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Is dilution of cows' milk formula necessary for dietary management of acute diarrhoea in infants aged less than 6 months?

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There is concern that feeding full-strength animal milk to infants aged less than 6 months with diarrhoea may have adverse consequences. We assessed the effects on clinical course of two feeding regimens in 159 Guatemalan and Brazilian infants aged 2 weeks to 6 months who had had acute diarrhoea for 120 h or less, showed signs of mild to moderate dehydration, and had no complications.

After correction of dehydration, infants were assigned randomly to receive continued full-strength milk feeding or initial feeding with diluted milk with regrading to full-strength milk over 48 h. There were no significant differences between feeding groups in rate of treatment failures (−1%, 95% CI −14 to 12%) or mean (SD) total stool output (full-strength milk 335 [268] g/kg, diluted milk 338 [354] g/kg) and duration of diarrhoea (92 [50] *vs* 92 [44] h). A significant association was found between presence of reducing substances in stools and treatment failure (OR 4·3, 95% CI 1·1 to 16·8), but reducing substances in stools were common both in treatment successes (61%) and in failures (87%).

Our study supports the conclusion that, for infants under 6 months of age with diarrhoea whose only food is animal milk or formula, the milk or formula normally given should be provided in full strength as soon as dehydration has been corrected.

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Introduction

Correct early feeding during diarrhoea can prevent weight loss with no increased risk of complications or severity.[1,2] However, there has been concern that certain foods, notably animal milk, may affect adversely the clinical course of diarrhoea.[3,4] This apprehension has been largely relieved by studies showing that infants and children who normally take solid foods can safely take full-strength milk formula during diarrhoea, provided that it is given with such solid foods, usually cereals.[5–12]

For infants whose sole nutrient is animal milk or formula, feeding during diarrhoea has remained problematic. Concern about the risks, in particular lactose intolerance, associated with feeding such infants full-stength animal milk or formula has led to recommendations that they be given reduced amounts of milk, either by diluting their usual milk formula and gradually regrading the intake over several days or by temporarily replacing milk formula with special lactose-free or milk-free formulae until diarrhoea stops.[13,14] These approaches, are, however, unsuitable for developing countries, where diarrhoea is a major cause of early childhood mortality and an important contributor to malnutrition. Reducing milk intake when it is the infant's only food carries a risk of weight loss and of deterioration in nutritional status; it may also encourage mothers to continue giving diluted milk after diarrhoea stops. In addition, special formulae are prohibitively expensive. In these circumstances, the continued intake of full-strength animal milk or formula would be highly advantageous for nutritional and economic reasons.

Two studies in infants aged less than 6 months[15,16] came to the conclusion that routine dilution of milk formula had no beneficial effect on the clinical course of illness. However, both of these studies were conducted in the UK, where diarrhoea is usually mild in infant under 6 months old and they are well fed,[17] and the results cannot be assumed to apply also to infants in developing countries who are frequently undernourished and in whom diarrhoea is often severe. We felt therefore that it was important to better define the risks associated with dilution of milk formula in developing countries. We present the results of a collaborative, randomised feeding trial in milk-fed infants aged less than 6 months with diarrhoea. Two dietary regimens were compared: continued full-strength milk formula and initial feeding of diluted milk formula with regrading to full strength over 48 h. A lactose-free or milk-free formula was not studied because such formulae are not affordable for most families in the study populations.

Subjects and methods

The study was conducted at the Metabolic Unit of the Instituto de Nutricion de Centro America y Panama (INCAP), Guatemala, and at the Hospital das Clinicas of the Universidade Federal de Minas Gerais, Belo Horizonte, Brazil. The protocol was approved by the ethics committees of both institutions and of the World Health Organization. Patients admitted to the study were boys aged 15 days to 6 months with acute diarrhoea (defined as three or more watery stools in the previous 24 h), no visible blood in the stool, and no clinical signs of severe dehydration. Only patients who had had diarrhoea for less than 120 h before consultation were enrolled. Infants were excluded if they had severe malnutrition (weight for age <60% of the National Centre for Health Statistics 50th percentile[18]), were exclusively or mostly breast-fed (infants who received most of their energy from breast milk), or had systemic infections or other diseases requiring specific additional treatments. Informed consent was obtained from the parent or guardian of every infant.

Patients who had clinical signs of dehydration on admission were rehydrated orally in 4 to 6 h with the standard WHO UNICEF glucose-based oral rehydration salts (ORS) solution before the start of the study. After rehydration and until diarrhoea stopped, ORS solution and plain water were offered according to WHO

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TABLE I—COMPOSITION OF THE FULL-STRENGTH COWS' MILK FORMULAE (PER 100 ML RECONSTITUTED FORMULA)

—	Brazil	Guatemala
Protein (%)	1·65	1·38
Fat (%)	3·40	3·39
Carbohydrate (%)	7·40	6·90
Energy (kJ)	280	260
Osmolarity (mOsmol)	295	290
Energy from protein (%)	9·8	8·9
Energy from fat (%)	45·7	49·2
Energy from carbohydrate (%)	44·2	41·2

recommendations for maintenance therapy. Feeding was started as soon as infants were considered to be fully rehydrated. They were then assigned randomly to one of two feeding regimens: full-strength milk formula (group A), or progressive reintroduction of full-strength milk formula (half-strength for the first 24 h, two-thirds strength for the second 24 h, and full-strength thereafter) (group B). One randomisation list per centre was established at WHO, Geneva, with random permuted blocks of variable length (6 to 12 subjects per block). Individual patient assignments, corresponding to the master randomisation lists, were then placed in sealed serially numbered envelopes and sent to the centre. Milk formulae were prepared by a dietitian who was not otherwise involved in clinical management of patients or collection of clinical data. The different formulae, which were similar in appearance, were administered through opaque feeding bottles; staff and investigators did not know which formula was being given. The macronutrient compositions of milk formulae used by each centre in the study are shown in table I; both formulae contained appropriate amounts of vitamins and minerals. Infants were offered 150 mL kg per day of milk, divided into eight feedings of equal volume.

For each infant, faecal and urine output, volumes of ORS solution, water, and milk consumed, the clinical evaluation, number and characteristics of stools passed, and the number of vomiting episodes were recorded continuously and summarised for 8 h periods from the beginning of the study until the cessation of diarrhoea, or for a maximum of 5 days, or until withdrawal from the study. Body weight was recorded at the end of every 8 h. Patients were regarded as treatment failures when there was: recurrence of clinical signs of dehydration during maintenance oral rehydration therapy; or weight loss of more than 5% of admission body weight, without clinical signs of dehydration, sustained over two consecutive 24 h periods; or a 50% increase in faecal weight for consecutive 8 h periods when the faecal weight in the previous 8 h was less than 50 g kg; or a 25% increase in faecal weight over two consecutive 8 h periods when the faecal weight in the previous 8 h was more than 50 g kg. Treatment failures were removed from the study and their feed was changed to a soya-based formula.

On admission, a stool sample was taken to identify rotavirus by enzyme-linked immunosorbent assay (Dakopatts A S, Glostrup, Denmark). Reducing substances in the stool were tested by Clinitest (Ames)[19] on admission and on every alternate stool. The pH of every stool was measured with pH paper.

The study was designed to detect a 20% difference between treatment groups in total faecal output. We calculated that 68 patients per group would have to be enrolled in the study to show this difference with a power of 80% and a significance of 5%.[20] This calculation was based on an investigation showing that the mean (SD) total stool output of patients with diarrhoea in the study age group was 284 (111) g/kg (A. H. Madkour, personal communication).

Statistical analyses were done with SPSS PC+ software. A two-tailed Student's *t* test was done for comparisons between measures. Continuous variables with skewed distribution were normalised by log transformation, and a two-tailed *t* test was applied to transformed data.[21] Qualitative variables were compared with the χ^2 test.

TABLE II—CHARACTERISTICS OF PATIENTS ON ADMISSION BY DIETARY GROUP

Characteristic	Full-strength milk (n = 80)	Diluted milk (n = 79)
Age		
Mean (SD) months	3·8 (1·6)	3·6 (2·0)
Number < 3 mo	23	19
Number > 3 mo	57	60
Mean (SD) weight (kg)	5·1 (1·3)	5·0 (1·3)
Mean (SD) weight for age (z-scores)	−1·44 (−1·12)	−1·39 (−1·14)
Median (IQR) duration of diarrhoea before admission (h)	72 (46 to 82)	72 (30 to 96)
Median (IQR) stools passed in previous 24 h	8·5 (6·5 to 10·5)	8·0 (5·0 to 10·0)
No of patients who vomited in previous 24 h	57	46
Hydration status on admission (no)		
No signs of dehydration	54	53
Some dehydration	26	26
Severe dehydration	0	0
Feeding pattern on admission (no (%))		
Breast-feeding	30 (38)	22 (30)
Diluted milk formula	15 (19)	12 (16)
Solids	10 (13)	10 (13)

IQR = interquartile range

From April, 1989, to June, 1991, 159 patients were enrolled in the study—71 at the Hospital das Clinicas and 88 at the Metabolic Unit of INCAP. 80 patients were assigned randomly to receive full-strength milk formula and 79 to receive diluted milk formula. 143 patients were eligible for analysis: 2 patients (1 in each treatment group and 1 at each centre) were excluded shortly after treatment had begun when informed consent was withdrawn, and 14 patients (7 in each treatment group) were removed from the study because of severe infection requiring antibiotic treatment (bronchopneumonia [11], urinary-tract infection [1], measles [1], sepsis [1]). The characteristics of the two treatment groups on admission to the study were comparable (table II), and the admission characteristics of patients who were withdrawn from analysis were similar to those of patients who were included in the final analysis (data not shown).

Of the 143 eligible patients, 115 were regarded as treatment successes since they did not fulfil any of the criteria for treatment failure defined above (table III). For 101 of those patients, diarrhoea stopped within the 5-day study period; 14 patients (7 in each treatment group) still had diarrhoea after day 5. Of 10 of these patients seen daily after discharge, 9 ceased to have diarrhoea within 5 days without further medical intervention. 1 patient had diarrhoea for more than 14 days; his diet was changed to a lactose-free formula after discharge and he was also treated for an urinary-tract infection. The other 4 patients were lost to follow-up. 28 patients (20%) were considered to be treatment failures (table III). The difference between treatment-failure rates in the two groups was not significant

TABLE III—CLINICAL OUTCOME AFTER REINTRODUCTION OF MILK FEEDS

Clinical outcome	Full-strength milk (n = 80)	Diluted milk (n = 79)
Treatment successes		
Diarrhoea stopped within 5 days	51 (71)	50 (79)
Diarrhoea continued beyond day 5	7 (10)	7 (10)
Treatment failures		
Recurrent dehydration*	6 (8)	6 (9)
Increased stool output†	8 (11)	5 (11)

Number of patients (%) are shown
*Treated with intravenous fluids, †treated by change in diet

TABLE IV—MEAN (SD) CLINICAL FEATURES OF PATIENTS AFTER REINTRODUCTION OF MILK FEEDS UNTIL CESSATION OF DIARRHOEA OR DISCHARGE FROM STUDY

—	Full-strength milk (n=72)	Diluted milk (n=71)	—
Stool output at 24 h (g/kg)	98 (68)	77 (55)	1·3 (0·9, 1·8)*
Total stool output (g/kg)	335 (268)	338 (354)	1·1 (0·8, 1·5)*
Total stools passed	36 (22)	39 (26)	−3 (−11, 5)†
Total ORS intake (mL/kg)	238 (212)	227 (291)	1·1 (0·7, 1·7)*
Total milk formula intake (kJ/kg)	1318 (900)	1351 (971)	−8 (−83, 67)†
Diarrhoea duration (h)	92 (50)	92 (44)	1·0 (0·7, 1·3)*
Weight gain at discharge (%)	0·8 (4·7)	0·3 (4·4)	1·0 (0·6, 1·7)*

None of the comparisons between treatment groups was statistically significant.
*Ratio of population (geometric) means (95% CI calculated on transformed data and then reconverted to the normal scale).
†Difference between arithmetic means (95% CI).

(−1%, 95% CI −14 to 12%). After inclusion as treatment failures of the 14 patients who were removed from the study because of severe infection, there was no difference between treatment-failure rates (−0·3%, 95% CI −14% to 13%).

Data collected for all 143 patients, up to the time of their withdrawal from the study or their discharge from the hospital on day 5, were included in the final analysis (table IV). There were no significant differences between treatment groups in the main outcome variables, including total stool output. However, mean (SD) energy consumption during the first 24 h was significantly higher in the group that received full-strength milk formula (310 [130] *vs* 172 [67] kJ/kg; $p < 0·05$). Duration of diarrhoea, taking into account only patients whose diarrhoea stopped within the 5-day study period, did not differ between treatment groups. Weight gain was similar in infants successfully treated with either diluted or full-strength milk formula. However, among treatment failures, weight gain was better for the group given full-strength milk (2·2% *vs* −2·3%).

Stool reducing substances were measured for 74 patients, of whom 23 were treatment failures. There was no significant association between presence of reducing substances in stools and treatment group. On the other hand, a significant association was found between presence of reducing substances in the stools and treatment failures (OR 4·3, 95% CI 1·1 to 16·8). However, reducing substances in the stools were common both in treatment successes (61%) and in failures (87%).

133 of the 143 eligible patients were tested for rotavirus, which was isolated from 47 (35%). There was no association between presence of rotavirus and treatment failure (OR 0·8, 95% CI 0·3 to 2·0) or between presence of rotavirus and lactose intolerance (defined as stool reducing substances >0·5%) (OR 2·7, 95% CI 0·9 to 7·7).

Discussion

Dilution of milk formula during diarrhoea has been advocated to reduce the risk of clinically significant milk intolerance (lactose intolerance) in infants. Our study, the first conducted in developing countries and which included patients with severe diarrhoea and a significant proportion who were malnourished (48% of the patients had a weight/age z-score below −1·5), shows that routine dilution of milk formula has no beneficial effect on the clinical course of illness and does not reduce the risk of treatment failure. In fact, total stool output, total number of stools passed, duration of diarrhoea, and total intake of ORS solution, water, and milk formula were similar in the two treatment groups. In addition, routine dilution of milk formula provided less energy and thus may contribute to malnutrition, as suggested by our data.

The rate of treatment failures (20%) leading to a change of diet is higher in our study than is usually reported for hospitalised infants with acute diarrhoea (5–10%).[22] This finding is probably a result of the sensitive definition of treatment failure that we used. Usually, only patients who cannot be rehydrated orally because of recurrent dehydration are regarded as treatment failures. If this definition had been applied, the rate of treatment failure would have been about 8% (12 treatment failures from 143 patients), which is well within the usual range reported for this age group. In addition, in our study the rate of treatment failures leading to a change of diet (20%) is only half of that reported by a UK study (42%).[16] We believe that this is because we used only clinical indices to define treatment failure (ie, reappearance of signs of dehydration at any time after admission, and increased stool volume during treatment), whereas treatment failure in the British study was defined as continuing diarrhoea with the presence of 0·5 to 2% reducing substances in stools.

Although we found that treatment failures occurred almost entirely among infants with faecal reducing substances, suggesting a role for lactose intolerance, it should be noted that 60% of the infants who had reducing substances in their stools were not treatment failures, even with the sensitive clinical criteria used in the study. This finding confirms other observations suggesting that presence of reducing substances in stools is not sufficient as an indicator of clinically important lactase deficiency.[23,24] Despite the high incidence of rotavirus infection (35%), we did not find any association between rotavirus infection and presence of reducing substances in stools, as has been reported by others.[25]

Our findings support the conclusion that for infants aged under 6 months with diarrhoea whose only food is animal or formula milk, the milk or formula normally given should be provided in full strength as soon as any dehydration has been corrected; routine dilution of milk formula for such infants does not reduce the risk of treatment failure. However, the study does not provide any information on how to manage the minority of children who are regarded as treatment failures. The association of treatment failure with faecal reducing substances supports efforts to reduce dietary lactose, but this should not be at the expense of adequate nutrient intake. At least two approaches are possible: replacing milk temporarily with yoghurt where this is available and culturally acceptable, or replacing milk formula temporarily with a lactose-free formula. Although effective, the latter approach is obviously too costly for many families in the developing world.

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Cysticercosis as a major cause of epilepsy in Peru

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In countries where cysticercosis is endemic, the proportion of epilepsy due to cysticercosis is not well documented. To investigate the association between cysticercosis and epilepsy, we used the enzyme-linked immunoelectrotransfer blot (EITB) assay to detect serum antibodies to *Taenia solium* in 498 consecutive outpatients at a neurology clinic in Lima, Peru. Every patient was classified as epileptic (n=189) or non-epileptic (n=309) after neurological, and where possible electroencephalographic, examination. A substantially higher proportion of epileptic than non-epileptic patients was seropositive in the EITB (22 [12%] *vs* 8 [3%], p<0·001). 19% of epileptic patients born outside Lima, 20% of those with late-onset epilepsy, and 29% of patients with both these characteristics were seropositive. Thus, in Peru, cysticercosis is an important aetiological factor for epilepsy.

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Introduction

Neurocysticercosis is common in rural areas of developing countries where free-ranging pigs are raised.[1,2] Clinically, the disorder can include many neurological symptoms, but epilepsy is the most common.[2–5] Rural areas of developing countries have higher rates of epilepsy[6,7] and of *Taenia solium* infection[8] than do urban areas and developed countries. Neurocysticercosis resulting from the higher *T solium* infection rate may contribute to higher rates of epilepsy in these areas.[9]

The proportion of epilepsy cases associated with neurocysticercosis has not been well documented. Serological tests used to measure the prevalence of cysticercosis in epileptic populations were not highly sensitive or specific.[10,11] However, the enzyme-linked immunoelectrotransfer blot (EITB) assay[12,13] is 98% sensitive and 100% specific and can accurately diagnose *T solium* infection. We used the EITB assay to define the relation between epilepsy and cysticercosis in individuals attending a neurology outpatient clinic in Lima, Peru.

Patients and methods

The Instituto Nacional de Ciencias Neurológicas is the neurological reference centre for Peru and mainly serves the lower and middle class sectors of the population. New patients are randomly assigned to one of six neurology outpatient clinics for evaluation. All new patients attending one such clinic (consultorio no 2) between April, 1990, and June, 1991, were enrolled in this study after they had given informed consent. The study was approved by the ethical review boards of the Universidad Peruana Cayetano Heredia and the Johns Hopkins University.

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