceeded 1.0 for rice cereal with incremental lifetime cancer risks that ranged from $10^{(-6)}$(50th) to $10^{(-5)}$(75th percentile). The maximum contaminant level for arsenic in rice cereal reached up to 0.4 mg/kg and should be considered [57].

Bowel movements

Bean gum may act as vegetable fiber with a prebiotic effect that can possibly modify bowel frequency. In three studies with locust AR-F, bowel movements increased in 10% of infants but without severe diarrhea [14,38,39]. No difference in stool consistency or frequency were reported in six other studies [16,40,46,50,56,61].

Conversely, difficulty to defecate occurred in infants who were fed a rice TF at a high concentration (one heaping tablespoonful every 30 mL [29] or 5 g/100 mL [31]). Of 53 infants, 8 developed mild difficulty and 11 reported severe difficulty in defecation during rice-based feedings [56]. A pretreated rice AR-F did not cause constipation [28].

Cough

An increased in coughing has been reported in infants who were fed rice TFs [32] but not those who were fed rice AR-F [28].

Allergy

Risk of allergy to thickening agents is currently unknown. An isolated case of allergy to carob gum in infants has been published [70].

Special concerns in preterm infants

A possible association between thickened feedings and necrotizing enterocolitis in preterm infants has been highlighted [71]. In 2011, the U.S. Food and Drug Administration issued a warning with regard to the use of a thickening agent that contains xanthan gum in infants who are born before 37 wk of gestation and who receive hospital care or are discharged from the hospital within the previous 30 d [3].

Moreover, locust bean gum TFs should be excluded from meals for premature infants or those with a low birth weight [8] because 0.2 g to 0.5 g/100 mL locust bean gum TFs increased the frequency of defecation, metabolic acidosis, and hypokalemia in six infants who were born premature and vomited [72].

Conclusions

The approach for infants who regurgitate consists of parental reassurance and education about position and feeding. AR-F reduces regurgitation with an effect depending on the thickening agent, concentration, protein ratio, and hydrolysis. Although locust bean gum increases viscosity more than other thickening agents, there is no evidence that one thickener is clinically better than another. AR-F offers the advantage of a balanced composition, controlled viscosity, and calories compared with the addition of thickening agents to a SF. Recent data suggest that thickened HF may also reduce regurgitations and accelerate gastric emptying.

Physicians may consider the use of AR-F in infants with persisting troublesome regurgitations while weighing cost, efficacy, parental concern, and possibly the reduction of the use of unnecessary medications and medical referrals.

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