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A randomized clinical trial to compare the efficacy of erythromycin, ampicillin and tetracycline for the treatment of cholera in children

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Abstract

To compare the clinical outcome of treatment of cholera in children with ampicillin, erythromycin or tetracycline, a double-'blind' randomized four-cell trial was carried out in Bangladesh. Ampicillin was chosen as additional therapy for acute respiratory tract infection, present in many subjects with diarrhoea. One hundred and eighty-four children aged 1–5 years who were not wasted, with diarrhoea of duration <48 h, signs of some or severe dehydration, dark-field stool microscopy demonstrating *Vibrio cholerae*, and a baseline purging rate >4 mL/kg/h over 6 h were enrolled in the study. Ampicillin, tetracycline, erythromycin or placebo were given orally every 6 h for 3 d. After 3 d of antibiotic treatment, diarrhoeal stool volume was significantly reduced in all antibiotic groups, with mean volumes per kg body weight as follows: tetracycline, 318 mL (SEM=50), ampicillin, 335 mL (SEM=30); erythromycin, 323 mL (SEM=25); placebo, 498 mL (SEM=37). Compared to tetracycline, the clinical recovery rates by 96 h were 75% with placebo, 91·3% with ampicillin, and 95·7% with eythromycin. Compared to tetracycline, the total mean times to recovery were increased by 66% with placebo ($P<0·001$), 25% with ampicillin ($P<0·017$), and 9% with erythromycin ($P=0·37$). These results indicated comparable clinical efficacy of tetracycline, ampicillin and erythromycin. We therefore recommend that, unless *V. cholerae* is resistant, ampicillin should be used as a cost-effective alternative to erythromycin for paediatric cholera, especially in children with concomitant acute respiratory infection.

Keywords: cholera, *Vibrio cholerae*, ampicillin, erythromycin, tetracycline, children, Bangladesh

Introduction

Cholera remains one of the leading causes of death in many developing countries and is endemic in Asia, Africa and Latin America. Efficient case management leads to early recovery and reduces mortality. While oral rehydration therapy is the mainstay of management of cholera, antibiotics such as tetracycline, doxycycline, furazolidone and chloramphenicol are useful in reducing the duration and severity of diarrhoea as well as faecal excretion of *Vibrio cholerae*, when the organism is not resistant. Tetracycline is often preferred in the management of cholera due to its lower cost and its excellent antibacterial activity. However, there is concern about its use in young children due to its potential to cause yellow discoloration of teeth. Erythromycin is an alternative which is safe for use in children, but it is much more expensive than tetracycline and ampicillin. The emergence of *V. cholerae* resistant to multiple antibiotics, including tetracycline, has become a major problem in many regions (KHAN *et al.*, 1988). The identification of clinically efficacious alternative antibiotics is therefore necessary for use in children with cholera. Although *V. cholerae* is sensitive to ampicillin *in vitro*, ampicillin has not been subjected to clinical trial. Tetracycline, sulphamethoxazole/trimethoprim and erythromycin are recommended by the World Health Organization for treatment of cholera in children. WALLACE *et al.* (1968) reported equal clinical efficacy between erythromycin and sulphamethoxazole/trimethoprim in the treatment of cholera. Children with cholera and other diarrhoeal diseases often also have respiratory tract infections, so a single effective antibiotic would be desirable (RAHMAN *et al.*, 1990). We conducted a clinical trial to determine the comparative efficacy of ampicillin, tetracycline and erythromycin.

Materials and Methods

Children of either sex aged 1–5 years, who attended the International Centre for Diarrhoeal Disease Research, Bangladesh hospital in Dhaka, Bangladesh with a history of watery diarrhoea of <48 h duration, signs of some or severe dehydration, who had not received any antimicrobial agent, and in whom dark-field microscopical examination of stool revealed *V. cholerae* and the stool output was at least 4 mL/kg/h during the 6 h initial rehydration phase, were enrolled in the study. Informed written consent was obtained from parents. Children with systemic illness or who were malnourished (weight-for-height ratio <80% of the National Center for Health Statistics median value) were excluded. A medical history was obtained and a detailed physical examination, including vital signs and assessment of dehydration, was performed. The children were rehydrated within 4 h using the 'Dhaka' solution (sodium 133 mmol/L, potassium 13 mmol/L, chloride 98 mmol/L and bicarbonate 48 mmol/L) and their hydration status was maintained using a rice-based oral rehydration solution. Urine was separated from stool using paediatric urine collectors and stool and urine output were recorded every 8 h during the 96 h study period. Stool culture for isolation of *V. cholerae* was done and the antimicrobial susceptibility was determined by the disk diffusion (Kirby–Bauer) method upon enrolment (zero hour) and after 24 h and 48 h. Body weight was determined on admission after complete rehydration, upon enrolment in the study, and daily thereafter. Stool output, urine output, the volume of vomitus, and the intake of intravenous and oral rehydration fluids were recorded every 8 h during the observation period. Cereal plus milk and rice curry were given to provide an average of 100 kcal/kg/d. After the initial 6 h observation/rehydration phase, children were given erythromycin 50 mg/kg/d, or tetracycline 25 mg/kg/d, or ampicillin 50 mg/kg/d, or placebo every 6 h for 3 d. (The placebo group was formed with the consent of the parents after explanation of the hospital routine of 'round-the-clock' management of dehydration with oral and intravenous fluids under the supervision of health workers, nurses, physicians and the investigators.) Stool characteristics were determined by direct examination and recorded every 8 h. Recovery was defined as the first occurrence of a soft formed stool which was subsequently maintained for at least 48 h.

Results

In total, 184 children were recruited to the study. The admission characteristics of the children in each group, and their mean stool output during the initial observation and rehydration phase, were similar (Table 1). All *V. cholerae* isolates were serotypes Ogawa or Inaba of the El Tor biotype; 99% were sensitive to ampicillin,

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Table 1. Admission characteristics of children with *Vibrio cholerae* infection

Characteristics	Treatment[a]			
	Placebo	Erythromycin	Ampicillin	Tetracycline
No. in group	48	46	47	43
Age (months)	43·5±12·2	43·6±10·6	35·8±13·3	38·3±3·9
Height (cm)	88·4±2·0	90·5±1·3	86·1±1·2	86·9±1·2
Weight (kg)	10·1±0·4	10·4±0·3	9·6±0·3	9·7±0·2
Weight/height[b]	82·8±1·0	84·0±0·9	83·6±0·9	84·7±0·9
Stool weight (g/6 h)	743±347	795±421	634±315	739±405
No. dehydrated				
Moderately	9(19%)	8(17%)	13(28%)	14(33%)
Severely	39(81%)	38(82%)	34(72%)	29(67%)

[a]Values are means±SD except for no. dehydrated. None of the differences between treatments was significant.
[b]Percentage of National Center for Health Statistics median value.

Table 2. Fluid intake and output of children with *Vibrio cholerae* infection

	Treatment[a]			
	Placebo	Erythromycin	Ampicillin	Tetracycline
No. in group	48	46	47	43
Fluid intake (i.v.) (mL)	2722±460	1551±330	1193±237	670±113
Oral rehydration solution (mL)	3918±229	3186±190	3122±180	3035±208
Urine output (mL)	2439±291	2412±274	1818±143	2286±247
Stool volume (mL)	6034±481	3664±481	3467±305	3335±553

[a]Values are means±SEM from 0 to 96 h; placebo group values differed significantly from those in all other treatment groups ($P<0·0001$).

Table 3. Numbers of children from which *Vibrio cholerae* could be isolated

Treatment group	At start of therapy	After antibiotic therapy for 24 h	48 h
Placebo	48	44	42
Erythromycin	46	15	7
Ampicillin	47	33	31
Tetracycline	43	9	4

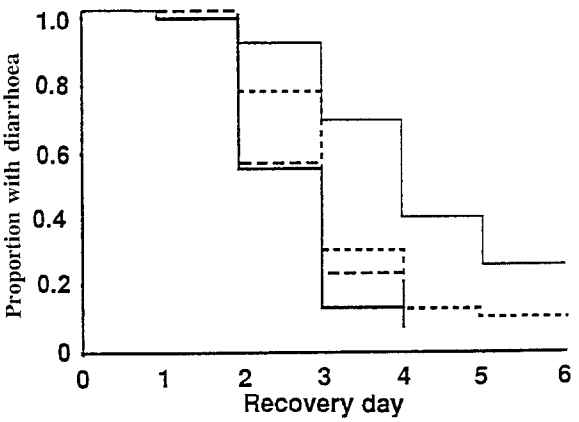

Figure. Duration of diarrhoea in patients infected with *Vibrio cholerae* and treated with ampicillin (dotted line), erythromycin (dashed line), tetracycline (heavy continuous line) or placebo (light continuous line).

98% were sensitive to erythromycin, 76% were sensitive to tetracycline, 20% were sensitive to furazolidone, and 5% were sensitive to sulphamethoxazole.

The need for intravenous and additional oral rehydration fluids was significantly greater among children who received placebo and there was no significant difference between children who received the different antibiotics (Table 2). Erythromycin and tetracycline were more efficient in reducing the number of children excreting *V. cholerae* in stool than ampicillin and placebo (Table 3). Children in the placebo group continued to have high purging rates even after 6 d. After the first 24 h of treatment, stool volume was significantly reduced in the treatment groups compared with those receiving placebo, and that in the tetracycline group was significantly less than in children receiving ampicillin or erythromycin ($P<0·001$). The mean length of time to clinical recovery was 66% greater in the placebo group than in those receiving tetracycline ($P<0·001$); there was no significant difference between the ampicillin and erythromycin groups ($P>0·05$) (Figure). The clinical recovery rate by 96 h was 75% in the placebo group, 91·3% in the ampicillin group, 95·7% in the erythromycin group, and 100% in the tetracycline group ($P<0·001$ compared with the placebo group).

Discussion

Correction of fluid and electrolyte deficits, and maintenance of hydration using appropriate intravenous and/or oral rehydration fluid, remain the corner-stone in the management of cholera irrespective of age (HOLMGREN, 1981). Appropriate antibiotics reduce the volume of watery stools, duration of diarrhoea, and duration of excretion of *V. cholerae* (see WALLACE *et al.*, 1968). In controlled clinical trials in adults tetracycline, chloramphenicol, erythromycin, sulphamethoxazole/trimethoprim and furazolidone have all been found to reduce the volume and duration of diarrhoea. Although *V. cholerae* were sensitive to tetracycline in previous decades (GREENOUGH *et al.*, 1964), tetracycline resistance has been increasingly identified from several countries (MAHLU *et al.*, 1979). In less than one year (September 1991–June 1992), the proportion of *V. cholerae* strains resistant to tetracycline increased from 2% to 90% in Bangladesh (KHAN *et al.*, 1995). The present study demonstrated that, compared to placebo, children treated with tetracycline, ampicillin or erythromycin had a significantly lower mean total stool output. The mean time to recovery from diarrhoea was nearly double in children in the placebo group compared to treated children. The requirement for intravenous and oral rehydration fluids was significantly less in children who received ampicillin, erythromycin, and tetracycline compared to those who received placebo. The World Health Organization recommends erythromycin for the

treatment of cholera caused by tetracycline-resistant strains of *V. cholerae*. Our results showed that the efficacy of ampicillin was comparable to that of erythromycin, and it should be considered as a potential alternative treatment for cholera in children. Although tetracycline is safe in children older than 8 years, and for short term therapy (3 d or fewer) of younger children, there is general reluctance to use it in young children. Erythromycin is effective and safe for use in children with cholera, but it is usually more expensive than tetracycline and ampicillin. In Bangladesh the cost of a 3 d course of ampicillin is about one-third of the cost of 3 d of erythromycin treatment. *Haemophilus influenzae* is an important cause of respiratory tract infection among children <5 years old, and ampicillin is an effective treatment for *H. influenzae* infections, which are generally resistant to tetracycline. Thus it would be advantageous to treat children with cholera and concomitant respiratory tract infection with a single agent. A significantly greater proportion of children in the ampicillin group continued to excrete *V. cholerae* in stool beyond 48 h of treatment, despite clinical improvement. In developing countries where cholera is endemic, shortening the duration of illness and reducing disease severity, with a consequently reduced requirement for rehydration fluids, are the major objectives of antimicrobial therapy. Shortening the duration of excretion of *V. cholerae* as a means of reducing transmission is generally not a major objective due to the heavily contaminated environment. Based on the results of this study, we conclude that ampicillin is effective in the management of childhood cholera, and may be a cost-effective therapy for cholera in children, particularly where tetracycline-resistant *V. cholerae* is common; it might be particularly suitable for treatment of children with cholera who have a respiratory tract infection for which an antibiotic is indicated.

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References

Greenough, W. B., III, Rosenberg, I. S., Gordon, R. S. & Davis, B. I. (1964). Tetracycline in the treatment of cholera. *Lancet*, **i**, 335–357.

Holmgren, J. (1981). Actions of cholera toxin and the prevention and treatment of cholera. *Nature*, **292**, 413–417.

Khan, M. U., Eeckels, R., Alam, A. N. & Rahman, N. (1988). Cholera, rotavirus and ETEC diarrhoea: some clinico-epidemiological features. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **82**, 485–488.

Khan, W. A., Begum, M., Salam, M. A., Bardhan, P. K., Islam, M. R. & Mahalanabis, D. (1995). Comparative trial of five antimicrobial compounds in the treatment of cholera in adults. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **89**, 103–106.

Mahlu, M. S., Mmari, P. W. & Ijumba, J. (1979). Rapid emergence of El Tor *Vibrio cholerae* resistant to antimicrobial agents during first six months of fourth cholera epidemic in Tanzania. *Lancet*, **i**, 345–347.

Rahman, M., Huq, F., Sack, D. A., Butler, T., Azad, A. K., Alam, A., Nahar, N. & Islam, M. (1990). Acute lower respiratory tract infection in hospitalized patients with diarrhoea in Dhaka, Bangladesh. *Reviews of Infectious Disease*, **12**, supplement 8, 899–906.

Wallace, C. K., Anderson, P. N., Brown, T. C., Khanna, S. R., Lewis, G. W., Pierce, N. F., Sanyal, S. N., Segne, C. V. & Waldman, R. H. (1968). Optimal antibiotic therapy in cholera. *Bulletin of the World Health Organization*, **39**, 239–245.

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