

# Effects of Thickened Feeding on Gastroesophageal Reflux in Infants: A Placebo-Controlled Crossover Study Using Intraluminal Impedance

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**ABSTRACT.** *Objective.* Thickening of formula feedings is part of the therapeutic approach for gastroesophageal reflux (GER) in infants. However, its mechanism of action, especially regarding the occurrence of nonacid (pH >4) GER, has not yet been clearly described. The aim of this randomized, placebo-controlled crossover study was to examine the influence of formula thickened with carob (St. John's bread) bean gum on acid and nonacid GER.

*Methods.* Infants with recurrent regurgitation and without other symptoms were fed alternately (A-B-A-B-A-B) with thickened (A) and nonthickened (B) but otherwise identical formula. Documentation of GER episodes during the study was performed by simultaneous intraesophageal impedance measurement (intraluminal electrical impedance; IMP) and pH monitoring. The IMP technique is able to detect bolus movements inside a luminal organ. The use of multiple measuring segments on a single catheter allowed the analysis of direction, height, and duration of the bolus transport. Continuous videorecording and visual surveillance of regurgitation frequency and amount resulted in a severity score.

*Results.* Fourteen infants (42 ± 32 days old) were examined during 6 feeding intervals each for a total measuring time of 342 hours. A total of 1183 GER episodes and 83 episodes of regurgitation were registered. Regurgitation frequency (15 vs 68 episodes) and amount (severity score 0.6 vs 1.8) were significantly lower after feedings with thickened formula. The difference regarding the occurrence of GER documented by IMP was also pronounced (536 vs 647 episodes). Although not statistically significant, maximal height reached by the refluxate in the esophagus was decreased after thickened feedings. Mean GER duration and the frequency of acid (pH <4) GER were not altered.

*Conclusions.* Thickened feeding has a significant effect on the reduction of regurgitation frequency and amount in otherwise healthy infants. This effect is caused by a reduction in the number of nonacid (pH >4) GER episodes, but also because of a decrease of mean reflux height reached in the esophagus. However, the occurrence of acid GER is not reduced. The combination of IMP and pH monitoring allows the complete registration and description of these GER episodes. Thickening of formula feedings with carob bean gum is an efficient therapy for uncomplicated GER in infants. *Pediatrics* 2003;111:e355–e359. URL: <http://www.pediatrics.org/cgi/content/full/111/4/e355>; *gastroesophageal reflux, infants,*

*thickened feeding, intraluminal electrical impedance technique, placebo-controlled study.*

ABBREVIATIONS. GER, gastroesophageal reflux; IMP, intraluminal electrical impedance; Formula A, thickened; Formula B, non-thickened.

The thickening of formula feedings is part of the stepwise therapeutic approach for gastroesophageal reflux (GER) in infants.<sup>1–4</sup> Esophageal pH monitoring is considered a standard test to diagnose GER.<sup>3,5,6</sup> However, buffering gastric acidity and frequent feeding of infants are known to prolong periods of hypoacidity, and, especially after feedings, reflux events with pH >4 are not detected by pH monitoring.<sup>7,8</sup> Even so, to investigate the effects of thickened (Formula A) feedings, most studies relied on the validity of esophageal pH monitoring for the diagnosis of GER.<sup>9–13</sup>

Carob (St. John's bread) bean gum is a galactomannan, which is refined from the carob tree, *Ceratonia siliqua*. Both rice cereal and bean gum are used in dietary preparations as thickening agents. As opposed to rice cereal, which is broken down by salivary amylase, bean gum is not split by these enzymes and thus maintains its thickening effect also after reaching the stomach. It provides no nutritional value and does not alter the energy distribution of infant formula.<sup>2</sup>

The objective of this prospective, randomized, placebo-controlled crossover study was to evaluate the effect of formula thickened with carob bean gum<sup>2</sup> on the number and the characteristics of acid (pH <4) and nonacid (pH >4) GER events by using a combination of pH monitoring and the pH-independent multiple intraluminal electrical impedance (IMP) technique.<sup>8,14–17</sup>

## METHODS

Otherwise healthy infants with recurrent regurgitation that fulfilled the inclusion criteria (Table 1) were evaluated. During the initial surveillance period of 3 consecutive days, regurgitation frequency and amount were documented. To exclude GER secondary to other medical conditions, the following prestudy examinations were performed: complete blood count, total immunoglobulin E, radioallergosorbent test (cow's milk protein, casein,  $\alpha$ -lactalbumin,  $\beta$ -lactoglobulin), skin prick test (formula before study entry, both study formulas, normal saline, histamine), ultrasound of the abdomen and head, urinalysis, and stool cultures. Any abnormal finding from these examinations resulted in exclusion from the study. During the following 24-hour prestudy phase, all included infants were switched from their initial formula to Formula B (Table 2).

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**TABLE 1.** Inclusion and Exclusion Criteria for Infants Entering Study

Inclusion Criteria	Exclusion Criteria
Recurrent regurgitations: >5 regurgitations of at least a small volume (5 mL), or at least 1 regurgitation of at least half of the feeding per day, during a surveillance period of 3 consecutive d	No or <5 regurgitations of a small volume (5 mL) per d, during a surveillance period of 3 consecutive d
<4 mo old	Suspected food allergy
Body weight >2000 g	Gastroenteritis
Exclusively formula-fed	Other acute infection
	Apneas and/or bradycardias
	Regurgitation secondary to other cause
	Medication influencing esophageal motility

Investigation for GER was performed by combined measurement of intraesophageal pH and multiple electrical impedance.<sup>8,17</sup> The principle of IMP registration is based on the measurement of electrical impedance changes between 2 neighboring electrodes during the passage of a bolus inside a luminal organ. By arranging multiple electrodes sequentially on a catheter, the direction of bolus movement can be described. In this study, a single flexible catheter with 7 impedance electrodes (outer diameter 1.5 mm), representing 6 bipolar impedance channels (Helmholtz-Institut für Biomedizinische Technik, Aachen, Germany), and a pH-sensitive antimony electrode was used. A GER episode is defined as a decrease in impedance starting in the most distal channel and subsequently extending orally to the more proximal channels. The catheter was passed transnasally under fluoroscopy. The distance between each impedance electrode was 1.5 cm, resulting in a total measuring length of 9 cm. Measuring segments were positioned from just above the cardia (channel 6) to the pharynx (channel 1), with the pH sensor situated at the level of channel 5, ie, ~3 cm above the gastroesophageal junction. The acquisition rate of pH and impedance signals was 50 Hz per channel.

The infants were randomized to receive the 2 study formulas in an alternate fashion. The order of treatment was randomly assigned by a computer-generated method with the individual infant as the unit of randomization. Formula A contained 0.4% carob bean gum and was otherwise identical with Formula B (Table 2). During the study period, group I received alternate feedings beginning with Formula A (A-B-A-B-A-B) and group II received alternate feedings beginning with Formula B (B-A-B-A-B-A), according to the crossover study design and their randomization. Study formulas were prepared by a second independent caregiver after breaking the randomization code. The study phase lasted for at least 24 hours and at least 6 feedings, and was continued for at least 2 hours after the sixth feeding. During the study, each infant was fed with its individual feeding intervals and by the same caregiver. The study groups (I or II) were blinded to the investigators during the study and the data analysis.

Regurgitation amount and time were documented in a protocol by continuous visual surveillance and by continuous videorecording. The amount of a single regurgitation was scored visually as: ≤5 mL; >5 mL; about half of the feeding; or the complete feeding. The online regurgitation protocol was verified and eventually amended by analysis of the videorecording. Severity of regurgitations after a single feeding was quantified by a scoring system (Table 3).<sup>11</sup>

All impedance and pH data were stored simultaneously in a computer system at bedside. Data analysis for GER events was performed using custom software (Motility; Helmholtz-Institut für Biomedizinische Technik, Aachen, Germany) and visual validation. Impedance recordings were visually analyzed for the typical IMP pattern of GER, indicated by a retrograde esophageal

**TABLE 2.** Composition of Formula A and Formula B

Formula A and B	Per 100 g Powder	Per 100 mL Formula
Energy (kcal)	467	66
Protein (g)	12.2	1.72
Whey:casein	20:80	20:80
Lipids (g)	21	3.0
Carbohydrate (g)	58	8.2
Additionally in Formula A		
Carob bean gum (g)	3	.4

**TABLE 3.** Regurgitation Score After a Single Feeding

Score	Severity
0	No regurgitation
1	1 regurgitation of ≤5 mL
2	2 regurgitations of ≤5 mL, and/or 1 regurgitation of >5 mL
3	>2 regurgitations of ≤5 mL, and/or <3 regurgitations of >5 mL
4	≥3 regurgitations of >5 mL
5	Regurgitation of about half of the feeding
6	Regurgitation of the complete feeding

volume flow (Fig. 1). In this study, GER was diagnosed only if this typical pattern was noted in the esophageal impedance.

Documentation during each GER included the minimal pH value, the maximal height reached by the refluxate in the esophagus, and the duration of GER. GER duration was defined as time after the onset of a reflux episode needed to reach 50% of the initial impedance value in the most distal impedance channel (channel 6), which corresponds to a clearance >90% of the reflux volume in the measuring segment.<sup>8</sup>

Mean values were calculated for most parameters, including regurgitation score and reflux height, eventually resulting in "virtual" decimal values (Tables 4 and 5). Statistical analysis was performed using the paired Wilcoxon test (SAS/STAT 8.01; SAS Institute, Cary, NC). Significance was established by a value of  $P < 0.05$ .

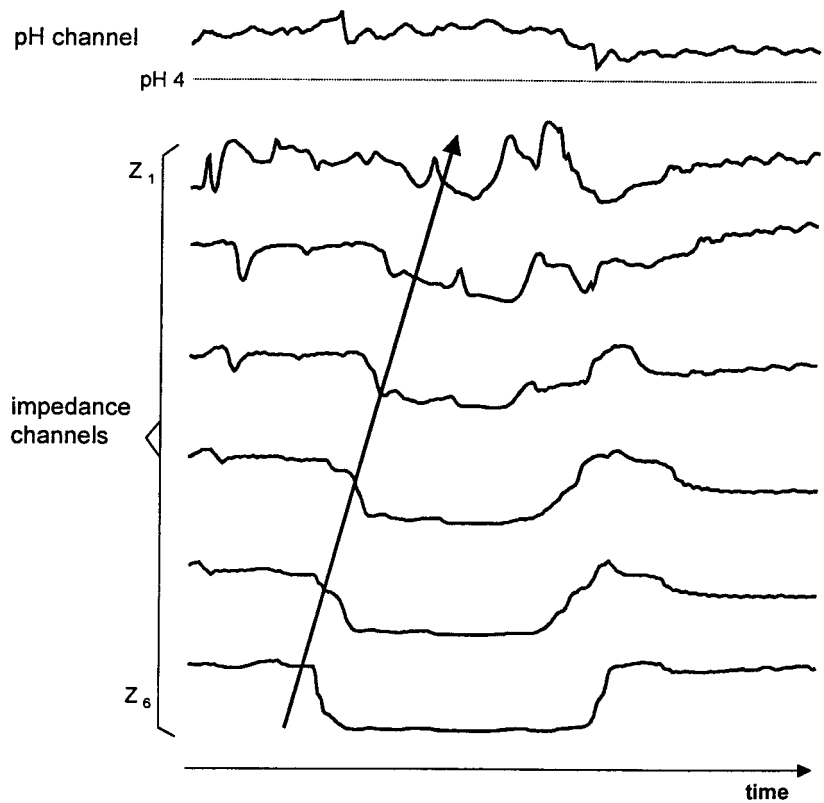
The study protocol was approved by the Ethics Committee of the Medical Faculty of the University Aachen (Aachen, Germany). Before beginning any evaluation of an infant, written informed consent was obtained from the parents.

## RESULTS

Fourteen infants (mean age at study  $42 \pm 32$  days; 9 female, 5 male) that fulfilled the inclusion criteria were examined. There were no dropouts during the prestudy or the study phase. No infant showed signs of a secondary cause of GER or regurgitation. Seven infants were randomized to study group I, and 7 infants to study group II. The study formula was tolerated well by all infants.

During a total measuring time of 342 hours, 83 regurgitations (15 after Formula A, 68 after Formula B;  $P < .0003$ ) were documented by visual surveillance and video analysis. Calculated from 3 feeding periods in each infant, the mean regurgitation score for a single feeding was 0.6 after Formula A, and 1.8 after Formula B ( $P < .003$ ). Seven infants (50%) did not regurgitate at all after Formula A; 1 (7%) of these 7 infants also did not regurgitate at all after Formula B.

A total of 1183 GER episodes (536 after Formula A, 647 after Formula B;  $P < .02$ ) were detected by the typical pattern in the impedance tracings. Reflux events occurred in all patients. For technical reasons



**Fig 1.** Original tracing of a typical nonacid GER. The retrograde esophageal bolus passage is characterized by a decrease of impedance ( $Z$ ) starting in the most distal channel ( $Z_6$ ) and subsequently extending orally to the most proximal channel ( $Z_1$ ). The pH is remaining  $>4$  throughout the entire GER episode. The pH sensor is situated at the level of channel 5; the arrow indicates the bolus passage from distal to proximal.

**TABLE 4.** Details of GER Episodes in Individual Infants: 3 Feedings of Formula A Versus 3 Feedings of Formula B

Patient Number	Group	Regurgitation Frequency ( $n$ ) After Formula		Regurgitation Score After Formula		GER Episodes ( $n$ ) After Formula		GER Height (Impedance Channel) After Formula		GER Duration (Seconds) After Formula		Acid GER ( $n$ ) After Formula	
		A	B	A	B	A	B	A	B	A	B	A	B
1	II	3	14	6.5	9.5	73	96	2.6	2.8	15.4	13.1	43	59
2	II	1	2	1.0	10.0	12	25	3.2	2.5	22.0	36.7	3	3
3	I	0	2	0	2.0	7	22	3.3	3.0	56.3	85.5	2	14
4	I	6	12	7.5	7.5	64	56	2.2	2.1	22.8	17.5	20	26
5	II	0	0	0	0	27	36	2.9	2.4	32.5	32.3	17	13
6	I	0	2	0	2.0	36	39	2.6	2.5	30.7	31.4	5	4
7	II	0	7	0	5.5	49	53	2.7	2.6	56.0	35.7	24	28
8	I	1	7	1.0	6.5	67	82	2.2	2.2	29.3	26.9	27	21
9	I	1	3	5.0	3.0	43	38	2.0	1.9	52.3	32.3	2	3
10	II	0	2	0	2.0	27	40	2.6	2.9	20.7	20.2	1	1
11	II	0	4	0	5.0	28	39	2.9	2.6	26.5	19.5	10	11
12	I	0	5	0	5.0	28	51	2.5	2.2	43.3	28.6	6	4
13	II	1	2	1.0	2.0	23	28	2.6	2.8	48.2	67.4	4	4
14	I	2	6	3.5	13.5	52	42	2.2	2.0	50.3	28.4	13	9

All figures calculated as mean values, resulting in "virtual" decimal values for regurgitation score and GER height. (Group I: infants fed A-B-A-B-A-B; Group II: infants fed B-A-B-A-B-A).

the pH of 5 GER in 1 patient (number 11) could not be determined. A total of 377 (32.0%) GER were acidic (pH  $<4$ ), and 4 (0.3%) alkaline episodes (pH  $>7$ ) were recorded. Calculated mean GER height was impedance channel 2.6 after Formula A, and impedance channel 2.5 after Formula B ( $P = .08$ ), with channel 1 being the most proximal channel. Mean GER duration was 36.2 seconds after Formula A, and 33.9 seconds after Formula B ( $P = .3$ ). The number of acid GER episodes (pH  $<4$ ) was 177 after Formula A and 200 after Formula B ( $P = .6$ ).

The majority of reflux events was nonacid (801 nonacid GER vs 377 acid GER;  $P < .007$ ). Calculated mean GER height was impedance channel 2.5 during

a nonacid GER, and impedance channel 2.6 during an acid GER ( $P = .2$ ). Mean GER duration of a nonacid GER was 30.4 seconds, and of an acid GER 43.1 seconds ( $P < .05$ ).

Data from individual infants are summarized in Tables 4 and 5.

## DISCUSSION

There has been controversial discussion as to whether there is a place for thickened feeding in the therapeutic regimen for GER in infants.<sup>1,4,18</sup> However, in most studies examining this question, the diagnostic tool used to detect GER episodes was pH monitoring.<sup>3,5,6</sup> Various authors using pH monitor-

**TABLE 5.** Details of GER Episodes in Individual Infants After 6 Feedings: Nonacid (pH >4) Versus Acid (pH <4) GER

Patient Number	Group	GER Episodes ( <i>n</i> )		GER Height (Impedance Channel)		GER Duration (Seconds)	
		Nonacid	Acid	Nonacid	Acid	Nonacid	Acid
1	II	67	102	2.6	2.8	10.2	16.7
2	II	31	6	2.7	3.2	24.4	66.7
3	I	13	16	3.4	2.8	36.5	112.6
4	I	74	46	2.2	2.2	20.0	20.9
5	II	33	30	2.6	2.7	33.9	30.7
6	I	66	9	2.4	3.2	29.3	44.6
7	II	50	52	2.6	2.8	27.5	62.7
8	I	101	48	2.2	2.3	28.0	27.9
9	I	76	5	2.0	1.8	44.7	16.4
10	II	65	2	2.8	2.5	20.3	23.0
11	II	41	21	2.7	2.9	20.4	25.9
12	I	69	10	2.3	2.6	31.0	53.1
13	II	43	8	2.6	3.1	58.0	62.5
14	I	72	22	2.1	2.0	40.7	39.8

All figures calculated as mean values, resulting in "virtual" decimal values for GER height. (Group I: infants fed A-B-A-B-A-B; Group II: infants fed B-A-B-A-B-A).

ing in their studies did not find a significant influence on acid (pH <4) GER.<sup>9,10,13</sup> It is known from previous studies that the majority of reflux events in the infant age group are nonacid (pH >4), especially because of postprandial gastric neutralization after milk feedings.<sup>7,8</sup> These GER episodes are undetectable by pH monitoring.<sup>17</sup> Therefore, we used the pH-independent IMP technique in combination with pH monitoring<sup>7,8,14</sup> and continuous visual and video surveillance.

To exclude secondary causes of GER, infants were evaluated carefully before entering the study.<sup>11</sup> To exclude an influence of the different infant formulas fed before the study on the results, all infants received the same Formula B during the final prestudy day. To exclude interference by handling variation because of caregiver experience, each individual infant was fed by the same caregiver during the whole study phase. Initially, the study was designed as double-blind and placebo-controlled. When applying strict study criteria, we found that by their appearance the 2 study formulas could be distinguished by experienced personnel. Therefore, "double-blind" was deleted from the study design. However, during data analysis, the study groups, and thus the order of treatment, were blinded to the investigators. Furthermore, in the chosen crossover design, each individual infant served as its own control.

There was a significant decrease of regurgitation frequency and amount (score) after feeding Formula A. Half of the infants did not regurgitate at all after Formula A. This effect was mostly caused by a significant reduction of GER episodes after Formula A, with GER events occurring in every single infant.

It is known from previous studies<sup>8</sup> that most GER episodes reach the uppermost impedance channel (channel 1, located in the pharynx). This is true for GER with and without regurgitation. In light of these findings, the slight reduction of reflux height reached in the esophagus after Formula A, although not statistically significant ( $P = .08$ ), probably also contributed to the decrease of regurgitation frequency.<sup>19</sup> However, there was no significant difference in

reflux height regarding acid versus nonacid GER. As demonstrated previously,<sup>10,13</sup> the occurrence of acid (pH <4) GER was not significantly reduced after thickened feeding. Because the majority (68%) of reflux events was nonacidic (pH >4), one must assume that especially their reduction led to a decrease of regurgitation frequency. Alkaline (pH >7) GER episodes were rare (0.3%), and their role is not yet clear in this age group.

There has been concern about a suspected increase of regurgitation amount after thickened feeding as a result of delayed retrograde and anterograde gastroesophageal motility.<sup>9</sup> This could not be confirmed by our study results. Mean GER duration was not significantly prolonged after feeding Formula A. As expected from previous studies using pH monitoring and impedance,<sup>8,15</sup> the duration of acid GER was longer than that of nonacid GER. This is because of a delay of acid clearance versus volume clearance.

The effects of thickened feeding were analyzed in detail with this study. The combination of pH and impedance measurement was able to deliver valuable new information regarding gastroesophageal motility.<sup>7</sup> We conclude from our results that formula thickened with carob bean gum<sup>2</sup> is an efficient therapy for uncomplicated GER and regurgitation in infants. There is an obvious advantage of using prethickened feedings versus individually added thickener regarding hygiene and handling. Following the recommendations, thickened formula should only be used under medical supervision and after parental advice and reassurance.<sup>1,3,18,20,21</sup>

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