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# Antibiotic Therapy of Cholera in Children*

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*In a controlled trial of the effects of oral antibiotics in treating cholera in children in Dacca, East Pakistan, tetracycline was the most effective of 4 antibiotics tested in reducing stool volume, intravenous fluid requirement, and the duration of diarrhoea and positive stool culture. Increasing the duration of tetracycline therapy from 2 to 4 days, or increasing the total dose administered, resulted in shorter duration of positive culture, but did not affect stool volume or duration of diarrhoea. Only 1 % of the children receiving tetracycline had diarrhoea for more than 4 days. Tetracycline was significantly more effective than intravenous fluid therapy alone, regardless of severity of disease.*

*Chloramphenicol, while also effective, was inferior to tetracycline. Streptomycin and paromomycin exerted little or no effect on the course of illness or duration of positive culture. Therapeutic failures with these drugs were not due to the development of bacterial resistance.*

*From these findings, tetracycline appears to be the drug of choice against* Vibrio cholerae *infection in children. Oral therapy for 48 hours is effective clinically, but is associated with 20 % bacteriological relapses when the drug is discontinued; it is not known whether extending the therapy for a week or more would eliminate such relapses.*

In recent years several groups have conducted clinical trials of antibiotic therapy in adult patients with cholera (Greenough et al., 1964; Carpenter et al., 1966; Uylangco et al., 1965, 1966; Kobari, 1965; Lindenbaum et al., 1967). Children have not been included in these studies, however, and it is not known whether results obtained in adults apply to children as well. It has recently been shown, however, that childhood cholera is in most respects clinically similar to that seen in adults (Lindenbaum et al., 1966). We present here the results obtained in a series of 243 consecutively admitted children with documented *Vibrio cholerae* infection, in whom the oral administration of single antibiotics (tetracycline, chloramphenicol, streptomycin, or paromomycin) in addition to intravenous fluid replacement was compared with treatment with intravenous fluids only.

## METHODS AND MATERIALS

The patients included in the present report were all individuals weighing less than 15 kg who were admitted to the wards of the Pakistan–SEATO Cholera Research Laboratory with diarrhoeal disease associated with stool cultures positive for *V. cholerae* during the epidemic periods in Dacca of 1964-65 and 1965-66. The results obtained in patients weighing 15 kg or more have been described in an earlier report (Lindenbaum et al., 1967). The design of the present study, the bacteriological methods, the fluid replacement therapy utilized, the allocation of patients to study groups according to day of the week admitted (including one day of the week for control patients who received intravenous fluids only), and the criteria of therapeutic response were identical to those described in detail in the preceding report.

Five of the 243 patients were excluded from the analysis (2 were unable to take oral medications owing to persistent coma; 1 received multiple antibiotics; and 2 received incorrect doses owing to error). There were 2 deaths in the series of 243 consecutive patients. They occurred 2 and 15 hours

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after admission, respectively, in the 2 patients omitted from the final analysis owing to coma. Neither patient had received antibiotic therapy.

Seven patients in the series admitted with a history of diarrhoea had no further purging after admission. Since all but one of these patients were clinically dehydrated on admission and had elevated total plasma proteins, and since our intention was to evaluate antibiotic therapy in patients with cholera of varying severity, they have been included in the tabulated results.

Weight percentile tables were calculated on the basis of the weights of 5194 East Pakistani children 10 years of age or younger obtained by the Nutrition Survey of the Government of Pakistan (data kindly supplied by Dr M. L. Reiner). Patients were assigned to percentile groups based on stated age and weight at discharge from hospital (rather than weight on admission, when varying degrees of dehydration were present). In view of the short duration of hospitalization and the similar degree of weight gain between admission and discharge noted in all percentile groups, weight at discharge appeared to be a reliable reflection of weight prior to onset of illness.

The age of the patients ranged from 6 weeks to 10 years, with a mean of 4.0 years. In varying dosage schedules (see Tables 2 and 5 below), the patients were treated with tetracycline, chloramphenicol, streptomycin, paromomycin, or no antibiotic.

### COMPARABILITY OF TREATMENT GROUPS

The various treatment groups were similar to each other and to the untreated controls (Table 1) in mean age, body-weight, duration of symptoms prior to admission, and degree of dehydration (reflected both in plasma protein elevation and the presence or absence of peripheral pulses). There were a few significant differences (the term " significant " will be used to refer to differences in which $P < 0.05$ or less unless otherwise specified). The tetracycline and control groups consisted mainly of male patients, while females predominated in

TABLE 1
COMPARISON OF TREATMENT GROUPS [a]

| | No antibiotic | Tetracycline | Chloramphenicol | Streptomycin | Paromomycin |
|---|---|---|---|---|---|
| Number of cases | 50 | 103 | 47 | 23 | 15 |
| Duration of symptoms before admission (hours) | 20.1 (2-128) | 21.1 (3-192) | 14.3 (2-63) | 11.2 (3-37) | 21.9 (3-120) |
| Age (years) | 3.9 (7/12-8) | 4.0 (2/12-10) | 4.0 (1-8) | 3.9 (1-8) | 4.3 (2-8) |
| Body-weight at discharge (kg) | 11.1 (6.5-17.2) | 11.4 (5.1-16.7) | 11.8 (6.0-16.1) | 12.0 (6.4-17.6) | 10.9 (7.5-15.4) |
| Number in 10th weight percentile or lower | 15(30%) | 28(27%) | 8(17%) | 1(4%) | 5(33%) |
| Male : female ratio | 1.8 : 1 | 1.5 : 1 | 1 : 1.8 | 1 : 1.3 | 1 : 1.2 |
| Number pulseless | 20(40%) | 51(50%) | 21(45%) | 9(39%) | 5(33%) |
| Plasma protein (g 100 ml) | | | | | |
| On admission | 9.3 (6.6-12.4) | 9.5 (5.7-13.8) | 9.8 (7.6-12.2) | 9.5 (7.2-12.4) | 9.4 (7.7-12.2) |
| At convalescence | 7.1 (5.6-9.0) | 7.2 (5.4-8.8) | 7.2 (6.0-8.4) | 7.5 (6.7-8.7) | 7.2 (6.2-8.4) |
| Difference between admission and convalescence values | 2.2 | 2.3 | 2.6 | 2.0 | 2.2 |

[a] Mean values are shown, with the range in parentheses (except for the number pulseless).

the group receiving chloramphenicol. The possible effects of the sex of the patient on the clinical course of cholera will be discussed below. The mean duration of symptoms prior to admission was significantly shorter in the streptomycin group than in the control and tetracycline groups, but the degree of dehydration on admission was similar in all three groups. The patients receiving chloramphenicol were slightly more dehydrated on the average than the other groups, but not significantly so. There were fewer patients markedly under weight in the groups receiving chloramphenicol and (especially) streptomycin. The possible effects of nutritional status on response to therapy will be discussed below.

## RESULTS

*Comparison of antibiotic and control groups* (Table 2 and the figure)

*Paromomycin.* There were no significant differences between the paromomycin and control groups in duration of diarrhoea, percentage of therapeutic failures, total stool volume, total intravenous fluids administered, duration of positive culture, or frequency of bacteriological relapse.

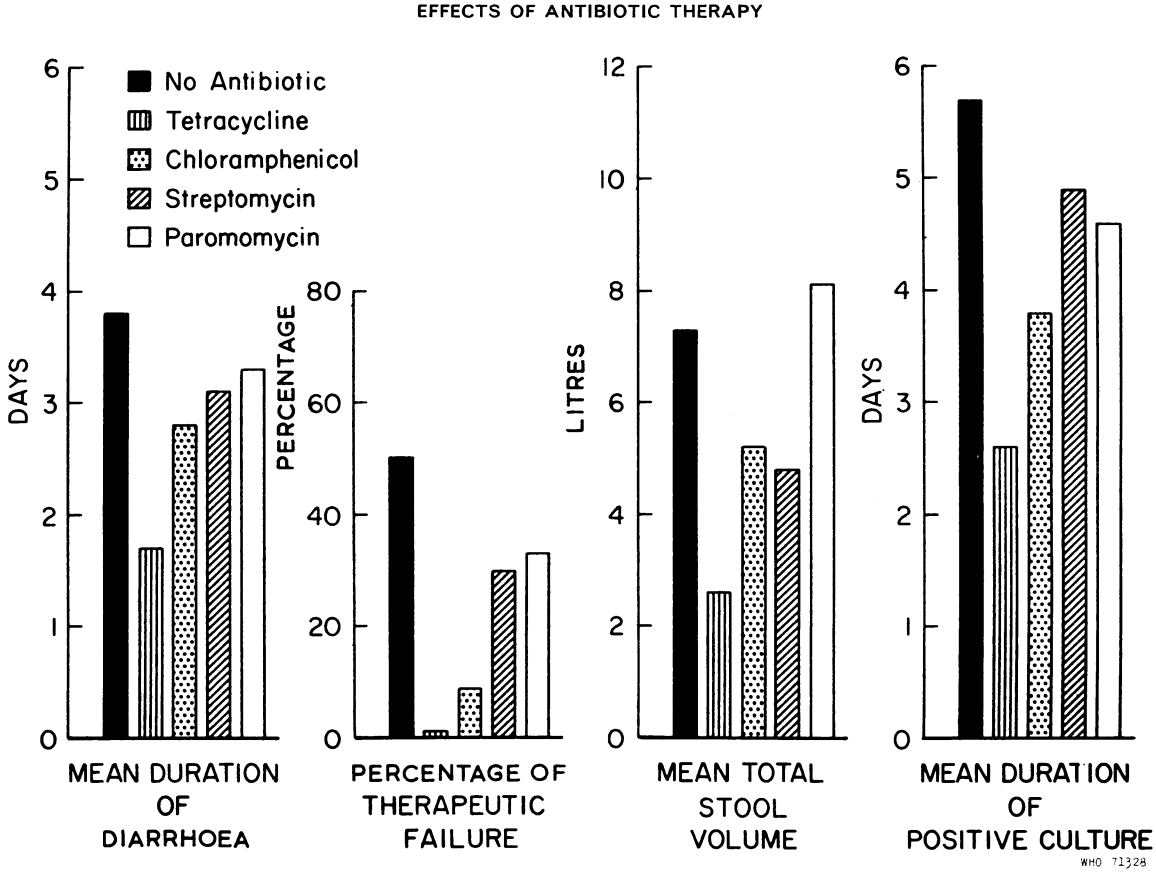
*Streptomycin.* A slight therapeutic effect was seen in streptomycin-treated children compared with those who received no antibiotics, but there were no significant differences in duration of diarrhoea, percentage of therapeutic failure, total intravenous fluids given, or duration of positive culture (Table 2). There was a trend towards lower total stool volume in the streptomycin group, but it did not achieve significance ($0.10>P>0.05$). Bacteriological relapse, however, was significantly more common than in patients receiving no antibiotic.

*Chloramphenicol.* Children receiving chloramphenicol differed significantly from the controls in duration of diarrhoea ($P<0.005$), percentage of therapeutic failure ($P<0.005$), and duration of positive culture ($P<0.001$). There was a trend

TABLE 2
EFFECTS OF ANTIBIOTIC THERAPY

| | No antibiotic | Tetracycline [a] | Chloramphenicol [a] | Streptomycin [a] | Paromomycin [a] |
|---|---|---|---|---|---|
| Number of cases | 50 | 103 | 47 | 23 | 15 |
| Duration of diarrhoea | | | | | |
| Mean days | 3.8 | 1.7 | 2.8 | 3.1 | 3.3 |
| Mean 8-h periods (Range of 8-h periods) | 11.3 (0-18) | 5.0 (0-13 | 8.4 (2-23) | 9.4 (2-23) | 10.0 (0-23) |
| Diarrhoea ≥ 4 days | 25(50%) | 1(1%) | 9(19%) | 7(30%) | 5(33%) |
| Clinical relapses | 1 | 0 | 1 | 2 | 1 |
| Total stool volume (l) | | | | | |
| Mean (Range) | 7.3 (0-33.1) | 2.6 (0-14.1) | 5.2 (0.5-22.7) | 4.8 (0.5-17.8) | 8.1 (0-24.7) |
| Total intravenous fluids (l) | | | | | |
| Mean (Range) | 7.9 (0-33.8) | 3.8 (0-14.3) | 5.9 (0-29.9) | 6.6 (1.8-18.9) | 9.4 (0-29.0) |
| Days of positive culture | | | | | |
| Mean (Range) | 5.7 (2-13) | 2.6 (1-14) | 3.8 (1-9) | 4.9 (1-8) | 4.6 (1-9) |
| Bacteriological relapses | 8(16%) | 19(18%) | 11(26%) | 10(44%) | 5(33%) |

[a] Dosage schedules:
Tetracycline: see Table 3.
Chloramphenicol: 125 mg or 250 mg or 500 mg 6-hourly for 48 hours or 72 hours.
Streptomycin: 500 mg 6-hourly for 48 hours or 72 hours.
Paramomycin: 125 mg 6-hourly for 48 hours or 72 hours; or 250 mg 6-hourly for 72 hours.




towards lower stool volumes ($0.10>P>0.05$), but no significant differences from the controls in parenteral fluids given, or frequency of bacteriological relapse.

*Tetracycline.* There were highly significant differences between the tetracycline and control groups in duration of diarrhoea, percentage of therapeutic failure, total stool volume, intravenous fluids administered, and duration of positive culture ($P<0.001$ in each instance). Tetracycline-treated children did not differ from the controls in the frequency of bacteriological relapse.

*Comparison of one antibiotic with the others*

*Paromomycin.* There were no significant differences between the paromomycin and streptomycin groups in duration of purging, percentage of therapeutic failure, fluids administered, total stool volume, or duration of positive culture. The children receiving paromomycin did not differ significantly from those receiving chloramphenicol in any of the criteria of therapeutic response. On the other hand, tetracycline was significantly more effective than paromomycin in reducing duration of diarrhoea ($P<0.01$), percentage of therapeutic failure ($P<0.0005$), total stool volume ($P<0.005$), fluids administered ($P>0.02$), and duration of positive culture ($P>0.01$). The paromomycin group did not differ from any of the other three antibiotic-treated groups in frequency of bacteriological relapse.

*Streptomycin.* There were no significant differences between the streptomycin and chloramphenicol groups in any of the criteria of therapeutic response. On the other hand, tetracycline was significantly more effective than streptomycin in reducing duration of diarrhoea ($P<0.005$), percentage of therapeutic failure ($P<0.0005$), total stool volume ($P<0.025$), fluids administered ($P<0.005$), duration

of positive culture ($P<0.001$), and frequency of bacteriological relapse ($P<0.025$).

*Tetracycline as against chloramphenicol.* Tetracycline was significantly more effective than chloramphenicol in reducing duration of diarrhoea ($P<0.001$), percentage of therapeutic failure ($P<0.0005$), total stool volume ($P<0.005$), intravenous fluid requirement ($P<0.02$) and duration of positive culture ($P<0.01$). The two antibiotic groups did not differ significantly in frequency of bacteriological relapse.

Rare clinical relapses occurred in all the treatment groups except those receiving tetracycline (Table 2).

In summary, when compared with the controls, a statistically significant therapeutic effect was obtained with tetracycline and chloramphenicol, but not with streptomycin or paromomycin. Tetracycline was significantly more effective than any of the other antibiotics, including chloramphenicol.

*Comparison of various tetracycline dosage schedules* (Table 3)

The effect on therapeutic response of varying the total amount of tetracycline administered or the duration of therapy is shown in Table 3. The various subgroups were similar in age, severity of dehydration, and sex predominance, except for the slightly greater initial dehydration (which was not statistically significant) in the patients receiving 125 mg 6-hourly for 72 hours (group A, Table 3), and the greater number of male patients in the small group of 10 patients (group D) receiving 125 mg 6-hourly for 96 hours. There were no significant differences between the four treatment subgroups in duration of diarrhoea or stool volume.

The duration of positive culture, however, appeared to be affected by both the total dose and the duration of antibiotic therapy. Thus, the patients given a total of 3 g of tetracycline over 72 hours (group B) had a significantly shorter mean duration of positive culture than those (group A) given half that dose over the same period (1.8 days as against 3.1 days; $P<0.01$). In addition, the patients given a total of 2 g of tetracycline over 96 hours (group D) had a shorter mean duration of positive culture than those given 2 g over 48 hours (group C); the difference was close to statistical significance (1.7 days as against 2.7 days; $t=1.990$; $0.10>P>0.05$). When

TABLE 3. COMPARISON OF VARIOUS TETRACYCLINE DOSAGE SCHEDULES

| | Regimen A: 125 mg 6-hourly for 72 hours | Regimen B: 250 mg 6-hourly for 72 hours | Regimen C: 250 mg 6-hourly for 48 hours | Regimen D: 125 mg 6-hourly for 96 hours | No tetracycline |
|---|---|---|---|---|---|
| Number of patients | 39 | 19 | 35 | 10 | 50 |
| Total dose (g) | 1.5 | 3 | 2 | 2 | 0 |
| Average daily dose given (mg/kg) | 43 | 96 | 89 | 40 | 0 |
| Mean age (years) | 4.1 | 3.6 | 4.3 | 3.9 | 3.9 |
| Mean admission plasma protein (g/100 ml) | 9.8 | 9.3 | 9.3 | 9.3 | 9.3 |
| Male: female ratio | 1.3 : 1 | 1.4 : 1 | 1.3 : 1 | 4 : 1 | 1.8 : 1 |
| Mean duration of diarrhoea (days) | 1.7 | 1.9 | 1.6 | 1.4 | 3.8 |
| Mean total stool volume (l) | 2.6 | 2.9 | 2.4 | 2.3 | 7.3 |
| Mean days of positive culture | 3.1 | 1.8 | 2.7 | 1.7 | 5.7 |
| Bacteriological relapses | 9 (23.1%) | 2 (10.5%) | 7 (20%) | 1 (10%) | 8 (16.0%) |

group D was compared with group A, stool culture was positive for a significantly shorter period in the former group, which received a greater total dose *as well as* therapy of longer duration (1.7 days as against 3.1 days; $P<0.005$).

Bacteriological relapse was also more common in patients receiving the smallest total dose (group A) and in those treated for 48 hours only (group C) than in the other groups (B and D), but the differences were not statistically significant. The difference in duration of positive culture between groups A and B was not merely due to the greater frequency of relapse in the former group; when relapsing cases are omitted from the totals the mean duration of positive culture for group A was 2.1 days, and for group B, 1.4 days. The difference in duration of positive culture between groups C and D, however, appeared to be attributable to the greater frequency of relapse in group C (with relapsing patients omitted, the duration of positive culture was similar: group C, 1.8 days; group D, 1.6 days).

Each of the tetracycline subgroups, however, regardless of dosage or duration of therapy, differed significantly from those receiving no antibiotic in duration of diarrhoea, total stool volume, and duration of positive culture (Table 3).

### *Effect of various factors on the clinical course of treated and untreated patients*

*Severity of dehydration.* In untreated patients, there was a significant positive correlation between severity of dehydration on admission to hospital (as indicated by the total plasma protein concentration) and duration of diarrhoea after admission ($r=0.318$; $P<0.05$). The correlation was also evident in patients treated with cloramphenicol ($r=0.302$; $P<0.05$), streptomycin ($r=0.515$; $P<0.02$), and paromomycin ($r=0.451$; $0.20>P>0.10$), but was less striking in those receiving the most effective antibiotic, tetracycline ($r=0.107$; $P>0.25$).

An unexpected finding was the complete lack of correlation between admission plasma protein level and duration of positive culture in both control patients ($r=0.041$; $P>0.7$) and antibiotic-treated patients (for tetracycline, $r=0.054$; $P>0.6$; for chloramphenicol, $r=0.086$; $P>0.5$). These findings contrasted with those in adults, reported earlier (Lindenbaum et al., 1967), where there was a strong correlation between duration of positive culture and admission plasma protein in untreated controls ($r=0.346$; $P<0.001$).

*Age.* In the relatively narrow age-range represented in the present study (6 weeks to 10 years), there was no correlation apparent between age and duration of diarrhoea in controls ($r=-0.026$; $P>0.6$) or antibiotic-treated patients (for tetracycline, $r=-0.076$; $P>0.4$; for cloramphenicol, $r=0.109$; $P>0.4$). Similarly, no correlation was apparent between age and duration of positive culture.

*Sex.* The sex of the patient did not appear significantly to affect the course of the untreated disease or the response to antibiotics. There were no significant differences between males and females in degree of dehydration on admission or duration of purging and positive culture within any of the treatment groups (Table 4). The duration of both diarrhoea and positive culture was significantly shorter in both males and females receiving tetracycline than in children of the same sex in the control group ($P<0.001$ in each instance). Tetracycline was significantly more effective than chloramphenicol in reducing the duration of purging in both sexes.

*Duration of symptoms before admission.* There was a trend towards an inverse correlation between duration of symptoms before admission and duration of diarrhoea or positive culture in the control patients and those receiving the less effective antibiotics (paromomycin, streptomycin, and chloramphenicol). These inverse correlations did not reach statistical significance except in 2 instances (in the chloramphenicol group, correlating duration of symptoms and duration of diarrhoea, $r=-0.369$; $P<0.02$; in the control patients, correlating duration of symptoms and duration of positive culture, $r=-0.404$; $P<0.005$). In the tetracycline-treated children, however, no relationship was apparent between duration of symptoms prior to admission and the subsequent course of the disease in hospital ($r=0.029$; $P>0.7$ for duration of diarrhoea; $r=0.039$; $P\simeq 0.7$ for duration of positive culture). These findings were similar to those in adults during the same epidemic periods (Lindenbaum et al., 1967). As in adults, there was a tendency for patients admitted with shorter duration of symptoms to be more severely dehydrated. The significance of these findings has been discussed in a previous paper (Lindenbaum et al., 1967).

*Weight percentile.* In order to determine whether nutritional status might affect the course of antibiotic-treated or untreated cholera, patients in the

TABLE 4
EFFECT OF SEX ON THE COURSE OF TREATED AND UNTREATED CHOLERA

| Treatment group | Number of patients | Mean admission plasma protein (g/100 ml) | Duration of diarrhoea (days) | Duration of positive culture (days) |
|---|---|---|---|---|
| Controls | | | | |
| Male | 32 | 9.2 | 3.8 | 5.8 |
| Female | 18 | 9.4 | 3.7 | 5.5 |
| Tetracycline | | | | |
| Male | 61 | 9.4 | 1.7 | 2.7 |
| Female | 42 | 9.6 | 1.7 | 2.4 |
| Chloramphenicol | | | | |
| Male | 17 | 10.2 | 2.6 | 3.5 |
| Female | 30 | 9.6 | 2.9 | 4.0 |
| Streptomycin | | | | |
| Male | 10 | 9.7 | 2.7 | 4.6 |
| Female | 13 | 9.4 | 3.4 | 5.2 |
| Paromomycin | | | | |
| Male | 7 | 9.0 | 2.8 | 4.7 |
| Female | 8 | 9.8 | 3.8 | 4.5 |

first or highest weight quartile (greater than 75th percentile) and the fourth or lowest quartile (25th percentile and lower) were compared. On admission, as judged by plasma protein levels, the patients in the highest quartile in the control, tetracycline, and chloramphenicol groups were, on the average, more dehydrated than those in the lowest quartile (Table 5). The greater degree of initial dehydration would have been expected to result in longer duration of purging in the better-nourished, first-quartile patients. Instead, however, purging lasted longer in poorly-nourished, fourth-quartile patients (Table 5). The differences in mean duration of diarrhoea were statistically significant in the antibiotic-treated children (tetracycline group, $P<0.001$; chloramphenicol group, $P<0.05$). It will be noted that diarrhoea lasted longer in the lowest-quartile patients receiving tetracycline despite the greater dose of antibiotic received.

The differences in the duration of positive culture between patients in the two quartiles in the various groups were not significant. Also, bacteriological relapse was as likely to occur in a well nourished as in a poorly nourished patient.

*Therapy of mild cholera*

In order to determine whether antibiotic therapy was of benefit in patients who were not severely ill with cholera on admission, the patients were divided into 4 groups, based on increasing degrees of dehydration on admission as reflected in the total plasma protein concentrations (Table 6). The differences in mean duration of diarrhoea and positive culture between the control and tetracycline-treated patients were significant in all groups, regardless of the severity of dehydration. The differences in duration of purging and positive culture were particularly striking in the group with minimal dehydration (plasma protein 8.0 g/100 ml or less; $P<0.001$ for both diarrhoea and positive culture). Untreated children with mild cholera, therefore, may have prolonged diarrhoea, and tetracycline is useful in shortening the duration of illness and of vibrio excretion.

TABLE 5
EFFECT OF NUTRITIONAL STATUS ON THE COURSE OF CHOLERA

| | Number of patients | Mean plasma protein (g/100 ml) | | | Mean dose of antibiotic (g/kg) | | Mean duration of diarrhoea [a] (days) | Mean duration of positive culture (days) |
|---|---|---|---|---|---|---|---|---|
| | | On admission | At convalescence | Difference between admission and convalescence values | Daily | Total | | |
| Controls | | | | | | | | |
| First quartile | 7 | 10.3 | 7.2 | 3.1 | — | — | 3.6 | 5.4 |
| Fourth quartile | 24 | 8.8 | 7.1 | 1.7 | — | — | 4.0 | 6.0 |
| Tetracycline | | | | | | | | |
| First quartile | 16 | 9.7 | 6.9 | 2.8 | 59 | 139 | 1.1* | 2.3 |
| Fourth quartile | 46 | 9.5 | 7.3 | 2.2 | 73 | 181 | 1.9* | 3.0 |
| Chloramphenicol | | | | | | | | |
| First quartile | 5 | 10.8 | 7.2 | 3.6 | 107 | 228 | 1.8** | 4.2 |
| Fourth quartile | 17 | 9.5 | 7.1 | 2.4 | 78 | 207 | 3.0** | 3.1 |

[a] Pairs of mean values marked * and ** differ significantly from each other.

## DISCUSSION

These findings indicate that oral tetracycline was as effective in the therapy of cholera in children as it had previously been shown to be in adults (Greenough et al., 1964; Carpenter et al., 1966; Lindenbaum et al., 1967). In most respects the results obtained in the present study were similar to those of simultaneously conducted antibiotic trials in adults in East Pakistan (Lindenbaum et al., 1967). As in adults, streptomycin was not as effective as tetracycline in shortening the duration of the disease, and patients who received paromomycin did little better than controls treated with intravenous fluids only. The relative ineffectiveness of chloramphenicol in children, however, constituted a major discrepancy. In adults, chloramphenicol appeared to be as effective, or nearly as effective, as tetracycline (Lindenbaum et al., 1967). In the present pediatric study, tetracycline was clearly superior (Table 2).

TABLE 6
SEVERITY OF DEHYDRATION ON ADMISSION AND THE SUBSEQUENT COURSE OF CHOLERA

| | Admission plasma protein (g/100 ml) | | | |
|---|---|---|---|---|
| | <8.0 | 8.1-9.0 | 9.1-10.0 | ≥10.1 |
| Mean duration of diarrhoea (days) [a] | | | | |
| Control | 3.5 (11) | 3.2 (11) | 3.5 (11) | 4.3 (14) |
| Tetracycline | 1.6 (18) | 1.7 (28) | 1.3 (21) | 1.9 (31) |
| Mean duration of positive culture (days) [a] | | | | |
| Control | 6.3 (11) | 4.7 (11) | 5.4 (11) | 6.3 (14) |
| Tetracycline | 2.3 (18) | 2.4 (28) | 2.6 (21) | 2.8 (31) |

[a] Numbers in parentheses indicate number of patients in each group.

The reason for the failure to achieve as good results with chloramphenicol in children is not certain. Vibrios cultured early and late in the course of the disease from patients in whom the antibiotic was ineffective were not resistant to chloramphenicol *in vitro* (Lindenbaum et al., 1967). The dosage of the antibiotic appears to have been adequate (in the 9 children who had diarrhoea for 4 days or more on this drug, the mean daily dose was 86.3 mg/kg). It may be important, however, that chloramphenicol was administered to children in the form of the *palmitate* syrup, while adults received capsules containing unbound chloramphenicol. Chloramphenicol palmitate is itself inert; hydrolysis by intestinal enzymes to the free form of the antibiotic is necessary for an antibacterial effect (Barber & Garrod, 1963). It is possible that hydrolysis of the palmitate was incomplete in our patients, owing either to rapid transit or to poor solubility of the lipid in the voluminous watery intestinal fluid of the cholera patient.

In the light of our current knowledge, therefore, tetracycline would appear to be the antibiotic of choice for the treatment of children with cholera. The ideal dosage and duration of therapy remain to be established, however. In the present series, there were no clinical relapses in the 103 children treated with tetracycline for 2–4 days, and there were no significant differences in duration of diarrhoea or total stool volume between the 4 dosage regimens employed (Table 3). Increasing the dose or lengthening the duration of therapy appeared to shorten the duration of positive culture. It is not known whether extending the period of therapy to a week or more would eliminate bacteriological relapses. Such prolonged therapy, while possibly ideal from a public health point of view, may be impracticable in a massive outbreak of epidemic cholera under field conditions where supplies may be short. In this situation, a regimen which is clinically effective in markedly reducing the duration of diarrhoea (such as regimen A, Table 3, i.e., 125 mg 6-hourly for 3 days) will prove useful. Future studies may indicate whether other antibiotics active against vibrios, such as erythromycin or the nitrofurantoins, will provide an acceptable therapeutic alternative to tetracycline. Sulfaguanidine has been shown to be of no value in cholera in children or adults.[1]

Clinicians have long held that recovery from cholera in a malnourished individual is less likely to occur than in a well-nourished one, though the observation has lacked objective documentation (Pollitzer, 1959). In other infectious diseases, including tuberculosis, whooping-cough, measles, herpes simplex, schistosomiasis, and acute nonspecific diarrhoeal illnesses, it has also been observed, again without convincing statistical proof, that the natural course of the illness or the response to therapy is adversely affected in the presence of malnutrition (WHO Expert Committee on Nutrition and Infection, 1965). In the present study we have shown that children affected with cholera in the fourth weight quartile had more prolonged diarrhoea than those in the first quartile (Table 5). The differences, which were statistically significant in the antibiotic-treated groups, occurred despite the greater initial dehydration in the first-quartile patients, which would have been predicted to result in longer purging in view of the generally direct relationship between severity of dehydration on admission to hospital and duration of diarrhoea. The data suggest, therefore, that a poorly nourished child with cholera recovers less quickly from the disease than a well-nourished one, even if antibiotic therapy is administered. It is also possible that nutritional status may contribute to the greater duration of diarrhoea associated with increasing age in antibiotic-treated adults (Lindenbaum et al., 1967). This interesting synergism between nutrition and infection is worthy of further study and documentation.

[1] J. Lindenbaum, data to be published.

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## RÉSUMÉ

Après avoir décrit précédemment les résultats de leurs essais d'antibiothérapie chez des cholériques adultes, les auteurs rapportent maintenant les observations faites à l'occasion du traitement similaire de jeunes enfants. Ce nouvel essai contrôlé a porté sur 238 patients de Dacca, Pakistan Oriental, âgés de 6 semaines à 10 ans, atteints de choléra confirmé. Un groupe témoin a été traité uniquement par administration de liquide de remplacement; les autres groupes ont reçu en outre l'un ou l'autre de quatre antibiotiques.

La tétracycline a donné les meilleurs résultats, les critères d'efficacité étant la diminution du volume des selles, une réduction des besoins en liquide de réhydratation ainsi que l'abrégement de la durée des phénomènes diarrhéiques et de la positivité des cultures. Un traitement prolongé (4 jours au lieu de 2) par cet antibiotique ou l'administration d'une dose totale plus élevée ont permis d'obtenir plus précocement des cultures négatives, mais n'ont eu aucune répercussion sur le volume des selles ou la durée de la diarrhée. Dans 1% des cas seulement, cette dernière a persisté pendant plus de 4 jours. Si grave qu'ait été l'infection, le traitement par la tétracycline a eu une efficacité de loin supérieure à celle du traitement par simple administration de liquide de remplacement.

En dépit d'une efficacité certaine, le chloramphénicol a donné des résultats moins favorables que la tétracycline chez les jeunes malades, ce qui ne concorde pas avec les observations faites antérieurement chez l'adulte. Quant à la streptomycine et à la paromomycine, elles n'ont eu qu'une action très faible ou nulle sur l'évolution clinique et bactériologique de la maladie.

La tétracycline apparaît donc comme l'antibiotique de choix pour le traitement des infections à *Vibrio cholerae* chez l'enfant. Administrée pendant 48 heures, elle est très active, mais on note une proportion de 20% de rechutes bactériologiques dès que le traitement est interrompu. On ignore actuellement si en prolongeant ce dernier pendant une semaine ou plus on parviendrait à réduire leur fréquence.

On a noté une corrélation évidente entre l'intensité de la déshydratation au moment de l'admission et la durée de la diarrhée chez tous les malades, indépendamment de l'instauration d'une antibiothérapie. Ni l'âge ni le sexe ne semblent avoir eu une influence sur l'évolution clinique de l'affection. Dans les groupes traités par antibiotiques, les déficiences de l'état de nutrition ont eu pour résultat d'allonger la durée des phénomènes diarrhéiques.


## REFERENCES


Barber, M. & Garrod, L. P. (1963) *Antibiotic and chemotherapy*, Edinburgh and London, Livingstone, p. 120

Carpenter, C. C. J., Barua, D., Wallace, C. K., Mitra, P. P., Sack, R. B., Khanra, S. R., Wells, S. A., Dans, P. E. & Chaudhuri, R. N. (1966) *Bull. Johns Hopk. Hosp.*, **118**, 216-229

Greenough, W. B., Gordon, R. S., Rosenberg, I. H., Davies, B. I. & Benenson, A. S. (1964) *Lancet*, **1**, 355-357

Kobari, K. (1965) *Treatment of Cholera El Tor with antimicrobial drugs.* In: *Proceedings of the Cholera Research Symposium, Honolulu, January 1965*, Washington, D.C., US Government Printing Office, p. 199

Lindenbaum, J., Akbar, A., Gordon, R. S., Greenough, W. B., Hirschhorn, N. & Islam, M. R. (1966) *Lancet*, **1**, 1066-1068

Lindenbaum, J., Greenough, W. B. & Islam, M. R. (1967) *Bull. Wld Hlth Org.*, **36**, 871-883

Pollitzer, R. (1959) *Cholera*, Geneva, p. 747 (*World Health Organization: Monograph Series*, No. 43)

Uylangco, C. V., Fabie, A. E., Mier, S. G. & Santiago, L. (1965) *J. Philipp. med. Ass.*, **11**, 763-769

Uylangco, C. V., Vasco, J. A., Calilong, V. P. & Villaroman, M. P. (1966) *J. Philipp. med. Ass.*, **42**, 529-538

WHO Expert Committee on Nutrition and Infection (1965) *Wld Hlth Org. techn. Rep. Ser.*, **314**, 7-11