Use of Nonhuman Milks in the Dietary Management of Young Children With Acute Diarrhea: A Meta-Analysis of Clinical Trials

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ABSTRACT. *Objective.* To assess the effects of continued feeding of nonhuman milks or formulas to young children during acute diarrhea on their treatment failure rates, stool frequency and amount, diarrheal duration, and change in body weight.

Methods. A total of 29 randomized clinical trials of 2215 patients were identified by computerized bibliographic search and review of published articles. Data were abstracted and analyzed using standard meta-analytic procedures.

Results. Among studies that compared lactose-containing milk or formula diets with lactose-free regimens, those children who received the lactose-containing diets during acute diarrhea were twice as likely to have a treatment failure as those who received a lactose-free diet (22% vs 12%, respectively; $P < .001$). However, the excess treatment failure rates occurred only in those studies that included patients whose initial degree of dehydration, as reported by authors, was severe, or that were conducted before 1985, when appropriate diarrhea treatment protocols were first widely accepted. Among studies of patients with mild diarrhea, all but one of which were completed after 1985, the overall treatment failure rates in the lactose groups were similar to the rates in the lactose-free groups (13% vs 15%). These results suggest that children with mild or no dehydration and those who are managed according to appropriate treatment protocols, such as that promoted by the World Health Organization, can be treated as successfully with lactose-containing diets as with lactose-free ones. The pooled information from studies that compared undiluted lactose-containing milks with the same milks offered at reduced concentration concluded that (1) children who received undiluted milks were marginally more likely to experience treatment failure than those who received diluted milk (16% vs 12%, $P = .05$), (2) the differences in stool output were small and of limited clinical importance, and (3) children who received the undiluted milk diets gained 0.25 SD more weight than those who received the diluted ones ($P = .004$). In addition, as with the previous set of studies, there were no differences in the pooled treatment failure rates between the respective groups in those studies of mildly dehydrated patients conducted after 1985 (14% vs 12%).

Conclusions. The vast majority of young children with acute diarrhea can be successfully managed with continued feeding of undiluted nonhuman milks. Routine dilution of milk and routine use of lactose-free milk formula are therefore not necessary, especially when oral rehydration therapy and early feeding (in addition to milk) form the basic approach to the clinical management of diarrhea in infants and children. *Pediatrics* 1994;93:17–27; *diarrhea, gastroenteritis, milk, milk intolerance, lactose malabsorption, lactose intolerance, nutrition, dietary therapy.*

ABBREVIATIONS. WHO, World Health Organization; CI, confidence interval; RR, relative risk.

The appropriate use of lactose-containing, nonhuman milks for young children with acute diarrhea is frequently debated. Whereas some clinicians routinely withdraw milk from the diets of children during diarrhea, primarily to avoid the potential consequences of lactose malabsorption, others continue to offer milk without apparent evidence of increased clinical complications. We have recently summarized background information on the rationales for each approach to therapy[1,2] and have presented descriptive reviews of published trials of dietary regimens containing varied amounts of milk and other dairy products.[2–4]

Notably, one of these reviews discovered that much of the difference in the results of the previous studies could be attributed to the nature of the comparison diet employed.[3] In particular, when diets including milk were compared with either milk-free regimens or with lactose-free milk products, children who received lactose-containing milks tended to have greater severity and duration of diarrhea and higher rates of clinical complications.

By contrast, when milk-containing diets were compared with other milk-based regimens that were either more dilute or introduced later during the course of therapy, there was little apparent difference between the treatment groups. It was concluded that although the majority of children can safely continue consuming diets based on nonhuman milks during diarrhea, "complications of milk feeding... will occur in a sizable sub-group of patients."[3]

To explore these issues further, we have completed a quantitative meta-analysis of available clinical trials. In one set of analyses, diarrhea outcome variables were compared for children treated with either lactose-containing milks or lactose-free products. In the second set of analyses, these same outcomes were studied for children who received either undiluted lactose-containing milk or the same product in either more dilute form or introduced later during hospitalization. The results of these meta-analyses are reported herein.

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Received for publication Mar 5, 1993; accepted Jun 16, 1993.

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METHODS

Identification and Selection of Studies

Published references were identified using the Medline computerized bibliographic database and the following key words: diarrhea, gastroenteritis, milk, milk intolerance, lactose malabsorption, lactose intolerance, nutrition, and dietary therapy. Additional studies were located from citations in these references, other bibliographic sources, and key informants working in this field. Except for two unpublished references, which were obtained from the Diarrhoeal Disease Control Programme of the World Health Organization (WHO), only published reports were considered in an attempt to ensure the quality of the research. The exceptions were allowed because the studies were closely monitored by WHO personnel. Other criteria for inclusion of individual studies were that (1) they were randomized clinical trials, (2) they reported at least one of the major outcome variables of interest, and (3) the study diets were compatible with the group assignments described above. Because the published reports generally provided limited information on the randomization techniques, we could not assess the validity of these procedures in the most cases. Studies of milk added to mixed diets were excluded unless milk was the predominant energy source, and studies of yogurt and of human milk were also eliminated. Projects that specifically included only children with persistent diarrhea were also excluded, although some of the accepted reports may have contained some patients with persistent illness. A total of 29 studies of 2215 patients were included in the final analyses.[5–33] All but two studies[13,15] included only hospitalized patients. The children's ages ranged from 0 to 59 months, although most studies included children younger than 36 months of age.

Summary of Outcome Variables and Statistical Analyses

Once a study was considered acceptable for inclusion, the major outcome variables were summarized in tabular form, separately for studies of lactose-containing vs non-lactose-containing diets and for studies of undiluted milk vs diluted or delayed introduction of milk. The data were summarized independently by two of the coauthors and any discrepancies were rectified. One study,[11] which included dietary groups permitting both sets of comparisons, was used twice. In several other studies in which more than two diets were compared, the groups that conformed most closely to the specific dietary hypothesis of interest were usually selected. However, in two studies[10,13] in which a lactose-containing formula was compared with several non-lactose-containing formulas, data from the latter groups were combined. When undiluted milk was compared with more than one dilution of milk, the group with the most extreme dilution was included in the analysis.

Outcome variables of interest included rates of treatment failures, stool frequency or amount, duration of diarrhea, and change in body weight. Treatment failures were defined in various ways by the different investigators, usually on the basis of increasing diarrheal severity or persistence of diarrhea or recurrence of dehydration. In some cases[14,16,24,26,28] no specific information on treatment failures was presented, but the limited severity of the patients' disease in these particular studies and the authors' implications that all were discharged from the study in timely fashion led us to conclude that no treatment failures had occurred.

When stool output data were presented separately for several days of treatment, we used the data for earlier days (when diarrhea was presumably more severe and the differences between the diets were usually greater) preferentially. When information on duration of diarrhea was not specified, but the authors stated that the patients were discharged from hospital when the diarrhea improved, we used the data for duration of hospitalization instead.[24,25,32,33] We also attempted to compare change in body weight as a result of dietary therapy during the studies, although the extensive variability in expression of this information and in the duration of follow-up measurements may have limited the usefulness of these analyses. The changes in body weight were monitored for periods ranging from 1 to 7 days; in six studies this increment was recorded for variable lengths of time between admission and discharge.

For each of the variables, the data from individual studies were compared separately and the combined results from all studies were also pooled together in a single comparison. The hypothesis of no treatment effect was assessed with the Stouffer's combined test, which is calculated by summing the z scores associated with the P values from the individual studies, and dividing by the square root of the number of studies, and which has a standard normal distribution under the null hypothesis.[34] When statistically significant differences were identified by treatment category, the magnitude of the effect of dietary treatment on the outcome of interest was then estimated for each individual study by dividing the difference between the means by the pooled standard deviation. For continuous variables, the average effect size was estimated using a weighted mean of the individual effect sizes, and homogeneity of effect sizes was tested using a weighted sum of squared deviations from the mean effect size,[35] which has a χ^2 distribution under the null hypothesis that the effect sizes are equal. Significant heterogeneity suggests that the individual studies were not similar enough to be compared in the same meta-analysis. When the effect sizes were nonhomogeneous, individual studies were reexplored to determine whether differences in study design or subjects might explain the extreme values. For treatment failure rates, the overall relative risk and its confidence interval were calculated from the logit estimator.[36] Because no tests for homogeneity of relative risks were readily available, the Breslow-Day test of homogeneity of odds ratios was used as a proxy for relative risks to assess whether they differed between studies.[36] All calculations were done with PC-SAS Release 6.04.

RESULTS

Studies of Lactose-Containing Versus Non-Lactose-Containing Diets

Fourteen studies were identified and considered acceptable for inclusion in this analysis.[5–18] Of these, three were unusual because they compared lactose-containing milk with lactase-treated, low-lactose milk[12] or compared milk with a mixture of either rice, beans, sugar, and oil[15] or plantain, chicken, and oil.[17] All of the remaining studies compared (1) a milk formula with a lactose-free soy formula, (2) a lactose-containing soy formula with a lactose-free soy formula,[13] (3) a lactose-containing milk formula with a lactose-free milk protein formula,[10,16] or (4) some combination of these diets.

Two of the studies deserve special mention because of the somewhat unusual characteristics of the patients included. Rajah et al[10] enrolled only those patients who had previously had more than 48 hours of diarrhea in hospital, still "required intravenous fluid to maintain hydration," and excreted more than 30 g/kg of stool per day. Rothman et al[16] only admitted patients with kwashiorkor and diarrhea. Because of the atypical nature of these subjects, the meta-analyses were conducted both with and without these two studies.

Treatment Failure Rates

Of the 14 studies identified, only one[18] did not provide information on treatment outcomes (Table 1). As indicated above, the criteria for treatment failures varied considerably among studies; but the authors' definitions, as summarized in Table 2, were accepted in all cases, even when they were not supported by objective clinical evidence. The treatment failure rates were significantly greater among children receiving the lactose-containing diets than among those receiving lactose-free diets in 6 of the 13 studies. There were no significant differences by dietary group in the remaining studies. Overall, 22% (95% confidence interval [CI] = 18%, 27%) of children who consumed lac-

TABLE 1. Treatment Failure Rates of Diarrhea Patients Receiving Either Lactose-Containing or Lactose-Free diets

Study	Dietary Group				Significance*
	Lactose		Nonlactose		
	No. of Patients	% Failures	No. of Patients	% Failures	
Sutton[5]	49	40.8	48	8.3	<.001
Leake[6]	11	63.6	11	9.1	.008
Gabr[7]	29	51.7	29	13.8	.002
Dagan[8]	35	14.3	40	0	.019
Naidoo[9]	56	25.0	56	7.1	.010
Rajah[10]	16	81.2	56	44.6	.010
Conway[11]	50	8.0	50	8.0	1.000
Brown[12]	28	14.3	30	20.0	.732
Groothius[13]	19	5.3	59	6.8	.814
Isolauri[14]	38	0	27	0	1.000
Bhan[15]	29	3.4	28	7.1	.532
Rothman[16]	6	0	6	0	1.000
Romer[17]	33	15.2	34	5.9	.259
Pooled data	399	22.3	474	11.8	<.0001

* P value, χ^2 analyses, or Fisher exact test.

TABLE 2. Characteristics of Studies That Did or Did Not Find Differences in Treatment Failure Rates When Lactose-Containing and Lactose-Free Diets Were Compared

Conclusions of Study	Study (Year)	Criteria for Rx Failure*	Severity of Illness†	Type of "Milk"‡
Increased treatment failure	Sutton[5] (1968)	F, D	Mild/severe-B	SF + lactose
	Leake[6] (1974)	F, D	Severe-B	Skim milk
	Gabr[7] (1979)	D	Mod/severe-A	MF
	Dagan[8] (1984)	D, R	Mod/severe-A	Cow milk + Glu
	Naidoo[9] (1981)	F, D, R	Severe-B	Cow milk
	Rajah[10] (1988)	F, D	Severe-A	MF
No difference	Conway[11] (1989)	R, W	Mild-A	MF
	Brown[12] (1991)	F, D, R	Mild/Mod-A	MF
	Groothius[13] (1986)	R	Mild-A (outpatient)	SF + lactose
	Isolauri[14] (1986)	. . .	Mild/Mod-A	MF or cow milk
	Bhan[15] (1988)	R, W + F	Mild-A (outpatient)	MF
	Rothman[16] (1980)	. . .	?	Cow milk
	Romer[17] (1991)	R, I	Mild/Mod-A	Cow milk

* Criteria for treatment failure: F, stool frequency or amount either worsening or greater than cutoff; D, duration of symptoms of diarrhea, vomiting, and/or dehydration greater than cutoff; R, recurrence of diarrhea and/or dehydration; W, weight loss; I, evidence of lactose intolerance.
† Degree of dehydration or "need for" fasting or intravenous solution, as reported by author. Mod, moderate; A, hydration status assessed by clinical signs; B, author's report of severity only.
‡ SF, soy formula; MF, milk formula.

tose were therapeutic failures compared with 12% (95% CI = 9%, 15%) of those who did not receive lactose ($P < .0001$).

The data on outcome of therapy were also analyzed as relative risks (RRs) for treatment failure (Fig 1). Children who received lactose in their diets had RRs of treatment failure that ranged from 0.5 to 7.0 in the different studies compared with those who did not receive lactose. The pooled RR was 2.1 (95% CI = 1.6, 2.7), which was significantly greater than 1.0 ($P < .0001$). However, the Breslow-Day test showed significant heterogeneity of odds ratios ($P = .016$). When the studies by Rajah et al[10] and Rothman et al[16] were excluded from the analyses, the results were similar, with overall treatment failure rates of 20% with lactose and 7% with nonlactose diets ($P < .0001$) and a pooled RR of 2.4 (95% CI = 1.6, 3.7). There was still significant heterogeneity of these results ($P = .012$).

Because of the heterogeneity of findings concerning treatment failure rates, we completed a second set of analyses to explore factors that may have explained the different results among studies. We considered the initial severity of diarrhea or dehydration (as reported by the authors), the criteria used to define treatment failures, and the type of milk used. These factors were compared for those studies that found either significantly different or similar outcomes of therapy (Table 2). In general, those studies that found increased rates of treatment failure among patients who received lactose-containing diets were those that included patients whose initial degree of dehydration, as reported by the authors, was severe. This classification of hydration status must, however, be accepted with considerable caution because, as mentioned earlier, the authors' reports of initial severity of dehydration were not always supported by objective clinical evidence. Among those studies that in-

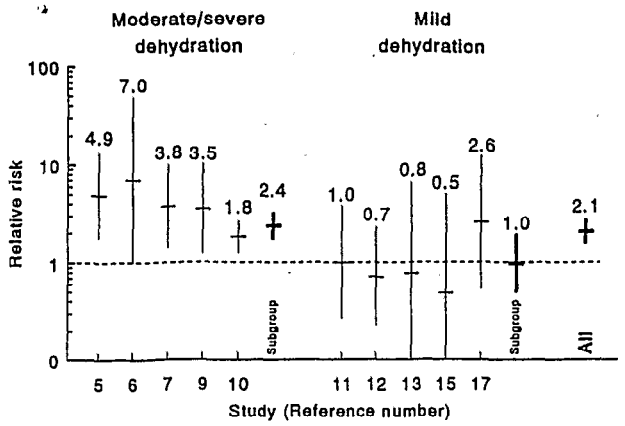

Fig 1. Relative risk of treatment failure with lactose-containing diet vs lactose-free diet, by initial severity of dehydration.

cluded patients with apparently severe dehydration initially, 38% (95% CI = 31%, 44%) of children became treatment failures with lactose compared with 16% (95% CI = 12%, 20%) who became treatment failures in the nonlactose groups ($P < .0001$). The RR of treatment failure with the lactose-containing diets was 2.4 (95% CI = 1.8, 3.3). The results of the test for heterogeneity were no longer statistically significant ($P = .80$). By contrast, when we examined the studies that included only patients with less severe dehydration, the treatment failure rates in the lactose groups (7%; 95% CI = 5%, 12%) were similar to those in the nonlactose groups (8%; 95% CI = 5%, 12%; $P = .94$). The RR of 1.0 (95% CI = 0.5, 1.9) was not significantly different from 1.0. Again, the results of the test for heterogeneity were nonsignificant ($P = .68$).

In addition to the apparent relationship between the initial severity of illness and treatment outcome, we discovered during this secondary analysis that all but one of the studies that detected higher rates of treatment failure with lactose-containing diets were conducted before the mid-1980s, when standardized diarrhea treatment protocols, including rapid correction of dehydration with oral rehydration salts solution and continued feeding, were first widely accepted. The one study reporting higher treatment failure rate with the lactose-containing diet, and conducted after 1985, included only patients with previous treatment failure.[10] By contrast, all but one of the studies that reported no differences in treatment outcomes by type of dietary therapy were completed after 1985. When the studies published before 1986 are considered, the rates of treatment failure were 33% (95% CI = 27%, 38%) with lactose-containing diets and 7% (95% CI = 4%, 10%) with lactose-free diets ($P < .0001$). The RR of treatment failure with lactose was 4.4 (95% CI = 2.5, 7.6), and the results of the test for homogeneity were nonsignificant ($P = .70$). Among studies completed after that date the overall treatment failure rate of 13% (95% CI = 9%, 17%) in the lactose groups was similar to the rate of 15% (95% CI = 12%, 19%) in the comparison groups.

Studies that reported increased failure rates in the lactose group also tended to apply criteria such as greater stool frequency or increased duration of symptoms to define treatment failure, whereas the other studies tended to rely on more stringent evidence of failure such as recurrent dehydration or weight loss, which are probably of greater clinical relevance. Interestingly, the type of milk used did not seem to explain the different findings of these two sets of studies.

In summary, the heterogeneity of results that was observed when all studies were analyzed together may have been due to (1) differences in the patients' initial severity of dehydration, (2) the year of the study and approach to management, or (3) the criteria used to define treatment failure. Regardless of which explanation is most important, we conclude that nondehydrated children can be managed as successfully with lactose-containing diets as with lactose-free regimens. Moreover, results of studies completed since 1985 suggest that children who are managed according to standardized treatment protocols, such as that promoted by WHO, can be managed as successfully with lactose-containing diets as with lactose-free ones regardless of their initial hydration status, although the results of one study[10] suggest that children who experience one treatment failure while receiving milk may be more likely to have a second if treated continuously with a lactose-containing diet.

Stool Frequency and Stool Amount

Only four of the reports provided information on stool frequency and four on stool amount. In all cases the stool frequencies were greater in the groups receiving lactose (Table 3), although these differences were statistically significant in just one study.[5] The

TABLE 3. Stool Frequency (No. of Bowel Movements per Day) During Hospitalization of Diarrhea Patients Receiving Either Lactose-Containing or Lactose-Free Diets

Study	Dietary Group				d*	P
	Lactose		Nonlactose			
	Mean ± SD	n	Mean ± SD	n		
Sutton[5]	5.0 ± 3.5	49	2.2 ± 2.8	48	0.882	<.001
Naidoo[9]	4.5 ± 3.3	56	4.2 ± 3.0	56	0.095	.616
Conway[11]	1.8 ± 1.5	50	1.6 ± 1.7	50	0.125	.534
Groothius[13]	5.9 ± 1.9	19	5.6 ± 2.0	59	0.152	.567
Pooled data	4.0 ± 3.2	174	3.5 ± 2.9	213	0.298	.004

* d = the standardized difference between treatment groups, calculated as

$$(\bar{X}_L - \bar{X}_{NL})/SD_p,$$ where $\bar{X}_L$ = mean value for lactose group, $\bar{X}_{NL}$ = mean value for nonlactose group, and SD_p = pooled SD of both groups.

pooled results showed a statistically significant difference between groups ($P = .004$). However, there was significant heterogeneity of these study results ($P = .02$), and the pooled differences could be explained entirely by the results of one study.[5] Notably, during the first day of this latter study, 10% sugar solutions containing either lactose or glucose were administered to the groups that received these respective sugars in their soy-based formula. It is likely that the high initial levels of sugar intake contributed to the excessive difference in stool frequency that was observed. When this study was removed from the analysis, the likelihood of rejecting the null hypothesis was no longer statistically significant ($P = .33$). Even when this study is included, however, the magnitude of the differences in stool frequency (0.30 SD or 0.2 to 2.8 bowel movements per day) is of minor clinical importance.

Four of the papers presented quantitative information on stool outputs (Table 4). The combined results indicated that there were significantly greater stool outputs by children in the lactose groups ($P = .005$), with differences between groups ranging from −132 to 165 g/d, an average effect size of 0.42 SD. However, the presence of significant ($P = .003$) heterogeneity of these results complicates the interpretation. Notably, the study that reported lower stool volumes with the lactose-containing diet employed an atypical design in which lactose-containing milk was compared with lactose-hydrolyzed milk. The osmolality of the latter formula was considerably greater than that of the nontreated milk, possibly overriding the ability to detect any negative effect of intact lactose. On the other hand, the two studies that reported significantly greater stool outputs with lactose enrolled patients with either severe malnutrition or with previous treatment failure.[10,16] Thus, excess stool volume may occur in response to lactose feeding only among this subgroup of patients. Considering the results pertaining to both indicators of diarrheal severity (ie, stool frequency and amount), it appears that the lactose-containing milks or formulas caused marginally greater stool outputs than the lactose-free ones, although these differences are unlikely to be of clinical importance except possibly among children with previous treatment failures or severe underlying malnutrition.

Duration of Diarrhea

Nine studies reported data on the duration of diarrhea following initiation of therapy (Table 5). The pooled results indicated that there was a small, but statistically significant, increase in mean diarrheal duration which ranged from −85 to 67 hours in the different studies when lactose-containing milk was consumed ($P = .001$). The average size of this effect amounted to 0.22 SD.

There was significant heterogeneity of the magnitude of difference in diarrheal duration by study group ($P < .001$). Three of the eight studies of diarrheal duration, including two of those in which the durations were longer in the nonlactose groups, permitted the patients to receive solid foods in addition to the milk formula diets.[11,14,15] Because of the potentially dramatic effect of additional foods on the duration of liquid stool excretion,[12,37,38] these other foods may have prevented the detection of any effect of lactose. When the data were reanalyzed excluding these three studies, the mean ± SD diarrheal duration was greater in the lactose groups than in the nonlactose groups (95 ± 69 hours vs 82 ± 53 hours, $P < .001$), although the effect sizes (average = 0.295 SD) were still nonhomogeneous ($P < .001$). Thus, it seems likely that inclusion of lactose-containing products in diets composed exclusively of milk or infant formulas increased the duration of diarrhea, but the results are not consistent across all studies. When other solid foods are provided in addition to milk, the inclusion of lactose in the mixed diet does not appear to affect the duration of illness.

Weight Gain

Only four studies[12,14,15,17] presented data on change in body weight during therapy. Of these, two[14,15] allowed other foods in addition to the study diets. The results were extremely variable, both within and between studies, and none of the differences by dietary group was statistically significant. Because of the small number of studies that reported this information and because of the use of other foods, we do not

TABLE 4. Stool Amount (Grams per Day or Grams per Kilogram Body Weight per Day) During Hospitalization of Diarrhea Patients Receiving Either Lactose-Containing or Lactose-Free Diets

Study	Dietary Group				d*	P
	Lactose		Nonlactose			
	Mean ± SD	n	Mean ± SD	n		
Rajah[10]	75 ± 55†	16	37 ± 41†	56	0.86	.004
Brown[12]	56 ± 39†	28	66 ± 44†	30	−0.24	.365
Rothman[16]	307 ± 105†	6	142 ± 61†	6	1.92	.008
Romer[17]	147 ± 105†	33	115 ± 66†	34	0.37	.143
Pooled data		83		126	0.42	.002

* d = the standardized difference between treatment groups, calculated as

$$(\bar{X}_L - \bar{X}_{NL})/SD_p,$$ where $\bar{X}_L$ = mean value for lactose group, $\bar{X}_{NL}$ = mean value for non-lactose group, and SD_p = pooled SD of both groups.

† Stool output reported as grams per day by Rothman et al and as grams per klilogram per day by other investigators. (No values provided for pooled data because the results were presented in different units.)

TABLE 5. Duration of Diarrhea After Initiation of Study (Hours) in Patients Receiving Either Lactose-Containing or Lactose-Free Diets

Study	Dietary Group				d*	P
	Lactose		Nonlactose			
	Mean ± SD	n	Mean ± SD	n		
Sutton[5]	101 ± 52	49	71 ± 28	48	0.72	<.001
Dagan[8]	151 ± 95	35	84 ± 35	40	0.96	<.001
Naidoo[9]	94 ± 38	56	115 ± 62	56	−0.42	.029
Conway[11]†	68 ± 44	50	51 ± 42	50	0.40	.051
Brown[12]	151 ± 86	28	119 ± 63	30	0.43	.110
Isolauri[14]†	29 ± 19	38	31 ± 17	27	−0.11	.664
Bhan[15]†	182 ± 259	29	267 ± 240	28	−0.34	.204
Romer[17]	76 ± 50	33	56 ± 49	34	0.40	.103
Haffejee[18]	70 ± 60	120	61 ± 44	75	0.17	.263
Pooled data	92 ± 95	438	88 ± 95	388	0.22	.001

* d = the standardized difference between treatment groups, calculated as

$$(\bar{X}_L - \bar{X}_{NL})/SD_p, \text{ where } \bar{X}_L = \text{mean value for lactose group,}$$
$$\bar{X}_{NL} = \text{mean value for non-lactose group, and}$$
$$SD_p = \text{pooled SD of both groups.}$$

† Studies permitting other foods in addition to formula diets.

believe that the effect of predominantly milk-based diets on weight change can be assessed reliably with the available information.

Undiluted Milk Versus Diluted or Delayed Milk

Sixteen acceptable studies were identified in which undiluted, lactose-containing milk was compared with either a reduced concentration of the same milk or introduction of that same milk at a later time during therapy.[11,19–33] In all but one of these studies,[24] the design called for greater dilution of milk rather than delayed introduction. The milks were diluted between twofold and sixfold with water for periods of time ranging from 1 to 6 days or, in some cases, until the severity of diarrhea declined.

Treatment Failure Rates

Fourteen studies presented data on treatment failure rates (Table 6). In 3 studies[24,26,28] no treatment failures occurred in either study group. Among the 11 remaining studies, treatment failure rates in the groups that initially received undiluted milk exceeded those in the comparison groups in eight cases, although these differences were statistically significant in only one. In none of the 3 studies in which the therapeutic failures of the diluted milk groups outnumbered those of the nondiluted milk groups were the differences statistically significant. The pooled treatment failure rate for undiluted milk was 16% (95% CI = 11%, 18%) and for diluted milk was 12% (95% CI = 7%, 13%; P = .05). This 4% absolute difference between groups in the rates of treatment failure was smaller than the effect seen when lactose-containing and lactose-free diets were compared. The RR of treatment failure when the undiluted milk groups were compared with the diluted milk groups ranged from 0.5 to 7.6 (Fig 2). The combined RR for all studies was 1.3 (95% CI = 0.9, 1.8), which was not

TABLE 6. Treatment Failure Rates of Diarrhea Patients Receiving Undiluted Lactose-Containing Milk or the Same Milk at Reduced Concentration or Introduced Later During Therapy

Study	Dietary Group				Significance*
	Undiluted		Diluted/Delayed		
	No. of Patients	% Failures	No. of Patients	% Failures	
Conway[11]	50	8	50	4	.400
Soeprapto[19]†	20	5	20	10	.548
Placzek[20]†	23	30	25	4	.014
Ransome[21]†	37	22	37	14	.359
McDowell[22]†	47	28	46	15	.144
Madkour[23]†	30	3	30	0	.313
Rees[24]	16	0	14	0	1.000
Dugdale[25]	28	25	32	9	.105
Pichaipat[26]	20	0	20	0	1.000
Armistead[27]	19	26	21	19	.583
Touhami[28]	35	0	35	0	1.000
Chiriboga[29]	38	8	37	11	.664
Chew[30]	72	19	71	20	.967
Fox[33]	30	43	32	41	.829
Pooled data	465	16.3	469	11.7	.050

* P value, χ^2 analyses, or Fisher exact test.
† Studies including patients with more severe dehydration at time of admission.

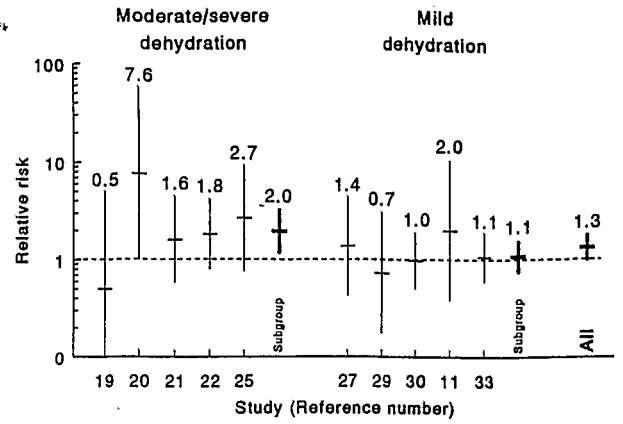

Fig 2. Relative risk of treatment failure with undiluted milk diet, by initial severity of dehydration vs diluted milk diet.

significantly greater than 1.0. The results of the test of heterogeneity were nonsignificant ($P = .45$).

When only studies of patients with more severe dehydration initially were compared,[19-22,25] the treatment failure rates with undiluted milk (20%; 95% CI = 15%, 25%) were greater than the rates with diluted diets (9%; 95% CI = 6%, 13%; $P = .003$). The RR of treatment failure was 2.0 (95% CI = 1.2, 3.3) and the results of the test for homogeneity were nonsignificant ($P = .44$). When studies of patients with milder disease were contrasted,[11,27,29,30,33] the treatment failure rates were 14% (95% CI = 10%, 17%) and 13% (95% CI = 10%, 17%), respectively ($P = .69$). The RR of 1.1 (95% CI = 0.7, 1.6) was not significantly different from 1.0. Thus, any adverse effect of continued intake of undiluted milk on treatment outcome was limited to those patients with more severe illness initially.

As with the aforementioned sets of analyses, we examined separately those studies conducted before and after 1985. The pooled treatment failure rate among the earlier studies was 21% (95% CI = 16%, 26%) with undiluted milk and 10% (95% CI = 6%, 14%) with diluted milk ($P = .005$). There were no differences in the pooled treatment failure rates between the respective groups in the later studies (14% vs 12%, $P = .60$). For the same reasons noted above, it is not possible to determine which of these factors, namely initial severity of dehydration or year of study, was more responsible for the observed differences in the clinical outcomes of the different studies.

Stool Frequency and Stool Amount

Six of the reports contained information on stool frequency and three on stool amount following introduction of the study diets. Four of the former studies found a greater number of bowel movements with the undiluted diet (Table 7), although only one of these sets of results[11] was statistically significant. One study[29] found a slightly, but nonsignificantly, greater stool frequency in the diluted milk group. The pooled data suggest that there was a slight increase in stool frequency with continued use of undiluted milk ($P = .046$). The excess number of bowel movements ranged between 0.2 to 1.0 per day (0.18 SD). There was no significant heterogeneity among study results ($P = .18$).

Of the three studies that provided quantitative information on stool outputs, two[28,30] found significantly higher outputs by children receiving undiluted milk (Table 8). The third[23] noted nearly identical excretion rates in both groups. The pooled results from these three studies indicate that the adjusted stool outputs were significantly greater among those who received undiluted milk ($P < .008$), with a magnitude of mean difference by treatment group ranging from 7 to 21 g/kg per day or 0.33 SD units across studies. The results were homogeneous across the small numbers of studies examined ($P = .47$). In summary, the analyses of both stool frequency and stool volume indicate that early introduction of undiluted lactose-containing milk diets is associated with a slight increase in stool output compared with diluted milk, but these differences are probably of minor clinical importance.

Duration of Diarrhea

Ten studies provided information on diarrheal duration (Table 9). Two found significantly increased durations of illness with undiluted milk,[28,31] and one reported the opposite.[32] The remaining reports described nearly identical durations of illness in both dietary groups. The pooled data indicate that there were no significant differences by dietary group over-

TABLE 7. Stool Frequency (No. of Bowel Movements per Day) During Hospitalization of Diarrhea Patients Receiving Either Undiluted Lactose-Containing Milk or the Same Milk at Reduced Concentration or Introduced Later During Therapy

Study	Dietary Group				d*	P
	Undiluted		Diluted/Delayed			
	Mean ± SD	n	Mean ± SD	n		
Conway[11]	1.8 ± 1.5	50	0.8 ± 1.7	50	0.62	.002
Madkour[23]	11.3 ± 2.3	30	11.1 ± 2.5	30	0.08	.748
Pichaipat[26]	5.6 ± 3.3	20	5.1 ± 3.2	20	0.15	.629
Chiriboga[29]	10 ± 10	38	11 ± 10	37	−0.10	.666
Chew[30]	10 ± 5	72	10 ± 5	71	0	1.000
Fox[33]	4.0 ± 3.0	30	3.0 ± 2.3	32	0.38	.144
Pooled data	7.3 ± 6.3	240	7.0 ± 6.6	240	0.18	.046

* d = the standardized difference between treatment groups, calculated as

$$(\bar{X}_U - \bar{X}_{DD})/SD_p, \text{ where } \bar{X}_U = \text{mean value for undiluted group,}$$
$$\bar{X}_{DD} = \text{mean value for diluted/delayed group, and}$$
$$SD_p = \text{pooled SD of both groups.}$$

TABLE 8. Stool Output (Grams per Day or Grams per Kilogram Body Weight per Day) During Hospitalization of Diarrhea Patients Receiving Either Undiluted Lactose-Containing Milk or the Same Milk at Reduced Concentration or Introduced Later During Therapy

Study	Dietary Group				d*	P
	Undiluted		Diluted/Delayed			
	Mean ± SD	n	Mean ± SD	n		
Madkour[23]	143 ± 65†	30	136 ± 77†	30	0.10	.705
Touhami[28]	407 ± 47†	35	381 ± 50†	34	0.54	.029
Chew[30]	98 ± 68†	72	77 ± 55†	71	0.34	.044
Pooled data		137		135	0.22	.056

* d = the standardized difference between treatment groups, calculated as

$$(\bar{X}_U - \bar{X}_{DD})/SD_p, \text{ where } \bar{X}_U = \text{mean value for undiluted group,}$$
$$\bar{X}_{DD} = \text{mean value for diluted/delayed group, and}$$
$$SD_p = \text{pooled SD of both groups.}$$

† Stool output reported as grams per day by Touhami et al and as grams per kilogram per day by other investigators. (No values provided for pooled data because the results were presented in different units.)

TABLE 9. Duration of Diarrhea (Hours) Following Initiation of Study in Patients Receiving Either Undiluted Lactose-Containing Milk or the Same Milk at Reduced Concentration or Introduced Later During Therapy

Study	Dietary Group				d*	P
	Undiluted		Diluted/Delayed			
	Mean ± SD	n	Mean ± SD	n		
Conway[11]	68 ± 44	50	64 ± 54	50	0.08	.686
Ransome[21]	63 ± 44	37	59 ± 48	37	0.09	.710
Madkour[23]†	60 ± 15	30	61 ± 18	30	−0.04	.887
Rees[24]	82 ± 36	16	86 ± 34	14	−0.11	.760
Touhami[28]	47 ± 9	35	39 ± 7	34	0.99	<.001
Chiriboga[29]†	36 ± 22	38	36 ± 25	37	0	1.000
Chew[30]	92 ± 50	72	92 ± 44	71	0	1.00
Haque[31]	91 ± 29	52	72 ± 34	52	0.60	.003
Maudgal[32]	70 ± 25	77	86 ± 15	82	−0.75	<.001
Fox[33]	101 ± 38	30	103 ± 41	32	−0.06	.810
Pooled data	72 ± 39	437	72 ± 40	439	0.02	.450

* d = standardized difference between treatment groups, calculated as

$$(\bar{X}_U - \bar{X}_{DD})/SD_p, \text{ where } \bar{X}_U = \text{mean value for undiluted group,}$$
$$\bar{X}_{DD} = \text{mean value for diluted/delayed group, and}$$
$$SD_p = \text{pooled SD of both groups.}$$

† Studies permitting other foods in addition to formula diets.

all. Removal of those studies that permitted consumption of other foods did not alter this conclusion.

Weight Gain

Seven reports contained interpretable information on weight change in response to therapy (Table 10). In all but one case the weight gains were greater (or less negative) in the group that received the more concentrated milk diet. The pooled data demonstrate a significant advantage of undiluted-milk feeding on body weight ($P = .002$), with an average effect size of 0.25 SD. The magnitude of the effect was homogeneous across studies ($P = .16$).

DISCUSSION

The appropriate use of lactose-containing, nonhuman milks and infant formulas for the dietary management of young children with acute diarrhea has been controversial, in part because relevant studies have included patients with varying severity of illness severity and have employed a variety of study diets and research designs. Moreover, individual studies have often been inconclusive because of the relatively small numbers of patients that were enrolled. To overcome these difficulties with the interpretation of available literature, we have completed a meta-analysis of randomized clinical trials that fulfill specific acceptance criteria. The advantage of this approach is that data from multiple different trials can be pooled to better assess the effects of different forms of therapy.[34,39]

Limitations of This Meta-analysis

Potential problems with the interpretation of meta-analyses occur when there is heterogeneity of the magnitude of treatment effects.[34,39] For this reason, our conclusions were intentionally conservative when heterogeneity was observed. Moreover, we attempted to reanalyze the results after removing the study or studies responsible for heterogeneity. We also analyzed separate subgroups of studies divided by either the initial characteristics of the patients or

TABLE 10. Change in Body Weight Following Initiation of Study in Patients Receiving Either Undiluted Lactose-Containing Milk or the Same Milk at Reduced Concentration or Introduced Later During Therapy

Study	Unit of Measure*	Dietary Group				d†	P
		Undiluted		Diluted/Delayed			
		Mean ± SD	n	Mean ± SD	n		
Soeprapto[19]	g/d; d11–d1	49 ± 56	20	6 ± 56	20	0.77	.020
Madkour[23]	%; rec-d1	4.8 ± 1.8	30	4.3 ± 1.9	30	0.27	.300
Dugdale[25]	g/d; d2-d1	−20 ± 250	28	−140 ± 210	32	0.52	.048
Touhami[28]	%; rec-d1	2.5 ± 0.6	35	2.6 ± 0.5	34	−0.18	.460
Chiriboga[29]	g; rec-d1	200 ± 290	38	100 ± 190	37	0.41	.082
Chew[30]	%; rec-d1	0.8 ± 4.7	72	0.3 ± 4.4	71	0.11	.510
Fox[33]	%; rec-d1	1.8 ± 5.0	30	0.4 ± 3.9	32	0.31	.220
Pooled data		‡	253	‡	256	0.25	.002

* Unit of measurement of weight change; period of observation (rec = day of recovery or discharge from study).
† d = the standardized difference between treatment groups, calculated as

$$(\bar{X}_U - \bar{X}_{DD})/SD_p, \text{ where } \bar{X}_U = \text{mean value for undiluted group,}$$
$$\bar{X}_{DD} = \text{mean value for diluted/delayed group, and}$$
$$SD = \text{pooled SD of both groups.}$$

‡ No values provided for pooled data because the results were presented in different units.

specific features of the study protocols that might have explained the heterogeneity of results. Naturally, this was possible only when there were a sufficient number of studies examining the outcome of interest. Factors that were considered as possibly influencing the major outcomes were initial severity of dehydration, as defined by the authors, year in which the study was reported, type of milk prescribed, other foods offered during treatment, and age and nutritional status of the patients. Regrettably, the studies rarely presented data that were sufficiently disaggregated to permit exploration of the latter two factors.

Another concern with meta-analyses is the possibility of publication bias. It is ordinarily assumed that clinical trials with negative results are less likely to be published. In this case, any publication bias would be likely to exaggerate the differences between whole milk and diluted or lactose-free milk. Although this possibility cannot be excluded, it is noteworthy that many of the studies did report seemingly negative results. Moreover, two nonpublished studies of sufficient quality to be considered, both with negative results, were also included.

Lactose-Containing Versus Lactose-Free Feeding

Because an earlier qualitative review discovered that study outcomes varied according to the diets that were employed,[3] independent analyses were completed for those studies that compared lactose-free diets with lactose-containing diets and for those that compared undiluted milk-based diets with the same milks offered at lower concentration or at a later point in convalescence. The results of these analyses confirm that the vast majority of young children with acute diarrhea can safely continue to receive undiluted, nonhuman milk. Nevertheless, the previously conducted clinical trials, taken as a whole, indicate that children who continue to receive lactose-containing milk diets during acute diarrhea are twice as likely to have a treatment failure as those who receive a lactose-free diet; the absolute excess treatment failure rate is about 10% of patients. This difference in clinical outcome is probably due to the somewhat greater stool outputs that occurred with milk feeding. It is important to note, however, that adverse clinical outcomes were limited to that subgroup of studies that included patients with severe dehydration initially, as defined by the authors, previous treatment failures, or underlying severe malnutrition. There were no clinically significant complications of continued milk feeding in studies of non-severely dehydrated children. Moreover, nearly all of the more recently completed studies, which used widely accepted treatment protocols for oral rehydration therapy and early feeding, found no adverse effects of continued milk consumption during diarrhea, regardless of the patients' initial hydration status. Although the duration of diarrhea may be slightly prolonged in children who receive lactose-containing milks, the magnitude of this difference is probably of little clinical importance. Moreover, addition of solid foods to milk-containing regimens apparently eliminates the minor differences observed. Available data are inadequate to assess the relative effects of these feeding regimens on change in body weight.

Diluted Versus Undiluted Milk

When continued feeding with undiluted milk was compared with diluted or delayed reintroduction of milk, somewhat different conclusions emerged. As with the lactose-containing vs lactose-free diets, there was a significantly increased risk of treatment failure with undiluted milk when compared with diluted milk, but the magnitude of this difference was smaller and of marginal statistical significance. Again, the diluted milk regimens were more likely to show superior efficacy only when the underlying illness was more severe. Notably, however, the small clinical advantage of feeding with diluted milk was offset by the poorer weight gains of children who received these regimens. Thus, the decision with regard to patient management may require a trade-off between the very small excess risk of relapsing diarrhea vs suboptimal nutritional therapy. For children with relatively mild diarrhea, it would seem to be preferable to provide undiluted milk.

Relevance of This Analysis

The obvious critical question for clinicians and managers of diarrheal disease control programs is whether the small number of treatment failures attributable to continued feeding of undiluted, lactose-containing milks merits recommending a systematic change in diet, with its associated cost, complexity, and possible adverse nutritional effects, for children whose preillness regimen is based exclusively or predominantly on lactose-containing milk. Based on this meta-analysis, we conclude that routine dilution of milk and routine use of lactose-free milk formula are not justified, especially when oral rehydration therapy and early feeding with solid foods (in addition to milk) form the basic approach to the clinical management of diarrhea in infants and children. However, children with severe malnutrition[40] or with persistent diarrhea[41] and the few children whose diarrhea obviously worsens when given milk should probably be treated with dietary regimens that contain reduced lactose, although this should not be done at the expense of adequate nutrient intake. Alternative diets that may be used when low-cost, commercially prepared, lactose-free products are not available include cereal-milk mixtures or, possibly, fermented milk products. These latter possibilities have been reviewed previously.[2-4] Although human milk contains more lactose than cow milk and many infant formulas, available evidence indicates that human milk is well tolerated during diarrhea and may, in fact, reduce the severity[42] and duration[43] of illness. Thus, current recommendations in support of continued breast-feeding during childhood diarrhea should not be affected by the results of this meta-analysis.

ACKNOWLEDGMENTS

Funding was provided by the Diarrhoeal Disease Control Programme of the World Health Organization and the Applied Diarrheal Disease Research Project of the Harvard Institute of International Development from the US Agency for International Development, Cooperative Agreement No. DPE-5952-A-00-5073-00.

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PSYCHIATRIC EFFECTS OF EXPOSURE TO SUICIDE AMONG THE FRIENDS AND ACQUAINTANCES OF ADOLESCENT SUICIDE VICTIMS

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Abstract. The friends and acquaintances (N = 58) of 10 adolescent suicide victims were interviewed 6 months after the death of the victims, and the rates of psychiatric disorders that had onset after the death were compared with the 6-month incidence of psychopathology in 58 demographically and psychiatrically matched unexposed controls. The exposed group showed higher rates of any new onset major depressive disorder, but the rate of incident suicide attempts was the same in both groups. The median onset of incident depression among the exposed group was within the first month after exposure, and the majority of those exposed youth with incident depression were still depressed at interview 6 months after the death. Adolescent friends and acquaintances of suicide victims experience considerable psychiatric morbidity subsequent to exposure to suicide, most consistent with pathological grief. *J Am Acad Child Adolesc Psychiatry.* 1992;31(4):629–640. **Key Words:** suicide, bereavement, depression.