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Use of a Partially Hydrolyzed 100% Whey-Based Infant Formula with *Lactobacillus Reuteri* in Infants with Caregiver-Perceived Intolerance

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Abstract

This study evaluated the impact of switching exclusively formula-fed infants with caregiver-perceived formula intolerance to a reduced lactose, partially hydrolyzed 100% whey-based formula (PHF-W) with *Lactobacillus reuteri* and 2-fucosyllactose.

Infants identified as 'very' or 'extremely' fussy by caregivers were eligible for this single-arm, single-blind study. Subjects switched their current formula to study formula for three weeks. Gastrointestinal tolerance was assessed by the Infant Gastrointestinal Symptom Questionnaire (IGSQ) at baseline and end of the study. Caregivers ranked their infants' fussiness (not at all, slightly, moderately, very, extremely) after the first three feedings of study formula and 24 hours after enrollment. A paired t-test was used to compare the change in IGSQ score, and a paired t-test and Wilcoxon signed rank test were used to compare post-feeding fussiness scores to baseline.

Fifty infants (mean±std age 28.9±14.5 days) were enrolled; 41 completed the study per protocol. Mean (±std) baseline IGSQ score was 34.9±10.0, dropping to 22.1±7.5 after three weeks ($p < 0.001$). 48/50 (96%) caregivers stated their infants' fussiness improved after 24 hours, and 2 (4%) remained the same. 42/46 (91%) caregivers stated their infants' fussiness improved after the first feeding, and 4 (9%) remained the same. Caregiver-ranked fussiness significantly improved after the first, second, and third feedings and after 24 hours as compared to baseline ($p < 0.001$ for all).

IGSQ scores significantly improved after three weeks of feeding with PHF-W containing *Lactobacillus reuteri* and 2-fucosyllactose in infants with caregiver-perceived intolerance, and improvements in fussiness were noted as quickly as after the first feeding.

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Introduction

While breastfeeding is the best way to nourish infants, some caregivers choose to use infant formula, whether as a supplement to breastmilk or as sole source of nutrition. Functional gastrointestinal disorders (FGID), such as spit-up, colic, and constipation can occur in up to 50% of infants, regardless of feeding mode[1]. One cross-sectional study of children in the US revealed 37.9% of infants less than 1 year old met the Rome IV diagnostic criteria for at least one FGID, with regurgitation being the most common symptom reported[2]. When such events occur in the formula-fed infant, parents may believe these symptoms reflect formula intolerance and change their formula, frequently without seeking advice from their healthcare professionals[3].

Infant and toddler FGID have been defined as variable combinations of often age-dependent, chronic or recurrent symptoms not explained by structural or biochemical abnormalities[4]. Such conditions may be considered less concerning if their etiology is not due to a pathologic medical issue like cow's milk protein allergy; however, they can decrease the quality of life for the affected infants and families[5-6]. FGID can cause concern in parents who may seek ways to alleviate these conditions. One study showed that almost half of infant formula users switch their infants' formula in the first six months of life mainly because of reported regurgitation and restlessness[3]. Modifications to infant formulas have been made to address some of these common issues.

Functional GI disorders are currently recognized as being disorders of the gut-brain axis[7]. There is growing evidence that the microbiota plays a role in the development of certain FGIDs suggesting potential for probiotics for pediatric populations suffering from these symptoms[8]. *Lactobacillus reuteri* DSM 17938 has been studied as a candidate for its ability to help address symptoms that commonly occur in infancy. Supplementation of *Lactobacillus reuteri* DSM 17938 has been clinically shown to reduce spit-ups and improve gastric emptying significantly more than a placebo in healthy infants and in infants diagnosed with uncomplicated regurgitation[9-13]. Multiple studies have demonstrated *L. reuteri* reduces crying time significantly more than a placebo in colicky infants. *L. reuteri* may improve symptoms of colic and fussiness because of its influence on gastrointestinal motility via the gut-brain axis[9-11], by strengthening the mucosal barrier, altering gut motility, and balancing the microbiota[9-11,14-17].

Parents may perceive their infant is not tolerating an infant formula due to specific symptoms related to spit-up, stooling, or gas, or a combination of these issues, leading to generalized fussiness. If the parent attributes this to the infant's formula, they may switch infant formulas. This study evaluates the impact of switching infants with perceived formula tolerance issues to an infant formula containing partially hydrolyzed whey and *L. reuteri* with reduced lactose on measures of infant feeding tolerance.

Methods

Healthy, exclusively formula-fed, full-term infants (14-60 days of age) with caregiver-perceived fussiness were recruited. Caregivers were asked to rate their infants' fussiness based on their perception as being not at all fussy, slightly fussy, moderately fussy, very fussy, or extremely fussy. Infants whose caregivers identified them as 'very' or 'extremely' fussy were eligible for enrollment. A history of infant formula use was obtained, and infants who had already received more than three different infant formulas since hospital discharge were not eligible for enrollment nor were any infants receiving specialty infant formula (extensively hydrolyzed or amino acid-based). Infants who were currently receiving or had received the commercially available study formula in the past were not eligible for recruitment.

Subjects were recruited from six sites across the United States. Informed consent was obtained from the parents or guardians of all participating infants. Good clinical practice was followed by all sites throughout the study. The study protocol was approved by Advarra Institutional Review Board (Columbia, MD) and registered at clinicaltrials.gov (NCT03679234).

The primary outcome of this study was formula tolerance based on the Infant Gastrointestinal Symptom Questionnaire (IGSQ). The IGSQ is a validated 13-item questionnaire that assesses an infant's gastrointestinal-related signs and symptoms as observed by caregivers/parents over the previous week in five domains: stooling, spitting up/vomiting, flatulence,

crying, and fussing[18]. Caregivers/parents provide one response to each question as it is read to them by a trained interviewer, and each item is scored on a scale of 1 to 5, with higher values indicating greater GI distress. The total IGSQ score is calculated by summing all individual item responses. The possible range in scores is 13 to 65, where a score of 13 indicates no GI distress and a score of 65 represents extreme GI distress. The IGSQ was performed at baseline and then repeated after 3 weeks of study formula use.

The formula tested was a commercially available 100% whey, partially hydrolyzed infant formula (2.2 g protein/100kcal) with reduced lactose (30% of carbohydrate source), 2-fucosyllactose (0.25 g/ L reconstituted formula), and *L. reuteri* ($1x10^6$ CFU/g powder). Caregivers were blinded to the formula identity.

All subjects were switched to the study infant formula following the baseline visit, and caregivers were instructed to feed the study infant formula solely for a period of three weeks. After each of the first three feedings with the study formula, caregivers documented the volume consumed by the infant and ranked the infant's fussiness according to the same scale (not at all, slightly, moderately, very, or extremely fussy). Twenty-four hours after the study visit, study personnel called each caregiver and inquired about the infant's fussiness. Subjects then returned to the study site after 3 weeks of feeding study formula for the final study visit, and caregivers completed the IGSQ as well as a formula satisfaction questionnaire. Any serious or non-serious adverse events were recorded throughout the study period. For any adverse event, the study investigator assessed the possible relationship to the study product.

Subject demographics were summarized using means, standard deviations and ranges for continuous measures, and counts and percentages for categorical measures. Total IGSQ scores were calculated for each subject at baseline and at three weeks, according to the IGSQ scoring guidelines. The difference in IGSQ score was then calculated for each subject by subtracting the baseline score from the three-week score. A paired t-test was used to test for a significant change in IGSQ. Fussiness ratings were assigned scores from 0 for "Not at all fussy" to 4 for "Extremely fussy", and summarized as a continuous variable with means, standard deviations and ranges at each of the five time points recorded. Improvement in fussiness was defined as a reduction in the fussiness rating post-initiation compared to baseline fussiness. Paired t-tests and the non-parametric Wilcoxon signed rank tests were used to compare the continuous fussiness scores at each report to the baseline fussiness score. All significance tests were two-sided and alpha was set to 0.05. Analyses were conducted using Stata version 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP).

Sample size was estimated for the primary endpoint of change in IGSQ score assuming a 5-point reduction in the IGSQ from baseline to day 21, an alpha -level of 0.05 and 80% power. For sample size calculations, the mean IGSQ score at V0 was assumed to be 38, with a standard deviation of 8, based on a prior study of infants looking to switch formula[18]. At the final visit, the IGSQ score was assumed to be 33 (reduction by 5 points) with a standard deviation again of 8. Estimates of the correlation between the baseline and final IGSQ scores were derived from a previous study using the same base infant formula[19]. Assuming the most conservative (i.e. lowest) correlation of 0.11 as well as 80% power, alpha of 0.05, and a two-sided test, the resulting sample size requirement was 38 infants. Target enrollment was thus 55 subjects to allow for up to 30% attrition rate.

Results

A total of 50 subjects (54% male) were enrolled. Mean age was 28.9±14.5 days (mean±SD) at enrollment. Most subjects' caregivers rated them as 'very' fussy (76%), and the remaining were 'extremely' fussy (24%) at enrollment. The majority of subjects were African American (56%) and were receiving an intact protein-based infant formula at the time of enrollment (84%). Subject demographics are presented in Table 1.

Nine subjects did not complete the study per protocol. Three subjects were lost to follow-up, one subject moved, two subjects discontinued study formula and began consuming non-study formula during the study, and two subjects withdrew because of an

Table 1. Demographics, Intention to Treat (ITT)

	Total (N=50)
	N (%) or Mean [std] (range)
Gender	
Male	27 (54%)
Female	23 (46%)
Ethnicity	
Asian	1 (2%)
Black	28 (56%)
Caucasian	18 (36%)
Hispanic	2 (4%)
Other	1 (2%)
Delivery type	
Vaginal	33 (66%)
Caesarean	17 (34%)
Age at enrollment, days (mean [std], min-max)	28.9 [14.5] (8-61)
Gestational age at birth, weeks (mean [std])	38.9 [0.8]
Weight at birth, g (mean [std])	3194.5 [329.5]
Mother's age	27.7 [5.4]
Highest level of maternal education	
Grade school	0 (0%)
High School	20 (40%)
Some college	18 (36%)
College	12 (24%)
Other	0 (0%)
Baby ever breastfed	
No	26 (52%)
Yes	24 (48%)
Mean [std], days	17.8 [14.6]
# of formula switches before enrollment	0.4 [0.5] (0-2)

adverse event (one with hard stools, rash, GERD; one with bronchiolitis). One subject was enrolled while using a thickened formula, and it was subsequently determined that the subject's caregiver had started using the thickened formula without consulting her doctor, thus leading the site investigator to approve subject enrollment. This subject completed the study but was not included in the PP analysis as inclusion/ exclusion criteria had not been met.

Baseline IGSQ for the intention-to-treat (ITT) population was 34.9±10.0 (mean ±SD; PP: 34.1 ±10.0). After 3 weeks of study formula use, the IGSQ score had a mean decrease of 12.7 points down to 22.1±7.5 ($p<0.001$; Figure 1). The per protocol (PP) population was similar with a mean decrease of 12.7 points down to 21.4±7.0 ($p<0.001$).

The baseline fussiness score was 3.2±0.4 in the ITT population. Compared to baseline, the fussiness score was significantly decreased after the first, second, and third feedings and after 24 hours ($p<0.001$ for all time points), ranging from 1.2 to 1.4. Similar results were seen with the PP population. No subjects worsened in their fussiness score from baseline to any of the time points assessed.

Caregivers' satisfaction with the study formula was high. In the ITT population, 93% of caregivers stated their infants were comfortable on the formula, and 95% reported being satisfied with the study formula. All caregivers stated their infants liked the study formula. As expected, satisfaction was greater in the PP population, with 98% of caregivers stating their infants were comfortable on the formula, and all caregivers stating they were satisfied with the study formula.

Twelve subjects reported 17 adverse events throughout the study. Of these, one adverse event was

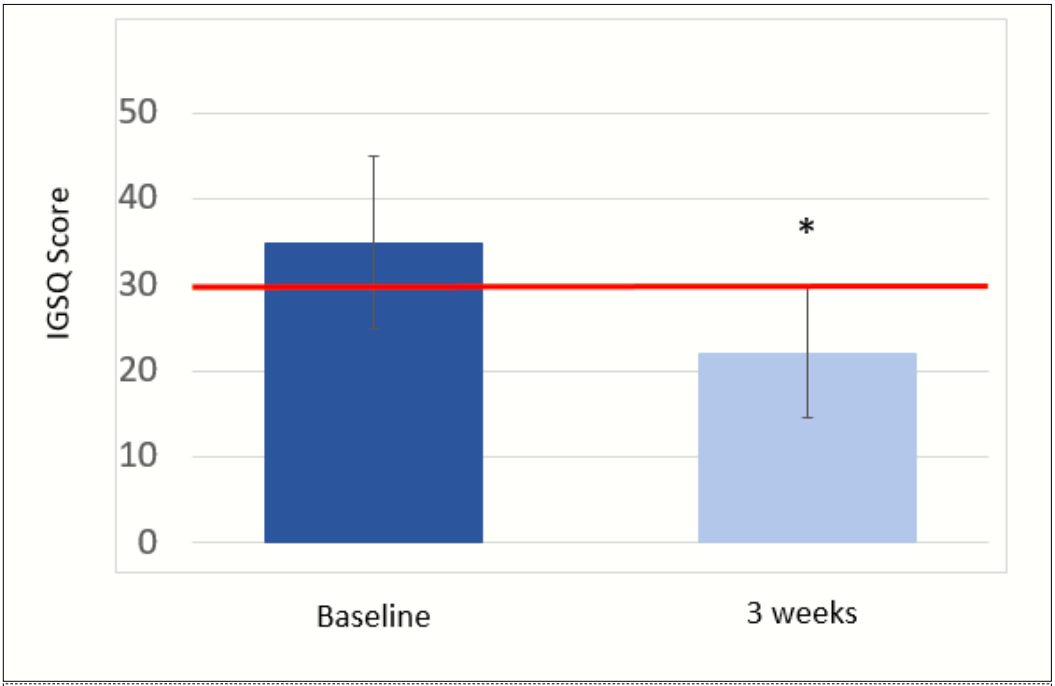

Figure 1. IGSQ Scores. Mean ± SD IGSQ scores at baseline and after 3 weeks of feeding. The IGSQ is a standardized, validated, interviewer-assisted questionnaire about stooling, vomiting, crying, fussiness, and flatulence, allowing parents to report the frequency and intensity of their infant's GI symptoms from the previous 7 days. For determination of the index score, the responses to questions are summed to produce a single score, which is a measure of the total GI symptom burden. Possible range of scores is 13-65, with higher scores indicating greater GI symptom burden. Red line indicates an IGSQ score of 30; scores ≥30 are indicative of GI distress[23]. IGSQ score was significantly decreased at 3 weeks compared to baseline (* indicates $p<0.001$ for mean difference ± standard deviation of -12.7 ± 1.5).

reported as having a probable relationship to study formula. This was hard stools reported by one subject who withdrew from the study. All other adverse events were not related to study formula. There were no serious adverse events.

Discussion

This was a single-arm study of healthy, exclusively formula-fed infants with caregiver-perceived intolerance. All subjects were switched from their usual formula to a commercially available formula with a partially hydrolyzed whey protein base, reduced lactose, 2-fucosyllactose and *L. reuteri*. IGSQ scores significantly decreased after three weeks of study formula feeding. In addition, fussiness as assessed by parents after the first three feedings of study formula and again 24 hours after enrollment, improved in nearly all subjects.

The use of the IGSQ tool in assessment of the subjects included in this study was advantageous for several reasons. The simplicity and broad assessment of GI symptoms is a major strength of the tool. The IGSQ is the only known tool to assess GI burden in infants to date that is simple to use, reliable and validated. To be enrolled in the study, subjects' caregivers had to perceive their infants as being 'fussy', with no strict definitions given. This fussiness could have been attributed to any one of several factors commonly seen in infants, and the IGSQ inquires about five different domains including stooling, spit-up, flatulence, fussiness, and crying. Therefore changes in the overall combined score can be reflective of differences in any singular domain, or more likely, in any combination thereof. This tool has been validated and used in several infant formula studies[18-21]. It is administered in a standardized way by trained personnel but answered by caregivers, providing an objective score for comparing an infant's GI symptoms. The intent of this research tool is to assess feeding tolerance through inquiries on GI distress and identification of non-normative patterns[18], which can translate into real-world situations of caregiver-perceived fussiness.

In this study, over 90% of caregivers documented improvements in fussiness as soon as after the first feeding, and this improvement in fussiness from baseline was maintained for the first three feedings as well as at 24 hours where 96% of caregivers reported an improvement. Importantly, the objective IGSQ scores which reflect gastrointestinal symptoms over the previous week were significantly decreased from baseline to three weeks after feeding of study formula. This indicates improvements in feeding tolerance occurred over the three-week period, remaining consistent with the reduction of fussiness perceived over the first 24 hours. From previous work, an IGSQ score of greater than 30 may be indicative of clinically meaningful digestive distress, and a score of 23 points has been observed for healthy infants[18]. In this single-arm study, subjects were enrolled with a mean IGSQ score of 34.9 points (indicating clinically meaningful GI distress) which then decreased after three weeks to a range associated with healthy infants without GI distress (score of 22.1).

Several attributes of the study formula may have contributed to the improvements recorded by caregivers. The protein base of the study formula was partially hydrolyzed whey which has been shown to empty rapidly from the stomach[22-24], thereby potentially reducing the likelihood for spit-up and also producing softer stools when compared to intact cow's milk protein -based infant formula[25]. *L. reuteri* strengthens the mucosal barrier, improves gastric emptying time, and balances the microbiota[9,14-15]. *L. reuteri* has been shown to reduce spit-up frequency in infants with regurgitation and reduce crying time in colicky infants[15,26-29]. The reduced lactose content in the study formula could also help in reduction in gas for any subjects who may have had a lactose sensitivity, though this is rare in infants.

The major limitation of this study was that it was a single-arm study. All subjects were switched to the same formula, and caregivers were aware this was not a randomized, controlled study. The placebo effect or a desire to please study staff on the 24 hour phone call could have played a role in caregiver-perceived fussiness. However, improvements were seen in fussiness in nearly all subjects (>90%) after the first feeding and after 24 hours (>95%) and post-hoc power calculations assuming a placebo effect for improved proportion ranging from 0.5 to 0.7 demonstrated over 80% power to detect the observed improved proportion

for both the first feeding and the 24-hour telephone call in the ITT and PP populations.

Conclusion

This trial demonstrated an improvement in feeding tolerance in infants considered to be very fussy or extremely fussy by their caregivers. It utilized a unique study design with a combination use of a validated feeding tolerance tool and solicitation of subjective perceptions of caregivers. Feeding a formula with 100% whey, partially hydrolyzed protein, reduced lactose, 2-fucosyllactose, and probiotic L. reuteri was associated with a perception of a rapid reduction in infant fussiness and improved gastrointestinal comfort after three weeks as assessed by an objective, validated tool, and high caregiver satisfaction.

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