

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Effect of a Low-Allergen Maternal Diet on Colic Among Breastfed Infants: A Randomized, Controlled Trial

David J. Hill, Neil Roy, Ralf G. Heine, Clifford S. Hosking, Dorothy E. Francis, Jennifer Brown, Bernadette Speirs, Joel Sadowsky and John B. Carlin

Pediatrics 2005;116:e709-e715

DOI: 10.1542/peds.2005-0147

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.pediatrics.org/cgi/content/full/116/5/e709>

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2005 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



Effect of a Low-Allergen Maternal Diet on Colic Among Breastfed Infants: A Randomized, Controlled Trial

David J. Hill, FRACP*‡; Neil Roy, FRACPS; Ralf G. Heine, MD, FRACP*‡||;
Clifford S. Hosking, MD, FRACP*; Dorothy E. Francis, APD*; Jennifer Brown, RN*; Bernadette Speirs, RN§;
Joel Sadowsky, FRACPS; and John B. Carlin, PhD‡||¶

ABSTRACT. *Background.* There is controversy regarding whether hypersensitivity to food proteins contributes to colic among breastfed infants.

Methods. A randomized, controlled trial of a low-allergen maternal diet was conducted among exclusively breastfed infants presenting with colic. In the active arm, mothers excluded cow's milk, eggs, peanuts, tree nuts, wheat, soy, and fish from their diet; mothers in the control group continued to consume these foods. Outcomes were assessed after 7 days, as the change in cry/fuss duration over 48 hours, with validated charts. The primary end point was a reduction in cry/fuss duration of $\geq 25\%$ from baseline. Mothers also assessed the responses to diet with categorical and visual analog scales.

Results. Of 107 infants, 90 completed the trial (mean age: 5.7 weeks; range: 2.9–8.6 weeks; 54 male infants). Infants in both groups presented with significant distress (geometric mean: low-allergen group: 690 minutes per 48 hours; control group: 631 minutes per 48 hours). In follow-up assessments on days 8 and 9, there were significantly more responders in the low-allergen group (74% vs 37%), ie, an absolute risk reduction of 37% (95% confidence interval: 18–56%). Cry/fuss duration per 48 hours was reduced by a substantially greater amount in the low-allergen group; the adjusted geometric mean ratio was 0.79 (95% confidence interval: 0.63–0.97), ie, an average reduction of 21% (95% confidence interval: 3–37%). Mothers' subjective assessments of the responses to diet indicated little difference between the groups.

Conclusion. Exclusion of allergenic foods from the maternal diet was associated with a reduction in distressed behavior among breastfed infants with colic presenting in the first 6 weeks of life. *Pediatrics* 2005; 116:e709–e715. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2005-0147; *breast milk, colic, crying, elimination diet, food allergy, infant.*

ABBREVIATION. VAS, visual analog scale.

From the *Department of Allergy and †Clinical Epidemiology and Biostatistics Unit, Royal Children's Hospital, Melbourne, Australia; ‡Murdoch Children's Research Institute, Melbourne, Australia; §Neonatal Services, Royal Women's Hospital, Melbourne, Australia; and ||Department of Paediatrics, University of Melbourne, Melbourne, Australia.

Accepted for publication May 24, 2005.

doi:10.1542/peds.2005-0147

No conflict of interest declared.

Reprint requests to (D.J.H.) Department of Allergy, Royal Children's Hospital, Flemington Rd, Parkville, Victoria 3052, Australia. E-mail: allergy.clinic@rch.org.au

PEDIATRICS (ISSN 0031 4005). Copyright © 2005 by the American Academy of Pediatrics.

Infantile colic affects up to 28% of infants in the first months of life.^{1,2} Colic symptoms usually peak at ~6 weeks of age and improve gradually over the following weeks.³ In a recent Canadian study, 6.4% of infants had persistent colic symptoms at 3 months of age.⁴ For breastfed infants with colic, episodes of distress are usually clustered in the late evening and early morning hours,^{5,6} which may cause significant disruption of family interactions^{7,8} and may lead to maternal exhaustion and distress.⁹ Colic is also associated frequently with secondary feeding difficulties.¹⁰ Generally, colic is thought to represent a transient, nonorganic, behavior dysregulation among otherwise healthy infants.^{9,11} However, the cause of infantile colic has remained unclear.^{2,9,11,12} Several psychosocial factors and maternal smoking have been shown to increase the risk of infantile colic.^{13,14}

The role of diet in infantile colic is controversial.⁵ Among formula-fed infants with colic, use of extensively hydrolyzed casein- and whey-based preparations is associated with significant improvement in colic symptoms.^{15,16} Breastfeeding does not seem to be protective against infantile colic.² However, several studies reported a reduction in persistent crying after elimination of cow's milk and other food proteins from the maternal diet.^{17–19} A systematic review examining studies on maternal diet modification and colic suggested a possible therapeutic benefit but findings remained inconclusive, mainly because of limitations in the studies included in the meta-analysis.²⁰

In our previous colic study,¹⁹ the greatest treatment benefit of 1-week maternal food allergen elimination was observed among breastfed infants <6 weeks of age. The statistical power in that study, however, was insufficient for drawing firm conclusions. In the present trial, we tested prospectively the significance of the findings; we evaluated the effect of a hypoallergenic maternal elimination diet on persistent crying among breastfed infants presenting with colic in this age group.

METHODS

Study Design

We performed a randomized, controlled trial to test the hypothesis that, among breastfed infants with colic presenting in the first 6 weeks of life, elimination of multiple, major, allergenic food proteins from the maternal diet is associated with a reduction in crying and fussing. The trial compared infants' cry/fuss duration

before and 1 week after implementation of a low-allergen maternal elimination diet. The study was approved by the Ethics in Human Research Committee at the Royal Children's Hospital, and written informed consent was obtained from the parents before randomization.

Recruitment

Between 2000 and 2002, exclusively breastfed infants <6 weeks of age with colic were recruited from metropolitan, community-based, well-infant centers in Melbourne, Australia. The recruitment phase was conducted by a lactation consultant (B.S.), who had no access to the randomization schedule. Only well, term infants (gestational age of >37 weeks) who were the result of a normal singleton pregnancy and who had an otherwise uneventful perinatal history (ie, no significant obstetric complications or history of maternal substance abuse) and no perinatal morbidity other than distress (ie, no perinatal asphyxia or perinatal infection) were enrolled.

Mothers were told the study was comparing the effects of 2 different diet programs that had been found previously to be of benefit in the treatment of infantile colic.¹⁹ Mothers on strict vegan diets were excluded from randomized treatment; 3 mothers on balanced ovo-lacto-vegetarian diets were included in the study.

Baseline Assessment

After recruitment, all infants underwent a detailed physical examination performed by a consultant neonatologist (N.R. or J.S.), and satisfactory breastfeeding technique was confirmed by a lactation consultant (B.S.) at the Royal Women's Hospital. A questionnaire to document sociodemographic data was administered. Mother-infant dyads were then referred to the Department of Allergy for diet randomization and completion of the study. For 3 dyads, this appointment was delayed for up to 3 weeks but distress continued; these 3 were assigned randomly to their diets at 7.4, 8.0, and 8.6 weeks of age. All other dyads commenced the intervention before completion of the sixth week of life (Table 1). Randomization occurred strictly in sequence of referral, following the randomization schedule provided by the statistician. Before they commenced the intervention program, mothers were asked to keep a detailed food diary while maintaining their usual diet and to record infant cry/fuss behavior on previously validated charts (days 1 and 2).^{6,21}

For the purposes of recruitment for the study, colic was defined on the basis of parent-reported estimation of distress exceeding 180 minutes per 24 hours on 3 days in the week before presentation. For all except 3 infants, parental perceptions of distress were in agreement with the subsequent cry/fuss chart recordings for the 48 hours before commencement of the diet (days 1 and 2). For these 3 infants, the recorded cry/fuss durations were 300, 330, and 345 minutes per 48 hours.

Interventions

The effects of 2 maternal diet programs, ie, a low-allergen diet that excluded major food allergens and a control diet that included these foods, were compared. Both diets avoided food preservatives, colors, and additives. Mothers were assigned to one of the diets by the research dietitian (D.E.F.), on the basis of a randomization schedule provided by the statistician (J.B.C.). The dietitian explained the diet and provided detailed written information but played no role in the collection or analysis of cry/fuss outcome data. The diet intervention commenced at 6 AM on day 3 and continued until 6 AM on day 10. Contact between the mothers was avoided, to prevent contamination of information between the groups. All infants were breastfed exclusively for the duration of the study. The diet regimens were isoenergetic and designed to provide adequate energy (1.16 MJ/day) and protein (protein 115 g/day) for breastfeeding mothers. Adherence to the diet was monitored with diet diaries maintained for 48 hours on days 8 and 9.

Low-Allergen Diet

For the low-allergen diet, mothers were instructed to exclude all foods containing dairy products, soy, wheat, eggs, peanuts, tree nuts, and fish from their diet. Their diet included a rice milk drink, meats, vegetables, fruits, and cereals (corn and rice). A calcium supplement (1.2 g/day) was prescribed. Mothers were supplied with a rice-based drink in powder form (500 mL/day), as well as a daily supply of fresh rice bread.

Control Diet

The control diet included all of the food items excluded from the low-allergen diet. Mothers received 7 days of rations of a soy and cow's milk powder mixture to make 500 mL of a milk drink per day (equivalent to 200 mL of soy milk and 300 mL of cow's milk). Mothers were asked to eat 1 serving of peanuts, 1 serving of wheat, and 1 chocolate muesli bar per day, which were supplied. Mothers also were encouraged to maintain their usual intake of vegetables, meats, rice, and other cereals.

Outcomes

Cry/fuss charts were recorded by mothers for 48 hours starting at 6 AM on day 1 of the study (baseline data, ie, days 1 and 2). Cry/fuss charts for outcome assessment were completed from 6 AM on day 8 to 6 AM on day 10 (outcome days 8 and 9). Cry/fuss charts were scored by the study nurse (J.B.) and an independent reviewer, both of whom were blinded to the diet allocations. For each 48-hour assessment period (days 1 and 2 or days 8 and 9), the total duration of crying/fussing was calculated independently by the 2 reviewers and the mean of the 2 assessments was used for analysis.

TABLE 1. Demographic Characteristics of Study Cohort and Infants Withdrawn Before Study Completion

	Completers		Noncompleters	
	Low-Allergen Diet	Control Diet	Low-Allergen Diet	Control Diet
No. of infants	47	43	6	11
Gender, no. (male/female)	28/19	26/17	4/2	8/3
First child, no. (%)	28 (59.6)	19 (55.6)	5 (83.3)	6 (54.5)
Mean age of onset of distress, wk	1.9 (<1-4)	2.1 (<1-5)	2.1 (1-3)	2.1 (<1-3.5)
Mean age at first telephone contact, wk	4.6 (2.3-6)	5.0 (2.3-6)	4.7 (3.3-6)	5.6 (3.6-6)
Mean age at start of diet, wk	5.5 (3.0-8.6)	5.9 (3.1-8.0)	5.7 (4.0-7.4)	6.3 (4.3-6.9)
Mean distress duration at start of diet, wk	3.2 (1-7)	3.4 (1-6.0)	3.0 (1-5.5)	3.7 (2-5.5)
Prior colic medication, no. (%)	8 (17.0)	11 (25.6)	0 (0)	2 (18.2)
Prior diet change, no. (%)	2 (4.3)	2 (4.7)	0 (0)	0 (0)
Mother's age, y	31.8 (20-40)	32.2 (22-40)	25.7 (18-34)	31.7 (27-38)
Mother Australian born, no. (%)	35 (74.5)	37 (86.0)	4 (66.7)	8 (72.7)
Maternal education, y	14.2 (10-19)	15.1 (10-21)	12.8 (10-17)	14.3 (11-17)
Maternal atopy, no. (%)	23 (48.9)	24 (55.8)	3 (50.0)	4 (36.4)
Single mother, no. (%)	1 (2.1)	2 (4.7)	3 (50.0)	3 (27.3)
Father's age, y	33.7 (22-50)	34.1 (25-49)	28.5 (22-36)	34.0 (24-40)
Father Australian born, no. (%)	37 (78.7)	36 (83.7)	4 (66.7)	6 (54.5)
Paternal education, y	13.9 (10-19)	14.8 (10-24)	10.7 (10-17)	14.3 (10-16)
Paternal atopy, no. (%)	11 (23.4)	8 (18.6)	1 (16.7)	1 (9.1)
Eczema, no. (%)	4 (8.5)	4 (9.3)	0	1 (9.1)

Values are number (percentage) or mean (range).

The primary end point of the study was a reduction in cry/fuss duration of $\geq 25\%$ between days 1 and 2 and days 8 and 9. Additional analyses were based on comparison of mean cry/fuss durations between groups. Analyses of the effects of diet were limited to infants for whom colic reportedly exceeded >3 hours/day for >3 days/week and had persisted for ≥ 3 weeks, according to the criteria described by Wessel et al.²² A final analysis was restricted to dyads for which complete adherence to the assigned diet was demonstrated.

Secondary outcomes involved maternal assessment of the infant's response to maternal diet change. On the morning of day 10, the research nurse (J.B.) asked mothers to categorize their infant's colic behavior as better, same, or worse. In addition, mothers graded their infant's level of distress on a 10-cm visual analog scale (VAS) of 0 (no crying/fussing) to 10 (maximal crying/fussing). Measurements were read to the closest 0.5-cm marking.

Sample Size

Sample size was determined on the assumption of a 50% response rate for the control group and an 80% response rate for the low-allergen group; these were judged to be conservative estimates on the basis of the results of our previous study.¹⁹ These assumptions led to a requirement for 45 patients in each group to provide a power of 80%, with a 2-sided significance level of .05.²³

Statistical Analyses

The primary analysis (intention-to-treat) compared the response rates between the 2 groups. We report the estimated dif-

ference in proportions with a standard 95% confidence interval and χ^2 test. The distribution of cry/fuss duration was skewed positively; therefore, we used logarithmically transformed values for analysis and reported geometric means as summaries, with ratios for comparison between groups. Analyses of the continuous cry/fuss data used analysis of covariance (with logarithmic values) to compare the cry/fuss duration between groups (expressed in relative terms, as the geometric mean ratio), with adjustment for group differences in baseline crying duration.

Maternal assessment categories (better, same, and worse) were compared between treatment groups with χ^2 analysis. The mean VAS score was calculated for each group, and values were compared with a 2-sample *t* test.

RESULTS

Study Groups

Recruitment, reasons for noncompletion, and study progress are detailed in Fig 1. Of the 107 infants who entered this study, 90 (84%) completed the randomized trial (mean age at the time of diet allocation: 5.7 ± 1.1 weeks; range: 2.9–8.6 weeks; 54 male infants). The completion rates were 47 (89%) of 53 for the low-allergen group and 43 (80%) of 54 for the control group ($\chi^2 = 1.64$, $P = .20$). The demographic characteristics of the study cohort (completers and noncompleters) are summarized in Table 1.

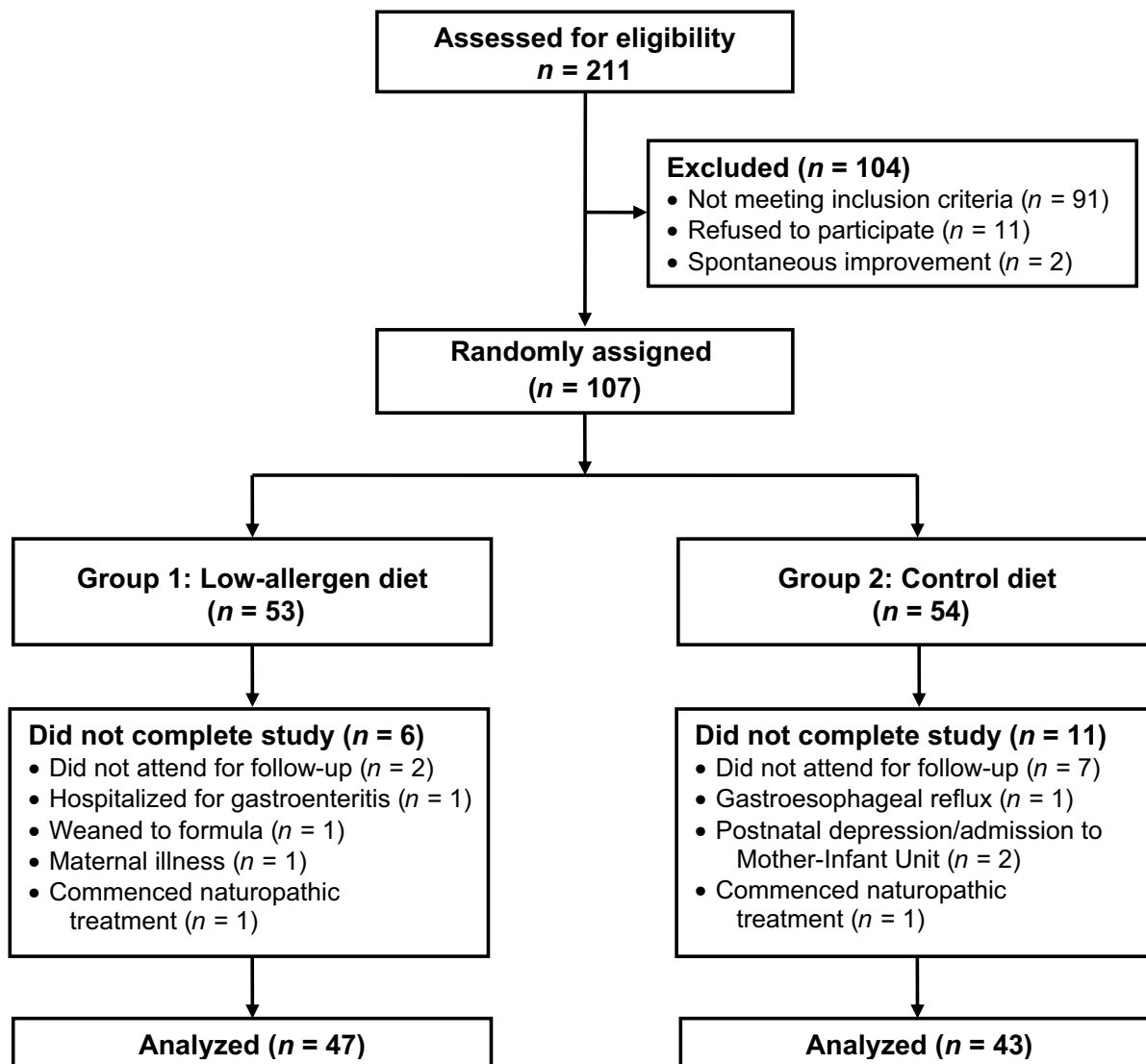


Fig 1. Diagram of patient enrollment and study progress.

Primary Outcome

On the basis of a reduction in cry/fuss duration of $\geq 25\%$, 35 (74%) of 47 infants responded to the low-allergen diet program, compared with 16 (37%) of 43 infants on the control diet, ie, an absolute risk reduction of 37% (95% confidence interval: 18–56%; $P < .001$) (Table 2). Changing the cutoff value to 20% or 30% did not alter these results substantially (Table 3). If all noncompleters were analyzed as nonresponders, then there was a 36% risk reduction for the low-allergen diet ($P < .001$) (Table 4). At the end of the study, 61 of 90 infants still had colic, ie, cry/fuss duration of ≥ 360 minutes per 48 hours (low-allergen group: 30 of 47 infants; control group: 31 of 43 infants; $\chi^2 = 0.70$, $P = .40$). Figure 2 plots the individual data for the study participants.

Table 2 summarizes mean cry/fuss durations and assesses between-group differences. There was a small average difference in cry/fuss duration between the 2 arms of the study at baseline, before commencement of the diet (days 1 and 2). At the end of the study, however, the cry/fuss duration per 48 hours was reduced by a substantially greater amount in the low-allergen group; the adjusted geometric mean ratio was 0.79 (95% confidence interval: 0.63–0.97; $P = .028$), ie, an average reduction of 21% (95% confidence interval: 3–37%). This corresponds to reductions in adjusted geometric mean of distress levels of 40% (274 minutes per 48 hours) in the low-allergen group and 16% (102 minutes per 48 hours) in the control group (Table 2).

Of the 90 mother-infant dyads that completed the study, 80 (89%) fulfilled the definition of colic provided by Wessel et al²² (≥ 3 hours of distress, on 3 days/week, for ≥ 3 weeks). Of these, 41 were assigned to the low-allergen diet and 39 to the control diet. Results were very similar in this subgroup, compared with the entire study cohort. In primary outcome analysis, 31 (76%) of 41 responded to the low-allergen diet, compared with 16 of 39 (41%) responding to the control diet ($P = .002$).

Secondary Outcomes

The categorical and VAS assessments were completed by 42 (89%) of 47 mothers in the low-allergen group and by 39 (91%) of 43 in the control group. There were no significant differences in the maternal categorical assessments of treatment responses (better, same, or worse) or continuous assessments with the VAS on day 10 between the 2 diet groups (Table 2).

Adherence to Diet Programs

At baseline (days 1 and 2), complete diaries were available for 87 of 90 patients (low-allergen diet: 46 of 47 patients; control diet: 41 of 43 patients). Before the study, there were only minor differences in diet between the groups. Patients assigned randomly to the control diet had a higher intake of wheat protein (mean intake: 31.2 g per 48 hours vs 26.2 g per 48 hours; $P < .05$), whereas the intake of peanut protein was higher in the group assigned to the low-allergen diet (mean intake: 2.0 g per 48 hours vs 0.9 g per 48 hours; $P = .05$). Intakes of milk, eggs, and chocolate were similar for the 2 groups at baseline.

At completion of the study (days 8 and 9), interpretable diet diary records were available for 45 (96%) of 47 patients on the low-allergen diet and 41 (95%) of 43 control patients. In the low-allergen group, 44 (98%) of 45 mothers were deemed compliant with the diet and had avoided all wheat, dairy, eggs, peanuts, and chocolate successfully; 1 noncompliant mother (identification number 93, responder) had eliminated milk, eggs, and chocolate but had continued to ingest wheat (23 g of wheat protein per 48 hours) and peanut (6.8 g of peanut protein per 48 hours). In the control diet group, complete diet adherence was achieved by 24 (59%) of 41 patients; the remaining 17 (41%) of 41 patients were partially compliant and had eliminated up to 3 food items on days 8 and 9. All had continued to ingest wheat, and none had commenced the full low-allergen diet. For the control diet group, the median protein intakes were

TABLE 2. Rate of Response to Treatment and Change in Cry/Fuss Scores at Baseline (Days 1 and 2) and Follow-Up (Days 8 and 9) Assessments

	Low-Allergen Diet	Control Diet	Difference, % (Mean), or Ratio (Geometric Mean)	95% Confidence Interval	P Value
Categorical analysis, no. (%)					
Improvement of $\geq 25\%$ (days 1 and 2 versus days 8 and 9)	35 of 47 (74)	16 of 43 (37)	37	18–56	<.001
Cry/fuss duration of ≥ 360 min per 48 h (days 8 and 9)	30 of 47 (64)	31 of 43 (72)	8	–11–27	.402
Continuous analysis, min per 48 h (geometric mean and 1-SD range)					
Days 1 and 2	690 (498–963)	631 (433–925)	1.1		
Days 8 and 9	431 (252–742)	509 (270–953)	0.85	0.66–1.08	.18
Days 8 and 9 adjusted*	416	529	0.79	0.63–0.97	.028
Secondary outcomes					
VAS score (mean \pm SD)	4.3 \pm 2.5	5.0 \pm 2.8	0.7	–0.43–1.87	.218
Maternal categories, no.					
Better	29	22			
Same	8	9			.45
Worse	5	8			

* Comparison adjusted for baseline differences with analysis of covariance.

TABLE 3. Treatment Response Rates With Different Cutoff Criteria

Reduction in Cry/ Fuss Duration	No. (%)		Difference, %	P Value
	Control Diet	Low-Allergen Diet		
≥10%	24 (56)	38 (81)	25	.010
≥20%	17 (40)	36 (77)	37	<.001
≥25%	16 (37)	35 (74)	37	<.001
≥30%	13 (30)	29 (62)	32	.003
≥40%	11 (26)	18 (38)	12	.197
≥50%	9 (21)	9 (19)	-2	.833

TABLE 4. Effect of Handling of Noncompleters in Statistical Analyses

Handling of Noncompleters in Statistical Analyses	Responders (Reduction of >25%), No. (%)		Difference, %	P Value
	Low-Allergen Diet	Control Diet		
Assume all are responders	41 of 53 (77)	27 of 54 (50)	27	.003
Assume all are nonresponders	35 of 53 (66)	16 of 54 (30)	36	<.001
Exclude all from analyses	35 of 47 (74)	16 of 43 (37)	37	<.001

[●] ID 6

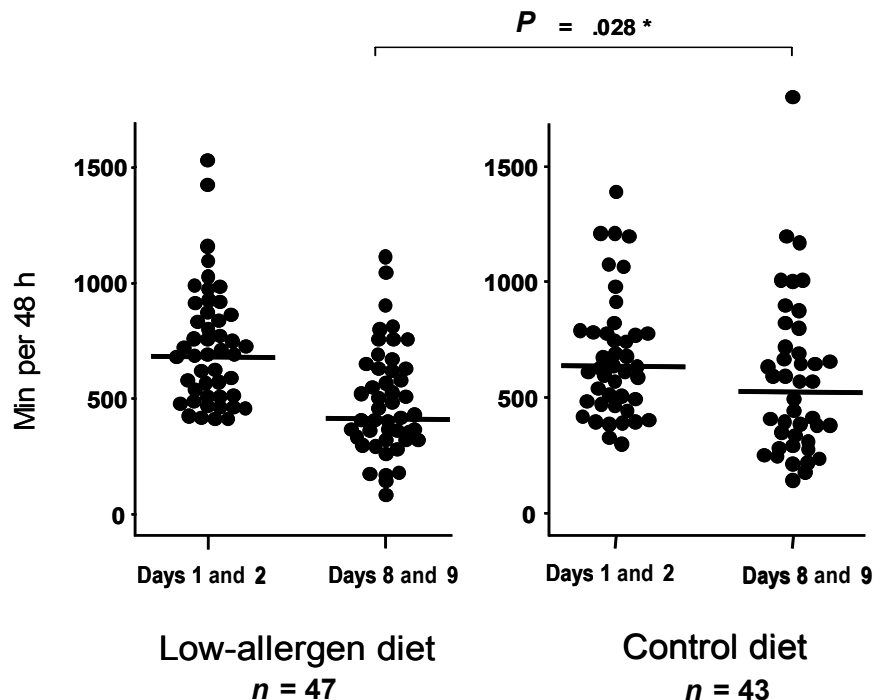


Fig 2. Crying duration at baseline (days 1 and 2) and outcome (days 8 and 9) in response to low-allergen and control diets. An outlier in the control group (identification number 6) is shown in square brackets. Horizontal bars depict the geometric means of cry/fuss duration. *Comparison adjusted for baseline differences with analysis of covariance.

31 g of wheat, 39 g of cow's milk, 6 g of eggs, 6 g of peanuts, and 7.6 g of chocolate per 48 hours.

There were 41 control group dyads with interpretable diet diaries, including 16 (39%) responders and 25 (61%) nonresponders. Of the 16 control group responders, 14 (88%) had adhered strictly to the diet, whereas only 10 (40%) of 25 nonresponders were deemed compliant. The remaining 15 mothers who had failed to respond to the control diet had subsequently removed food allergens from their diet, including the milk/soy drink ($n = 4$), eggs ($n = 11$), peanuts ($n = 6$), and chocolate ($n = 4$). Therefore, mothers of nonresponders in the control group were significantly more likely to breach the diet protocol than were those of responders (rate of noncompli-

ance in the control group: 2 of 16 responders vs 15 of 25 nonresponders; $\chi^2 = 7.22$, $P = .007$). When the primary outcome analysis was restricted to dyads that adhered fully to the assigned diet on days 8 and 9, as documented by dietary records, 33 (75%) of 44 responded in the low-allergen group, compared with 14 of 24 (58%) in the control group ($\chi^2 = 2.02$, $P = .15$).

DISCUSSION

The present study demonstrated that elimination of several major food allergens from the diet of breastfeeding mothers for 1 week was associated with a significant reduction in their infant's cry/fuss duration. The primary outcome analysis, based on

cry chart information, showed a response rate for the low-allergen diet of 74%, ie, a risk reduction of 37%, compared with the control diet. The mean difference in cry/fuss duration between the 2 groups at the end of the study was ~3 hours per 48 hours. When the primary outcome analysis was restricted to mother-infant dyads with distress, according to the definition of colic proposed by Wessel et al,²² the results were very similar. These findings suggest that maternal intake of food allergens is an important factor in the pathogenesis of infantile colic among breastfed infants.

The subjective maternal assessments of the responses to the diets did not reflect the differences demonstrated by cry charts. Previous studies validated the cry/fuss charts against voice-activated audiotapes,²¹ and their specificity and sensitivity have been confirmed among infants with and without colic.⁶ Unlike the cry/fuss charts, the instruments used for the subjective maternal assessments had not been validated against objective measures and might not have been sufficiently sensitive. In addition, the subjective maternal assessments might have been affected by confounding psychosocial factors associated with infantile colic.^{13,14} Several mothers of infants who had failed to respond to dietary treatment, as indicated by the cry charts, categorized their infants as "better" at the end of the study, which suggests that the assessments might also have been influenced by placebo and/or Hawthorne effects.

One third of the infants in the low-allergen group failed to respond. Some of their mothers might have inadvertently continued low intakes of eliminated food items. Although adherence to the low-allergen diet was good, dietary records are known to be prone to recall bias and might not have reflected the actual dietary intakes. Food antigens have been detected in breast milk for up to 9 days after dietary elimination,^{24,25} and the duration of this study might not have been sufficient to achieve complete dietary antigen elimination from breast milk for all infants. Therefore, a longer period of dietary restriction might have improved the response rate. However, the current study was designed to test prospectively the findings from our previous 1-week study.¹⁹ In addition, the low-allergen diet might have failed to exclude clinically relevant food antigens.

Adherence in the control group was influenced significantly by the infant's behavior during the trial. Among responders, for whom remission of symptoms occurred despite continued intake of potential food allergens, adherence was excellent. Conversely, more than one half of the mothers of nonresponding infants had modified their diets and eliminated food items. These observations highlight the difficulties of conducting clinical trials of dietary interventions, because subjects cannot be blinded with respect to treatment allocation. When the primary outcome analysis was limited to those dyads that complied fully with the dietary programs, the apparent treatment benefit for the low-allergen group was reduced. However, this analysis is difficult to interpret because noncompliance in the control arm was associated with a lack of early response to diet. This

might have resulted in a form of reverse causation (ie, a lack of early response to diet increased the risk of noncompliance and thus biased the remaining compliant control dyads toward a better treatment outcome).

The self-limiting nature of colic has precluded the use of invasive investigations to establish a pathophysiological model of infantile colic. The mechanisms through which maternally ingested food proteins elicit colic symptoms among breastfed infants thus remain speculative. Cow's milk,²⁶ egg,²⁷ peanut,²⁸ and wheat²⁹ antigens have been detected in human milk and may evoke gastrointestinal mucosal immune responses.³⁰ Mucosal IgE-containing plasma cells were increased in upper jejunal biopsies from infants with cow's milk-induced colic.³¹ Previous studies demonstrated that macromolecular gut permeability is increased among infants with colic, which may predispose these infants to food sensitization,^{32,33} as well as gastrointestinal³⁴ and cutaneous³³ manifestations of food allergies during early childhood. Infants with colic also show abnormalities in gastrointestinal hormones and regulatory intestinal peptides, including cholecystokinin and motilin.^{35,36} The effects of reduced cholecystokinin levels in colic are poorly understood but may involve impaired central regulation of satiety and behavior.³⁶ The finding of increased serum motilin levels among infants with colic provides indirect evidence of altered gut motility for these infants.³⁵ Motilin, a regulatory gut polypeptide, is the main stimulant for interdigestive migrating gut contractions.³⁷ We speculate that these propulsive gut contractions may cause visceral pain and trigger episodes of distress. Motilin has been found in human milk³⁸ and may trigger endogenous release of motilin among breastfed infants.³⁹ There is some evidence that maternal smoking, a recognized risk factor for colic, may cause gastrointestinal motility disturbances through increased plasma and intestinal motilin levels.⁴⁰ The effects of motilin are inhibited by atropine, which may explain why atropine and similar anticholinergic compounds ameliorate colic symptoms.^{41,42} It is unclear whether food proteins are able to stimulate endogenous motilin secretion either directly or indirectly, through immune-mediated mechanisms.

This study is the first randomized, controlled trial to demonstrate a clear effect of maternally ingested food proteins on colic symptoms among breastfed infants. Our observations were based on a representative, community-based sample of infants with colic, with age and clinical characteristics similar to those in previous interventional studies of colic.¹⁵⁻¹⁹ The study had several limitations. Because of the nature of the intervention, the study could not be conducted as a double-blind trial, although mothers in both diet groups had to make substantial changes to their diets. Therefore, the outcomes might have been affected by a placebo effect. Furthermore, challenges were not performed to demonstrate relapse of symptoms after reintroduction of food proteins into the maternal diet.

Our investigation was designed to provide proof of the concept and to test prospectively the observa-

tions from our previous study,¹⁹ rather than to evaluate the role of individual food proteins in infantile colic. However, it is acknowledged that factors other than diet may also be involved in the pathogenesis of infant distress. Elimination diets have associated risks, particularly if sustained for long periods, and the nutritional progress of the infant and the mother needs to be monitored closely by an experienced dietitian.⁴³ Additional studies are needed to define the pathophysiologic features and role of maternal elimination diets in infantile colic.

ACKNOWLEDGMENTS

The study was supported by a research grant from the Rice-growers' Cooperative Ltd (Leeton, Australia).

We acknowledge Suzanna Vidmar, Clinical Epidemiology and Biostatistics Unit, for statistical computing and Anne Peace, Department of Allergy, for secretarial assistance.

REFERENCES

- Lucassen PL, Assendelft WJ, van Eijk JT, Gubbels JW, Douwes AC, van Geldrop WJ. Systematic review of the occurrence of infantile colic in the community. *Arch Dis Child.* 2001;84:398-403
- Clifford TJ, Campbell MK, Speechley KN, Gorodzinsky F. Infant colic: empirical evidence of the absence of an association with source of early infant nutrition. *Arch Pediatr Adolesc Med.* 2002;156:1123-1128
- Brazelton TB. Crying in infancy. *Pediatrics.* 1962;29:579-588
- Clifford TJ, Campbell MK, Speechley KN, Gorodzinsky F. Sequelae of infant colic: evidence of transient infant distress and absence of lasting effects on maternal mental health. *Arch Pediatr Adolesc Med.* 2002;156:1183-1188
- Hill DJ, Hosking CS. Infantile colic and food hypersensitivity. *J Pediatr Gastroenterol Nutr.* 2000;30(suppl):S67-S76
- Hill DJ, Menahem S, Hudson I, et al. Charting infant distress: an aid to defining colic. *J Pediatr.* 1992;121:755-758
- Hiscock H, Wake M. Infant sleep problems and postnatal depression: a community-based study. *Pediatrics.* 2001;107:1317-1322
- Räihä H, Lehtonen L, Huhtala V, Saleva K, Korvenranta H. Excessively crying infant in the family: mother-infant, father-infant and mother-father interaction. *Child Care Health Dev.* 2002;28:419-429
- Barr RG. Colic and crying syndromes in infants. *Pediatrics.* 1998;102:1282-1286
- Miller-Loncar C, Bigsby R, High P, Wallach M, Lester B. Infant colic and feeding difficulties. *Arch Dis Child.* 2004;89:908-912
- Barr RG. Changing our understanding of infant colic. *Arch Pediatr Adolesc Med.* 2002;156:1172-1174
- Miller AR, Barr RG. Infantile colic: is it a gut issue? *Pediatr Clin North Am.* 1991;38:1407-1423
- Rautava P, Helenius H, Lehtonen L. Psychosocial predisposing factors for infantile colic. *BMJ.* 1993;307:600-604
- Søndergaard C, Olsen J, Friis-Hasche E, Dirdal M, Thrane N, Sørensen HT. Psychosocial distress during pregnancy and the risk of infantile colic: a follow-up study. *Acta Paediatr.* 2003;92:811-816
- Jakobsson I, Lothe L, Ley D, Borschel MW. Effectiveness of casein hydrolysate feedings in infants with colic. *Acta Paediatr.* 2000;89:18-21
- Lucassen PL, Assendelft WJ, Gubbels JW, van Eijk JT, Douwes AC. Infantile colic: crying time reduction with a whey hydrolysate: a double-blind, randomized, placebo-controlled trial. *Pediatrics.* 2000;106:1349-1354
- Jakobsson I, Lindberg T. Cow's milk proteins cause infantile colic in breast-fed infants: a double-blind crossover study. *Pediatrics.* 1983;71:268-271
- Evans RW, Fergusson DM, Allardyce RA, Taylor B. Maternal diet and infantile colic in breast-fed infants. *Lancet.* 1981;1:1340-1342
- Hill DJ, Hudson IL, Sheffield LJ, Shelton MJ, Menahem S, Hosking CS. A low allergen diet is a significant intervention in infantile colic: results of a community-based study. *J Allergy Clin Immunol.* 1995;96:886-892
- Garrison MM, Christakis DA. A systematic review of treatments for infant colic. *Pediatrics.* 2000;106:184-190
- Barr RG, Kramer MS, Boisjoly C, Vey-White L, Pless IB. Parental diary of infant cry and fuss behaviour. *Arch Dis Child.* 1988;63:380-387
- Wessel MA, Cobb SC, Jackson EB, et al. Paroxysmal fussing in infancy: sometimes called "colic." *Pediatrics.* 1954;14:421-434
- Fleiss JL. *Statistical Methods for Rates and Proportions.* 2nd ed. New York, NY: John Wiley & Sons; 1981
- Machtlinger S, Moss R. Cow's milk allergy in breast-fed infants: the role of allergen and maternal secretory IgA antibody. *J Allergy Clin Immunol.* 1986;77:341-347
- Jakobsson I, Lindberg T, Benediktsson B, Hansson BG. Dietary bovine β -lactoglobulin is transferred to human milk. *Acta Paediatr Scand.* 1985;74:342-345
- Sorva R, Mäkinen-Kiljunen S, Juntunen-Backman K. β -Lactoglobulin secretion in human milk varies widely after cow's milk ingestion in mothers of infants with cow's milk allergy. *J Allergy Clin Immunol.* 1994;93:787-792
- Kilshaw PJ, Cant AJ. The passage of maternal dietary proteins into human breast milk. *Int Arch Allergy Appl Immunol.* 1984;75:8-15
- Vadas P, Wai Y, Burks W, Perelman B. Detection of peanut allergens in breast milk of lactating women. *JAMA.* 2001;285:1746-1748
- Chirido FG, Rumbo M, Anon MC, Fossati CA. Presence of high levels of non-degraded gliadin in breast milk from healthy mothers. *Scand J Gastroenterol.* 1998;33:1186-1192
- Järvinen KM, Mäkinen-Kiljunen S, Suomalainen H. Cow's milk challenge through human milk evokes immune responses in infants with cow's milk allergy. *J Pediatr.* 1999;135:506-512
- Harris MJ, Petts V, Penny R. Cow's milk allergy as a cause of infantile colic: immunofluorescent studies on jejunal mucosa. *Aust Paediatr J.* 1977;13:276-281
- Lothe L, Lindberg T, Jakobsson I. Macromolecular absorption in infants with infantile colic. *Acta Paediatr Scand.* 1990;79:417-421
- Kalliomäki M, Laippala P, Korvenranta H, Kero P, Isolauri E. Extent of fussing and colic type crying preceding atopic disease. *Arch Dis Child.* 2001;84:349-350
- Iacono G, Carroccio A, Montalto G, et al. Severe infantile colic and food intolerance: a long-term prospective study. *J Pediatr Gastroenterol Nutr.* 1991;12:332-335
- Lothe L, Ivarsson SA, Ekman R, Lindberg T. Motilin and infantile colic: a prospective study. *Acta Paediatr Scand.* 1990;79:410-416
- Huhtala V, Lehtonen L, Uvnäs-Moberg K, Korvenranta H. Low plasma cholecystokinin levels in colicky infants. *J Pediatr Gastroenterol Nutr.* 2003;37:42-46
- Itoh Z. Motilin and clinical application. *Peptides.* 1997;18:593-608
- Liu J, Qiao X, Zian W, Hou X, Hayes J, Chen JD. Motilin in human milk and its elevated plasma concentration in lactating women. *J Gastroenterol Hepatol.* 2004;19:1187-1191
- Mochiki E, Satoh M, Tamura T, et al. Exogenous motilin stimulates endogenous release of motilin through cholinergic muscarinic pathways in the dog. *Gastroenterology.* 1996;111:1456-1464
- Shenassa ED, Brown MJ. Maternal smoking and infantile gastrointestinal dysregulation: the case of colic. *Pediatrics.* 2004;114(4). Available at: www.pediatrics.org/cgi/content/full/114/4/e497
- Savino F, Brondello C, Cresi F, Oggero R, Silvestro L. Cimetropium bromide in the treatment of crisis in infantile colic. *J Pediatr Gastroenterol Nutr.* 2002;34:417-419
- Lucassen PL, Assendelft WJ, Gubbels JW, van Eijk JT, van Geldrop WJ, Neven AK. Effectiveness of treatments for infantile colic: systematic review. *BMJ.* 1998;316:1563-1569
- Mofidi S. Nutritional management of pediatric food hypersensitivity. *Pediatrics.* 2003;111:1645-1653.

Effect of a Low-Allergen Maternal Diet on Colic Among Breastfed Infants: A Randomized, Controlled Trial

David J. Hill, Neil Roy, Ralf G. Heine, Clifford S. Hosking, Dorothy E. Francis, Jennifer Brown, Bernadette Speirs, Joel Sadowsky and John B. Carlin

Pediatrics 2005;116:e709-e715

DOI: 10.1542/peds.2005-0147

Updated Information & Services	including high-resolution figures, can be found at: http://www.pediatrics.org/cgi/content/full/116/5/e709
References	This article cites 38 articles, 16 of which you can access for free at: http://www.pediatrics.org/cgi/content/full/116/5/e709#BIBL
Citations	This article has been cited by 2 HighWire-hosted articles: http://www.pediatrics.org/cgi/content/full/116/5/e709#otherarticles
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Allergy & Dermatology http://www.pediatrics.org/cgi/collection/allergy_and_dermatology
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.pediatrics.org/misc/Permissions.shtml
Reprints	Information about ordering reprints can be found online: http://www.pediatrics.org/misc/reprints.shtml

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

