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ETIOLOGY OF CHILDHOOD DIARRHEA AND ORAL REHYDRATION THERAPY IN NORTHEASTERN BRAZIL[1]

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Acute diarrhea is a major cause of morbidity and death in northeast Brazil. The study reported here documents the presence of enterotoxigenic E. coli *and rotaviruses among children with diarrhea at a rehydration center in northeast Brazil and demonstrates the acceptability of oral glucose-electrolyte rehydration therapy administered by mothers in this setting.*

Introduction

Acute diarrhea of infants and children is the leading cause of morbidity and mortality in many parts of the world, including northeastern Brazil *(1)*. Treatment of diarrhea with adequate rehydration is often a lifesaving measure.

In recent years, oral glucose-electrolyte therapy has been shown highly effective in rehydrating patients with diarrhea caused by *Vibrio cholerae* or enterotoxigenic *Escherichia coli (2, 3)*. This treatment exploits knowledge that the secretory effect of cholera toxin leaves glucose-facilitated absorption of sodium ions and water intact *(4-6)* and that *E. coli* heat-labile enterotoxin (LT) behaves in a similar manner *(7, 8)*.

Oral glucose-electrolyte therapy has also been shown effective in treating children with rotavirus diarrhea *(9)*. However, the optimal sodium composition of oral rehydration fluids for infants and young children is still debated, with some workers favoring fluids containing 90 milliequivalents of sodium per liter, like the solution recommended by the World Health Organization *(10, 11)*, and some favoring fluids containing 30 milliequivalents of sodium per liter *(12)* to treat non-enterotoxin-mediated diarrheas. Other workers in Central America have used the WHO-recommended formula with supplemental free water at a ratio of 2:1 *(13)*.

Although cholera has not been reported in Brazil, research on diarrhea in southern Brazil has shown that 50 per cent of the cases studied were associated with *E. coli* that produce cholera-like heat-labile (LT) enterotoxin *(14)*. The aims of the study reported here were to determine the etiology of acute diarrhea cases treated at a rehydration center in northeast Brazil during the peak diarrhea season and to evaluate the acceptability and efficacy of the oral glucose-electrolyte solution recom-

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mended by WHO for children admitted to rehydration centers with acute diarrhea.

Methods

The study was conducted at the Marieta Cals Rehydration Center *(Centro de Rehidratação Marieta Cals)* from 8 March to 24 April 1978. The center, supported by the *Fundação de Saúde do Estado do Ceará* (FUSEC), is located in Fortaleza, Ceará, a city of 1.2 million people. Children treated at the center for diarrhea come primarily from the city's lower socioeconomic groups. Some 90 per cent of the households involved have no piped water, the majority have latrine toilet facilities or none at all, and an average of 6.4 people (including 2.2 children) live in an average of 3.6 rooms. Mothers at the center are required to stay by their children's bedsides.

Children three months of age or older who were admitted to the center for treatment of acute diarrhea were considered eligible for inclusion in the study. Acute diarrhea was defined as two or more liquid stools per day for a period of one to seven days. The liquid stools of all these patients conformed to the shape of their receptacles. Children who had taken antibiotics during the previous week were excluded from the study. Informed consent was obtained from the mothers of all children admitted to the study.

All the children involved were first examined by a center physician, who prescribed initial therapy for the study participants according to the center's customary procedure. Those included in the study group initially received no medications other than parenteral fluids.

A history was obtained from the mother of each child. The data requested included the day of onset of diarrhea, the number of stools per day, presence or absence of fever, occurrence of vomiting (including the number of occurrences in the last 24 hours), the presence or absence of anorexia or thirst, the time of last urination, and the number and characteristics of stools (including form, color, and presence of blood or mucus). The patient's weight and vital signs, as well as other significant physical findings, were recorded.

The patient's state of hydration was evaluated on the basis of orthostatic changes in blood pressure and heart rate, decreased skin turgor, sunken eyes or diminished ocular tension (as determined by palpation), dryness of mucous membranes, depressed fontanelle, and altered state of consciousness (each patient being assigned a score of 0-4 depending on whether the state in question was normal, irritable, lethargic, stuporous, or comatose). The admitting physician's assessment of dehydration was recorded as mild (estimated at less than 5 per cent dehydration), moderate (5-10 per cent), or severe (more than 10 per cent). These categories were associated with the following physical signs: mild—no signs; moderate—dry mucous membranes, mildly decreased skin turgor, sunken eyes, or depressed fontanelle; and severe—more severely decreased skin turgor plus lethargy.

Initial fluids, administered intravenously, consisted of normal saline or 5 per cent glucose with saline; these were supplemented with KCl and $NaHCO_3$ when considered necessary by the center's physician. Intravenous therapy was continued until objective signs of improvement (i.e., weight gain, improved level of consciousness, or urination) were observed by one of the investigators. The patients were then assigned by drawing lots to oral or continued intravenous treatment groups.

Treatment

Patients assigned to the continued intravenous treatment group were maintained on the regimens prescribed by the center physicians. Patients assigned to the oral group had their intravenous therapy discontinued and were started on the standard WHO oral rehydration solution containing the following ingredients per liter of water:

Na	90 milliequivalents
Cl	80 milliequivalents
HCO_3 ...	30 milliequivalents

K ..... 20 milliequivalents
Glucose ..110 millimoles

Intravenous fluid was given to patients in the intravenous group until completion of the prescribed regimen. Oral solution was given *ad libitum* until discharge. Patients did not receive supplemental free water, nor were they breast-fed during the study period. All the patients were closely monitored by their mothers (who administered the oral fluid to those in the oral therapy group) as well as by center personnel and the investigators.

Patients in the intravenous group were discharged by the center's nurses upon completing the prescribed therapy (the standard practice at the center).

Patients in the oral group were discharged by a center physician or nurse when the physician or nurse judged that they were ready. Thus the investigators did not influence each patient's length of stay, even though they did review the patient's status at discharge. All the children were reexamined and reweighed by the investigators before leaving the center, usually after the decision to discharge them had been made.

Oral therapy was considered successful if the signs of dehydration had diminished, the patient's state of consciousness had improved, urination had ensued, and weight was gained. Refusal to drink the oral solution, failure of the measured volume of oral intake to exceed the volume of stool and urine output, weight loss greater than 2.5 per cent of admission weight while on oral therapy, and intractable vomiting were considered indicators of treatment failure. When such conditions arose, the oral fluid therapy was stopped and intravenous therapy, as directed by the center physicians, was reinstituted.

Stool Examinations

Stool specimens were collected and examined immediately for leukocytes *(15)*. In addition a saline wet mount and a preparation stained with Lugol's iodine were examined for parasites, and a sample was placed in hypertonic saline to concentrate ova and cysts by flotation *(16)*. Hemoccult® tests were used to detect occult blood.

The routine enteric bacteriology tests performed included prompt inoculation of MacConkey's agar to detect coliforms, XLD[10] or SS[11] agar to detect salmonellae and shigellae, and TCBS[12] agar to detect vibrios. GN[13] broth was also inoculated to enrich for salmonellae and shigellae before subculturing onto MacConkey's and either XLD or SS agar, and phosphate-buffered saline (PBS) was inoculated and refrigerated at 4°C to select for certain species before subculturing onto MacConkey's agar at room temperature after two and four weeks. Isolates were identified using standard techniques *(17)*.

Strains were tested for production of LT using the Chinese hamster ovary (CHO) cell assay *(18)*, and for production of the heat-stable enterotoxin (ST) using the suckling mouse assay *(19)*. Tests were also performed on four or more lactose-fermenting organisms for invasiveness *(20)*. Antibiotic sensitivity testing was done on enterotoxigenic *E. coli* and *Shigella spp.* by the Kirby-Bauer disc diffusion method *(21)*.

Stools were also diluted 1:5 in phosphate-buffered saline and were examined for the presence of rotaviruses by enzyme-linked immunosorbent assay (ELISA) *(22)*. Positive results were confirmed by blocking with guinea pig anti-human rotavirus antibody *(23)*.

Formed fecal specimens were also collected from 13 control children seen at a Fortaleza outpatient clinic for reasons other than diarrhea. These specimens were analyzed for enterotoxigenic and other pathogenic bacteria, parasites, and rotaviruses as described above. None of these control children had experienced diarrhea or received antibiotics in the preceding two weeks.

[10] Xylose-lysine-deoxycholate.
[11] Salmonella-shigella.
[12] Thiosulfate-citrate-bile salts-sucrose.
[13] Gram negative.

Results

As Figure 1 shows, during the period January 1977-June 1978 diarrhea admissions to the center peaked in January-March of both years. These peaks are comparable to that reported by this center for 1967 *(24),* when admissions peaked during the months of February-May. Overall, the seasonal variation was most striking in children under two years of age with moderate and severe dehydration.

Other points brought out in Figure 1 include the following: These seasonal peaks occurred slightly before the period of maximal rainfall; they correlate with the season of maximal diarrhea mortality in Fortaleza between 1951 and 1960 *(25);* and they do not correlate with major temperature variations because the city experiences little seasonal variation in temperature.

Comparing the children in the two treatment groups (Table 1), there were 24 in the intravenous group and 29 in the oral group. Overall, they ranged in age from three months to seven years, mean ages in the intravenous and oral groups being 10 and eight months, respectively. Twenty-three (70 per cent) of the patients were under one year of age, 62 per cent of the intravenous group and 76 per cent of the oral group falling in this category; 19 per cent were 1-2 years of age; and all but one child were under five years of age. Although there were relatively fewer males in the oral therapy group, the sex distributions of the two groups were not significantly different. Illnesses were of comparable severity and duration, and fecal leukocytes occurred with comparable frequency in both groups.

Besides diarrhea, the major signs and symptoms presented in both groups were feverishness and vomiting (Table 2). Most pa-

Figure 1. Monthly data on admissions to the rehydration center in 1977-1978, the percentage of Fortaleza deaths due to diarrhea in 1951-1960, mean precipitation (mm per month) in 1931-1960, and mean monthly temperatures (showing mean maximum and minimum temperatures) in 1931-1960. The precipitation data were kindly provided by IBGE *(Fundação Instituto Brasileiro de Geografia e Estatística),* Ceará.

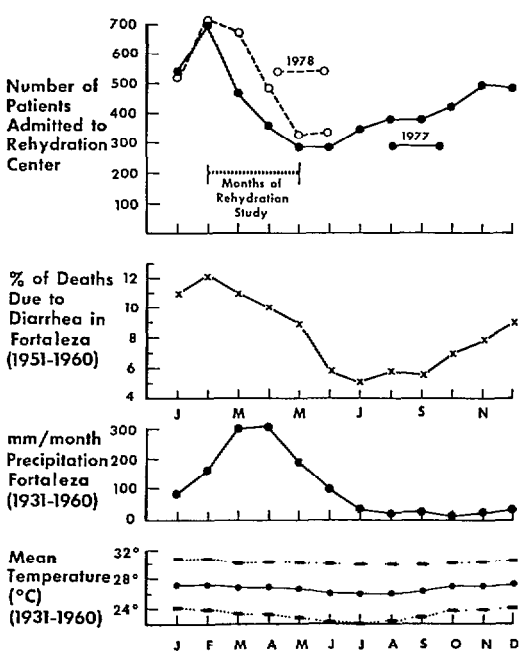

Table 1. A comparison of initial data obtained from the 53 study children who received intravenous maintenance therapy and oral maintenance therapy.

	Intravenous group (n = 24)	Oral group (n = 29)
Age:		
Mean age	10 months	8 months
Age range	3-36 months	3-84 months
Sex ratio (boys:girls)	13:11	11:18
Duration of illness at admission:		
Average duration	3.7 days	3.2 days
Range of durations	12 hours-7 days	12 hours-7 days
Number of stools per day:		
Average	4.3	4.5
Range	3-7	2-10
Fecal PMN[a] present:	8/24 (33%)	6/29 (21%)
Degree of dehydration:		
Mild	12	13
Moderate	12	15
Severe	0	1

[a]Polymorphonuclear neutrophil leukocytes.

Table 2. Disease signs and symptoms upon admission of children in the intravenous and oral rehydration treatment groups.

	Intravenous group %	Oral group %
Symptoms:		
Feverishness	67	65
Vomiting	33	37
Blood in feces	21	14
Anorexia	58	82
Thirst	96	93
Signs:		
Orthostatic hypotension (drop in systolic BP>10 mm Hg in upright position)	6	8
Fever (>37.5°C axillary)	35	41
Decreased skin turgor	38	28
Diminished ocular tension	8	17
Dry mucous membranes	25	24
Reduced fontanelle tension	60	54
Altered state of consciousness:		
Irritable	17	25
Lethargic	17	0
Stuporous	0	0
Comatose	0	4
Diuresis on morning of presentation	45	61

tients had lost their appetites, and most were thought to be thirsty. Approximately 40 per cent of the patients had fever upon admission, most of these being low-grade fevers. The frequency of the listed signs and symptoms, as well as the degree of dehydration, was comparable in both groups. The mean serum specific gravity was 1.026 with a standard deviation of ± .002 for both groups; mean hematocrits upon admission were 36.4 ± 4.0 and 36.9 ± 4.0 per cent, respectively, for the intravenous and oral groups.

Stools from 37 patients were examined for disease agents (Table 3). Enterotoxigenic *E. coli* were identified in stools from 27 per cent of these patients; ST-producing *E. coli* were present in 21.6 per cent of the patients, and LT-producing *E. coli* were present in the remaining 5.4 per cent. No strains that produced both LT and ST were found. Stools from two patients were found to contain *Salmonella enteritidis;* in addition, one stool specimen contained *Shigella dysenteriae,* two contained *Shigella flexneri,* and one contained *Giardia lamblia* motile trophozoites and cysts. Stools from four patients (10.8 per cent) were

Table 3. Potential causative agents isolated from the feces of 27 study children.

	Intravenous group	Oral group	Total No.	Total %
Number of children with feces cultured:	16	21	37	
Organisms isolated:				
Enterotoxigenic *E. coli:*				
ST-producing *E. coli*	5[a, b]	3[b]	8	21.6
LT-producing *E. coli*	1	1	2	5.4
Salmonella sp.	1[a]	1	2	5.4
Shigella sp.	1	2	3	8.1
Giardia lamblia	0	1	1	2.7
Rotaviruses	2[b]	2[b]	4	10.8

[a]Feces from one patient contained both ST-producing *E coli* and *Salmonella sp.*
[b]Feces from one patient in the intravenous group and one in the oral group contained both ST-producing *E. coli* and rotaviruses.

found to contain rotaviruses. Three patients had ST-producing *E. coli* in association with other pathogens (these pathogens being rotaviruses in two cases and *Salmonella* in one). Ten patients (27 per cent)—including one each with *Salmonella, Shigella,* and rotavirus—exhibited fecal leukocytes. Among the 13 control children with no diarrhea, two were infected with LT-producing *E. coli,* one with *Shigella boydii,* and one with rotavirus. None of the control children were found to be infected with salmonellae or ST-producing *E. coli.*

Of the 10 enterotoxigenic *E. coli* strains isolated from different patients, eight were resistant to tetracycline, nine were resistant to sulfonamides, and eight were resistant to ampicillin. Five of these strains exhibited the classic pattern of resistance to chloramphenicol, tetracycline, sulfonamides, and streptomycin. While all three *Shigella* species isolated were resistant to tetracycline and sulfonamides, none were resistant to ampicillin.

Stool rates, pulse rates, and blood pressures were comparable during the initial treatment and study periods for the oral and intravenous groups. During the initial rehydration period there were no significant differences between the two groups' duration of therapy, amount of fluid given, weight change, or level of consciousness (Table 4). However, during the subsequent study period highly significant differences occurred in the duration of therapy and total fluid intake required. Specifically, members of the oral treatment group required significantly less fluid (237 ml versus 545 ml) and significantly less treatment time than members of the intravenous group. Since the average (± one standard deviation) of the two groups' weights were 8.10 ± 2.3 kg for the intravenous group and 7.33 ± 2.0 kg for the oral group, the average amount of fluid required per kilogram of body weight was 67.3 ml in the intravenous group and 32.3 ml in the oral group. There was no significant difference in the weight changes experienced by the two groups.

Progress toward a normal level of consciousness was significantly greater among the members of the oral rehydration group. Members of the intravenous group also excreted more urine (as determined by making a gross estimate of the number of urinations and the volume voided) during their generally longer treatment period. Members of the oral treatment group drank enough fluid to maintain their weight or gain slightly, to improve their level of consciousness, and to excrete some urine before their generally earlier discharge. Only one of the 29 patients in this study was unable to tolerate the oral therapy because of vomiting. No complications of therapy were observed.

Discussion

This study indicates that enterotoxigenic *E. coli* and rotaviruses occur in association with

Table 4. Comparison of results obtained by providing the two study groups with initial intravenous therapy and subsequent oral (or intravenous) maintenance therapy. (The numbers shown are mean values plus or minus the standard error of the mean; the P values shown were obtained using Student's t test.)

	Initial rehydration period			Study period		
	Intravenous group	Oral group	P	Intravenous group	Oral group	P
Duration of treatment in hours	2.7 ± 1.1	2.8 ± 0.2	Not significant	8.6 ± 1.3	3.8 ± 0.3	<.001
Total fluid administered (ml/patient)	199 ± 18	236 ± 22	Not significant	545 ± 58	237 ± 22	<.001
Weight gain (as % of admission body weight)	0.88 ± .50%	1.09 ± .23%	Not significant	0.69 ± .55%	0.65 ± .42%	Not significant
Level of consciousness (improvement in score)	.02 ± .11	.04 ± .37	Not significant	0 ± .7	0.7 ± .5	<.01

diarrhea among children in Fortaleza during the peak diarrhea season. It also demonstrates that an oral glucose-electrolyte solution containing 90 milliequivalents per liter of sodium ion provides effective therapy in a vast majority of such cases, following initial intravenous rehydration.

In contrast to the predominance of LT-producing *E. coli* in Brazil's temperate southern areas *(14),* ST-producing *E. coli* was the major bacterial pathogen found in the tropical Fortaleza area. (We have recently confirmed the predominance of ST-producing *E. coli* in community surveillance of this area as well—*26).* Multiple antibiotic resistance was common among the rehydration center patients studied, 80 per cent of the enterotoxigenic isolates being resistant to tetracycline and ampicillin.

Oral rehydration therapy was both feasible and well-accepted. It also saved significant amounts of intravenous fluids and was administered quite effectively by the patients' mothers. That the intravenous therapy group may have received more fluid than necessary is suggested by the observation that weight gains were comparable in the two groups despite the fact that more fluid was administered to the intravenous therapy group. The difference is probably attributable to a greater output of urine during a relatively longer treatment period by members of the intravenous group. The usefulness of the oral fluid therapy was not significantly reduced by nausea, vomiting, or abdominal distension, nor was there clinical evidence of hypertonic dehydration or other serious electrolyte imbalance.

The individual attention required for successful administration of oral rehydration fluids to young children constitutes a logistical problem. While this can place great demands on the time of physicians or nurses, this study indicates the feasibility of having mothers administer the fluid. Constant maternal stimulation may have contributed to a more rapid improvement of mental status among children in the oral treatment group. Administration of the fluid by supervised mothers also produced the indirect benefit of teaching these mothers to recognize signs of worsening dehydration or therapeutic complications while bolstering confidence in their ability to treat their children.

Since a majority of children with acute diarrhea have either mild or moderate dehydration, and since patients in these groups do not require intravenous maintenance therapy, oral fluid therapy (especially if instituted early) may preclude the need for intravenous therapy in a majority of these patients. However, further investigation of oral rehydration in the study environment will be needed in order to assess its potential for initial treatment of acute diarrheal disease, its usefulness for providing earlier therapy in a community setting, and its impact upon the nutritional status of treated children.

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SUMMARY

Acute diarrheal diseases are the leading cause of morbidity and mortality among infants and children in northeast Brazil. However, little is known about their etiology or whether oral glucose-electrolyte rehydration therapy is effective in this setting. The study reported here was designed to determine the causes of acute diarrhea during the peak season among children admitted to a rehydration center in Fortaleza, the capital of Ceará State, and to gauge the efficacy and acceptability of oral rehydration therapy.

Patients admitted to this study were between 2 months and 7 years of age. All received intravenous rehydration fluids initially and were then selected at random to receive either oral rehydration or additional intravenous rehydration. (A total of 29 received oral rehydration and 24 received continued intravenous rehydration.) The oral fluid formula used, being that recommended by the World Health Organization, contained 90 milliequivalents (meq) of sodium, 80 meq of chloride, 30 meq of bicarbonate, 20 meq of potassium, and 110 mmol of glucose per liter of water. The solution was prepared by the investigators and administered by the patients' mothers under close supervision at the rehydration center. No additional free water or breast milk was given during the relatively short period of oral maintenance therapy.

This oral fluid therapy was well-tolerated by 28 of 29 patients. Overall, members of the oral treatment group required significantly less fluid and less treatment time than the intravenous group. They also showed a greater average improvement in their state of consciousness than did members of the intravenous group.

Regarding causes of these acute diarrhea cases, the most common etiologic agents isolated were *E. coli* producing heat-stable (ST) enterotoxin; these were found in stools from eight of the study children. Rotaviruses were found in stools from four of the children, and two children had both rotaviruses and ST-producing *E. coli. Shigella* species were isolated from three children, *E. coli* producing heat-labile (LT) enterotoxin were isolated from two, *Salmonella* species were isolated from two, and *Giardia lamblia* cysts were demonstrated in one. The distribution of pathogens was comparable in both treatment groups. Many of the bacterial pathogens isolated were resistant to common antimicrobial drugs.

This study points to enterotoxigenic *E. coli* and rotaviruses as the most common recognized pathogens infecting infants and small children with acute diarrhea during the peak diarrhea season in Fortaleza, Brazil. It also shows that oral glucose-electrolyte rehydration therapy is acceptable and efficacious when administered under the conditions prevailing in this study.

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RIVER BLINDNESS VACCINE SOUGHT

The parasite *Onchocerca volvulus,* taken from the skin of people afflicted with the tropical disease known as onchocerciasis or "river blindness," is being frozen and air-shipped to "worm banks" at the London School of Tropical Medicine and Hygiene.

Workers in Sudan are trained to collect and pack the parasite, using an inexpensive and portable liquid nitrogen device, so that it can be studied in the United Kingdom. The project provides a good example of cooperation between research institutions in developed and developing countries.

In this case the aim of the research is to develop a vaccine against the disease, which afflicts an estimated 15 to 20 million people in parts of Africa and Latin America.

Source: World Health Organization, *World Health,* 31 August 1981, p. 31