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Oral gentamicin is not effective treatment for persistent diarrhea

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We conducted a randomized, double-blind, placebo controlled clinical trial of oral gentamicin (10 milligrams/kilogram body weight/day for five days) in treatment of unselected cases of persistent diarrhea (duration 14–18 days at initiation of treatment) among 3–36-month-old children in a rural Guatemalan community. Following random assignment of each child to a treatment group, the appropriate dose of gentamicin or placebo was administered to the child three times daily by a study nurse; this nurse also identified the presence or absence of diarrhea on each day of treatment and for the next two days. Cure was defined as cessation of diarrhea during the five-day treatment period, sustained through at least the two days after completion of treatment. Among 92 evaluable cases who entered the clinical trial, there was essentially no difference in cure rate between gentamicin and placebo treatment groups (42% versus 43%). Enteroadherent strains of *Escherichia coli* were identified in 46% of children tested in this trial; no significant difference existed between treatment groups in frequency of isolation of this or any other enteropathogen. Among 40 children having successful duodenal cultures immediately prior to beginning treatment, $\geqslant 10^4$ aerobic organisms per milliliter of fluid were identified in 12 (30%); treatment groups did not differ substantially with respect to proportion of children identified with this level of duodenal microbial colonization. Failure of gentamicin treatment did not appear to be explained by emergence of resistance, although a small number of resistant enteropathogens were identified near the end of the study. We conclude that in this population and in the dose used, oral gentamicin has no value in the treatment of persistent diarrhea.

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In children of the developing world, one of the most important causes of diarrheal disease morbidity and mortality not preventable by oral rehydration therapy is persistent diarrhea, that is, diarrhea which begins as an acute episode, but lasts two weeks or longer (1). In several developing countries where its contribution to overall diarrhea mortality has been studied, persistent diarrhea has been reported to be one of the principal causes of diarrhea mortality, as well as one of the principal illnesses associated with severe malnutrition (1, 2).

The public health importance of persistent diarrhea lends urgency to the investigation of possibilities for improved management of these episodes. Among these possibilities might be the use of antimicrobial therapy directed against microorganisms associated with persistent diarrhea. A potential benefit from antimicrobial therapy was suggested by two lines of evidence from studies of persistent diarrhea: association of persistent episodes with small bowel bacterial overgrowth, principally with gram-negative enteric organisms (3–9), and the frequent isolation in such episodes of various types of enteroadherent *Escherichia coli* (EAEC) (10–16). A small number of hospital-based clinical studies and case reports suggested gentamicin, delivered by the oral route, to be the most promising antimicrobial agent for treatment of persistent diarrhea (17–18). The applicability of these findings to persistent diarrhea episodes in non-hospitalized young children in developing countries was uncertain.

In 1986, INCAP began a longitudinal study of persistent diarrhea among 0–36-month-old children in a rural indigenous community of Guatemala. This longitudinal study provided the opportunity to perform this controlled clinical trial of oral gentamicin therapy in treatment of non-hospitalized young children with persistent diarrhea.

Patients and methods

This was a double-blind placebo-controlled clinical trial conducted in the community. The trial was designed to test the hypothesis that, in children aged 3–35 months with diarrhea lasting 14–18 days, treatment for five days with oral gentamicin (10 milligrams/kilogram body weight/day divided in three doses) would cure a large proportion of cases. The ongoing longitudinal study indicated that 55% of diarrhea episodes lasting 14 days would end spontaneously by day 21. Therefore this trial

was designed to detect the cure of 55% of the patients plus an additional one-half of the other 45% of episodes in those treated with gentamicin.

Approximately 290 children enrolled in the INCAP longitudinal study of persistent diarrhea in Santa María de Jesús, Sacatepéquez, Guatemala, between April, 1988, and January, 1990 were eligible to participate in the clinical trial. The beginning of diarrhea episodes and their duration were identified by active surveillance through weekly household visits. Diarrhea was defined as four or more loose or watery stools in 24 h, as reported by the mother. The end of a diarrhea episode was defined by absence of diarrhea for longer than two consecutive days. Other illnesses, treatments given, and types of foods consumed (including breast-feeding) by each study child were also identified during household visits. Anthropometric measurements were obtained every month for all children and weekly during and immediately after diarrhea episodes. Mothers were requested to provide stool specimens at the beginning and during each subsequent week of diarrhea episodes; control specimens were obtained weekly from children free of diarrhea for at least two weeks. Stool specimens were tested at INCAP's central laboratories for the isolation and/or identification of *Shigella* sp., *Salmonella* sp., enterotoxigenic (ETEC), enteropathogenic (EPEC), HEp-2 adherent (EAEC) and auto-adherent (AUTEC), *E. coli*, *Campylobacter jejuni*, *Yersinia enterocolitica*, *Aeromonas* sp., *Cryptosporidium*, *G. lamblia*, *E. histolytica*, *C. difficile* cytotoxin, and rotavirus, using standard methods previously described (19). Stools were also examined for reducing substances, occult blood, and fecal leukocytes. Adherence patterns of HEp-2 adherent *E. coli* were identified by microscopic examination.

When a child experienced diarrhea lasting 11 or 12 days, the study procedures and treatment protocol were explained to the parents in simple, locally comprehensible language. Parents willing to participate were asked to give no medicine to their child for the next 48 h. If diarrhea lasted 14–18 days (depending on whether day 14 fell on a holiday or weekend) the study procedures were again explained and written informed consent was obtained from parents still willing to participate. A stool specimen from the sick child was requested, but was not mandatory, prior to entering the trial.

Children with dysentery at the time of enrollment were excluded from the trial and were offered appropriate antimicrobial therapy if it had not already been administered; however, children were eligible to participate if a diarrhea episode began as dysentery but continued to 14 days' duration following appropriate treatment and disappearance of blood from stools. Anthropometric measurements were performed at enrollment; children with weight-for-length < -2 Z relative to the NCHS median were excluded from the trial and offered nutritional therapy. Although dehydration after two weeks of diarrhea was uncommon, if it existed the child was rehydrated using oral rehydration therapy before admission into the clinical trial.

Treatment allocation was performed with random tables of block lengths 8 to 12, stratifying the children according to their feeding practices: exclusively breast-fed (except for additional clear liquids), breast-fed plus other liquid or solid foods, and fully weaned from the breast. Treatment vials were prepared by a microbiologist not related to the project, and numbered for sequential administration. Only that microbiologist and a statistician, neither of whom had contact with the patients, kept a list with the contents of each numbered vial.

In children whose parents accepted the tests requiring naso-duodenal intubation of their child, this procedure was performed on admission to the trial and before starting therapy. This was done in the morning; parents were requested not to give breakfast to the child on that day. A soft, gas-sterilized double-lumen tube was used. One lumen was open to permit aspiration of fluid for pH determination; the other lumen was plugged with sterile agar and filled with oxygen-free sterile water. Chloral hydrate was given orally to induce mild sedation, and the tube was introduced through the nose to the estimated level of the pylorus. Following the measurement of gastric fluid pH, the tube was advanced to the estimated level of the ligament of Treitz. Aspiration of bile-stained fluid with alkaline pH was used as confirmation of presence in the duodenum. The agar plug was then ejected, using 3 ml of oxygen-free water. After 10 min, a specimen of duodenal-jejunal fluid was aspirated through a three-way stopcock; this fluid was immediately injected into an oxygen-free CO_2-filled tube containing phenylethyl alcohol agar with 5% sheep blood. hemenine supplement, and vitamin K_1 for culture of anaerobic microorganisms. After vortex agitation, an aliquot was taken with an air-tight syringe and serial dilutions were made in sealed tubes containing the same media. These dilutions were immediately plated on anaerobic media and placed in a sealed jar with anaerobic atmosphere generated using the Gas-Pak catalyst (BBL Microbiology Systems, Cockeyville. MD). An additional specimen of duodenal fluid was obtained for quantitative cultures of aerobic microorganisms and for identification of *G. lambia*. All cultures were placed in an incubator at 37°C until transported to the central laboratory at day's end in temperature-stabilized containers.

After the tests, or on beginning the trial, one group received 10 mg gentamicin sulfate per kilogram body weight per day, divided in three equal daily doses. The other group received a 1% (w/v) solution of magnesium sulfate three times daily. Treatment vials were maintained under refrigeration in the study headquarters. Potency of gentamicin was tested periodically with United States Pharmaceutical standards.

The antibiotic and placebo solutions were both given in a volume of 0.5 ml/kg dose and had similar appear-

Table 1. Characteristics of study children on admission to the clinical trial, by treatment group.

	Gentamicin ($n=45$)	Placebo ($n=47$)
Age, months*	14±9	14±9
Male/female	24/21	26/21
Diet: breast/mixed/weaned	8/29/8	7/30/10
Weight, kg*	7.5±1.7	7.6±1.7
Length, cm*	68±8	68±7
Weight-for-length, Z score*	−0.3±1.3	−0.3±0.9
Days with diarrhea*	15.4±1.3	15.4±1.3

* Mean ± standard deviation.

ance and taste. Fifteen consecutive oral doses during five days were administered directly to the child by a field nurse who visited the child's household three times daily. The field nurse recorded in each morning visit the presence or absence of diarrhea as determined by the mother, as well as number and other characteristics of stools (consistency, mucus, blood). This information was obtained for seven consecutive days, including two days after the last treatment dose. It was also recorded daily for one additional week, and thereafter every other day until diarrhea stopped.

Cure was defined as cessation of diarrhea (<4 stools/day with a return to the child's normal stool characteristics, as assessed by the mother) during or at the end of five treatment days, sustained for at least 48 h after the end of treatment.

Following the completion of the clinical trial and of microbiological testing, treatment codes were broken and results analyzed.

Table 2. Results of microbiological testing of stool specimens among study children at admission to the clinical trial and at any time during episode prior to treatment, by treatment group. (Number positive/number tested for each microorganism.)

	Time of testing during diarrhea episode			
	Admission to trial		Any prior to treatment	
Microorganism	Gentamicin	Placebo	Gentamicin	Placebo
Shigella sp.	1/21	2/28	1/36	4/41
Salmonella sp.	0/21	0/28	1/36	0/41
Campylobacter jejuni	1/22	2/29	3/36	5/41
ETEC-LT	4/20	2/26	13/35	3/39
ETEC-ST	1/21	2/27	6/35	5/39
EPEC	1/21	3/27	6/35	7/39
EAEC (local)	1/20	3/26	3/35	6/39
EAEC (diffuse)	2/20	5/26	6/36	12/38
AUTEC	1/21	0/27	3/35	1/39
Rotavirus	0/15	0/17	1/34	3/37
Giardia lamblia	4/21	3/28	6/36	4/41
Cryptosporidium	0/21	3/28	0/36	2/41
Entamoeba histolytica	0/21	0/28	0/36	0/49

Table 3. Results of stool microbiology in 1–3 specimens tested prior to treatment, by enteropathogen category and treatment group.

Category	Gentamicin	Placebo
Any enterotoxigenic *E. coli*	13/35 (37)*	6/39 (15)
Any enteroadherent *E. coli*	15/35 (43)	19/39 (49)
Any *E. coli* pathogen	23/35 (66)	21/39 (54)
Any enteroinvasive organism (*Salmonella, Shigella, C. jejuni*)	4/36 (11)	9/41 (22)

* Numbers in parentheses are percentages.

Results

Of the 102 children who entered the clinical trial, 10 were excluded: four because duration of diarrhea was found to be >18 days after entry; two whose parents withdrew within two days of beginning treatment; three who received only 11 or 12 of 15 scheduled doses of gentamicin; and one because of conflicting evaluation by mother and study nurse regarding resolution of diarrhea. Eight gentamicin-treated children missed a single dose of treatment and were retained in these analyses.

Of the 92 cases evaluated, 45 received gentamicin and 47 received placebo. Comparison of these treatment groups on several basic variables is presented in Table 1.

There was virtually no difference between gentamicin and placebo recipients in the proportion of episodes cured: 19 (42%) of 45 gentamicin-treated children and 20 (43%) of 47 placebo-treated children were classified as cured during the treatment. The overall 42% "cure" rate was not substantially different from the 55% spontaneous rate of cessation of diarrhea between days 15 and 21 observed in persistent diarrhea episodes during previous years.

The results of microbiological testing in the gentamicin and placebo treatment groups are given in Table 2. Stool specimens were obtained in only about 62% of study patients during the first week of diarrhea, and in only 53% at the time of entry to the clinical trial. About 79% of the patients had at least one stool examination before days 14–18 of diarrhea.

Table 3 presents the results of microbiological testing in regard to categories of enteropathogens potentially important in response to gentamicin treatment or in the pathophysiology of persistent diarrhea. The total number of positive specimens for some categories is smaller than the number of positive individual isolates in that category, because more than one pathogen was sometimes identified in the same specimen or child. The children treated with gentamicin whose stools were tested prior to treatment had enterotoxigenic *E. coli* of any type identified more often than the placebo group,

whereas an invasive organism was identified more frequently among the placebo group. However, the numbers of children with these positive results were small and did not affect the outcome of the clinical trial.

The presence of mucus in stools, a characteristic significantly associated with persistent diarrhea in our population (21), did not affect the response to gentamicin treatment: among children with mucus in stool, 7 (30%) of 23 treated with gentamicin and 11 (42%) of 26 treated with placebo were cured during the treatment period. Although dysentery was of concern in this community, only one child with bloody stool entered the study, apparently because of our policy of treating dysentery during the acute phase.

Adequate duodeno-jejunal specimens for microbiologic analysis were obtained in 40 of the 92 children. Intubation was performed in more children, but transpyloric passage was not achieved within a period of time reasonable under field conditions. Twenty-eight (70%) of the 40 duodeno-jejunal specimens were either sterile or contained $< 10^4$ aerobic organisms per milliliter. The remaining 12 had $\geqslant 10^4$ or more aerobic organisms per milliliter; this level of colonization was identified in 5 (28%) of the 18 gentamicin-treated children with adequate specimens obtained, and in 7 (32%) of 22 placebo-treated children with adequate specimens. The presence of yeasts (two cases) was considered negative. EPEC was identified in the duodenal fluid of only one child; this child received gentamicin and was a treatment failure. One other child had ETEC in duodenal fluid; that child also received gentamicin, and was "cured" during treatment.

There was no difference in continuation of diarrhea after one week of treatment in relation to aerobic bacterial overgrowth in the duodenum: 4 (33%) of the 12 children with $\geqslant 10^4$ aerobes per milliliter of duodenal fluid and 11 (39%) of the 29 children with lower aerobe counts or sterile fluid resolved their diarrhea during the week after intubation. Anaerobic microorganisms were identified in duodenal fluid of 6 (15%) of the 40 children; only two of them also had $\geqslant 10^4$ aerobic microorganisms per milliliter. One of these six children was treated with gentamicin and was a treatment failure; the other five received placebo, and four were treatment failures. There were no differences in the continuation of diarrhea for one more week in relation to the presence or absence of duodenal anaerobes, regardless of treatment.

Other treatments were tried after the end of the seven-day treatment and observation period for some children who were treatment failures during the clinical trial. Continued observation during these secondary treatments identified resolution of diarrhea in 6 (43%) of 14 children given trimethoprim-sulfamethoxazole, 2 (67%) of 3 children receiving nalidixic acid, and 1 (17%) of 6 children who had received placebo during the clinical trial and who were subsequently treated with gentamicin. None of these secondary treatments appeared to offer any advantage over observation alone: 17 (81%) of 21 children who still had diarrhea at the end of the clinical trial and who received no additional treatment experienced resolution of diarrhea in the following week.

Table 4. Clinical evolution of 83 study children followed to resolution of persistent diarrhea episodes.

Day diarrhea ended	No. of children
15–21	38 (46)*
22–28	27 (33)
29–35	7 (8)
36–42	6 (7)
43–49	4 (5)
>49	1 (1)

* Numbers in parentheses are percentages.

Based on the fact that gentamicin treatment had no advantage, it was also assumed that it did not influence in a negative way the outcome of the disease. Adding the 39 treatment "successes" to the 44 "failures" who were followed until diarrhea ceased gives the pattern of apparently spontaneous remission of these episodes presented in Table 4. This seems to represent the "natural history" of the persistent diarrhea with which we were dealing in this population, unless gentamicin or any of the other secondary treatments prolonged the duration of the disease.

Discussion

The multiple potential factors in the persistent diarrhea syndrome, and the possibility of their interaction, suggest that it might be simplistic to expect a single treatment to be effective in most cases (1, 2, 20). However, it is also possible that an intervention which corrects one or several factors in this cycle might permit recovery in many children. Two lines of evidence suggested that treatment with antibiotic therapy directed against gram-negative enteric bacteria might be effective in persistent diarrhea of children. First among these was the association of persistent diarrhea with bacterial overgrowth in the small intestine. This condition has been found to be associated with severe malnutrition and in children living in environments heavily contaminated with fecal organisms (3, 4, 9). Several studies reported substantially higher levels of small bowel colonization among children with persistent diarrhea, compared with children with acute diarrhea or healthy children. In several of these studies the most prominent increases were in numbers of gram negative bacilli, coliforms, and/or *E. coli* (6–8).

The second rationale for a trial of antibiotic therapy directed against gram-negative enteric organisms was the association of persistent diarrhea with identification of enteroadherent strains of *E. coli* (EAEC), which sometimes, but not necessarily, belong to "enteropathogenic" serotypes (22). This association was first de-

scribed by Ulshen and Rollo in a young infant with persistent diarrhea; in that case, duodenal cultures revealed a pure culture of *E. coli* which on small bowel biopsy were seen to be tightly adherent to the mucosa with associated mucosal damage (10); intravenous gentamicin therapy was associated with remission of diarrhea within two days. Following that report, three other groups identified up to 15 cases of persistent diarrhea associated with identification of EAEC in stool (one study) or small bowel aspirates (two studies) (11–13). Pathologic changes in small bowel mucosa in these studies were similar to those observed by Ulshen and Rollo. Clauson and Christie found that these *E. coli* also adhere to cultured Hep-2 cells (13). In two of these studies, treatment with oral neomycin or intravenous gentamicin was associated with prompt remission of diarrhea (11, 13). The third study did not evaluate treatment, but found susceptibility to gentamicin in 14 of 15 stains and resistance to trimethoprim-sulfamethoxasole in 13 of 15.

Two hospital-based trials of oral gentamicin therapy in prolonged diarrhea suggested its potential usefulness in broader treatment of persistent diarrhea. One study in South Africa evaluated various combinations of oral gentamicin (50 mg/kg/day), cholestyramine, and metronidazole, and found significant reduction in diarrhea after the first day only in the 20 children who received gentamicin (17). No "conventional" enteropathogens were found in this study, but EAEC were not sought and duodenal cultures were not performed. Patients in that study were very young infants (mean age 4.8 months) with diarrhea of duration seven days after admission who continued with very high stool volumes requiring intravenous fluids to maintain hydration.

The other trial compared placebo with oral gentamicin (10 mg/kg/day) in treatment of persistent diarrhea among hospitalized infants in a developed country. In that study, Craft and Halsey found a significant reduction of diarrhea by the third day in the gentamicin group (18). This reduction was almost totally attributable to the significantly greater cure rate with gentamicin among the 10 study children who had enteroadherent strains of *E. coli* isolated from stool or duodenal fluid. The nutritional and clinical characteristics of the subjects of this trial have not been published.

Prior to the present study, no adequate controlled trial of oral gentamicin treatment of unselected cases of persistent diarrhea in a developing country had been performed. The potential importance of such treatment, if it were effective, was great. On the other hand, the widespread use of gentamicin in developing countries could promote resistance to one of the most important and readily available antimicrobial agents for use against gram negative infections.

The results of our study demonstrate conclusively that in our population and at the dose used, oral gentamicin treatment offered no advantage over placebo in the management of persistent diarrhea. Although data from other communities in developing countries are limited, those data suggest that our study population is similar to others in which persistent diarrhea is an important problem. In our population just over 10% of diarrhea episodes among children 0–36 months of age lasted $\geqslant 14$ days (20); this proportion is intermediate among those identified by the World Health Organization in various developing countries (1). As in many other developing populations in rural areas, our persistent diarrhea patients tended to be young children (most in the first or second year of life), chronically but not acutely malnourished, and receiving breast milk (most in addition to other foods). One or more enteroadherent strains of *E. coli*, among the anticipated targets of oral gentamicin therapy, were identified in 46% of children tested in this clinical trial. Overgrowth of the proximal small bowel by aerobic enteric organisms ($\geqslant 10^4$ ml) was identified in 30% of study children successfully intubated.

Resistance to gentamicin was not a likely explanation for the clinical failure of this therapy in cases of persistent diarrhea infected by *E. coli*. Gentamicin resistance had not been identified among *E. coli* from children's stools in this community prior to starting the clinical trial. Testing during this reporting period of a substantial number of *E. coli* (including 115 strains of enteroadherent *E. coli*) obtained from stools of children from the community, including many of the children participating in this treatment study, identified no gentamicin resistance. However, a small number of gentamicin-resistant strains of *Salmonella* sp. and *Shigella* sp. were identified in the community (but not among children in the clinical trial) during the second year of the study. The appearance of gentamicin resistance in our community underscores the potential danger of broader resistance which might result from widespread use of this antimicrobial agent, now generally limited to parenteral use in hospital settings.

Our results of subsequent treatment of clinical trial failures with other agents failed to suggest any potential usefulness of other antimicrobial agents in persistent diarrhea, and the medical literature has not suggested any likely therapeutic agents. Thus, antimicrobial therapy does not presently appear to be a useful approach to persistent diarrhea. For these reasons, our present efforts to respond to the challenge of persistent diarrhea are focused on evaluating the effects of overall reduction of diarrheal morbidity on occurrence of persistent diarrhea and on nutritional management of both acute and persistent diarrhea.

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