Optimal Antibiotic Therapy in Cholera


Intravenous replacement of the diarrhoeal fluid and electrolyte losses to restore a physiological state of hydration is well established as the basis for successful management of cholera patients. The use of oral tetracycline as an adjunct in reducing the volume and duration of diarrhoea, as well as eradicating the vibrio from the gastrointestinal tract, has been proven beneficial. An optimal dose schedule has not been established previously, and clinical or bacteriological relapses have been generally reported. Chloramphenicol and sulfaguanidine have also been mentioned as adjuncts. The present report shows that 3 g or 4 g of tetracycline in one of 3 dose schedules were predictably efficacious. Chloramphenicol, while of benefit, was not as effective and sulfaguanidine was of little benefit compared with the tetracycline regimens.

The efficacy of tetracycline as an adjunct to the intravenous replacement of fluid and electrolyte losses in the treatment of cholera was substantiated independently at this centre and at the Pakistan–SEATO Cholera Research Laboratory, Dacca, East Pakistan, in 1963 (Carpenter et al., 1964; Greenough et al., 1964). In these studies patients were given both oral and intravenous tetracycline in relatively large doses. Subsequently, the efficacy of oral tetracycline alone was tested (Wallace et al., 1965). With a total oral dose of only 2 g, the amount and duration of diarrhoea were reduced. This dose schedule, however, was not recommended as optimal as several patients continued to excrete vibrios for a longer period than did patients in the control group, who received no antibiotic. We share the belief that “it is imperative to minimize the cost [and time] of the therapeutic regimen of cholera without sacrificing its clinical effectiveness” (Lindenbaum et al., 1967a) and we have continued our attempts to find an optimal oral antibiotic regimen for cholera patients. This report presents our findings from such tests made during 1965 and 1966.

Patients and Methods

This study included only male patients over 15 years of age and more than 25 kg in body-weight who had been admitted to Calcutta’s Infectious Diseases Hospital with watery diarrhoea and hypotension (systolic blood-pressure below 80 mm Hg) and who subsequently proved to have cholera. None had received antibiotics during the week prior to hospital admission. There was no other selection and all patients were assigned to a therapeutic regimen by one of the authors in accordance with a previously randomized schedule. During 1965 three regimens were employed: one treatment group received 500 mg of tetracycline orally every 6 hours for 8 doses, a total of 4 g; the second treatment group received 250 mg of tetracycline every 6 hours for 12 doses, a total of 3 g; the control group received no antibiotics. Antibiotics were administered at 6 a.m., noon, 6 p.m. and midnight, regardless of the time of admission. During 1966 four therapeutic regimens were employed: one treatment group was given 2 g of tetracycline orally immediately after initial intravenous rehydration and 2 g 24 hours later, a total of 4 g of tetracycline; a second group received 500 mg of chloramphenicol orally every 6 hours for 12 doses, a total of 6 g; the third study group was given a total of 42 g of oral sulfaguanidine, 2 g every 4 hours for 6 doses, and then 2 g every 8 hours for 15 doses (as recommended by Indian physicians in treating non-specific diarrhoea); a control group received no antibiotics.

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Upon admission all patients were placed on cholera cots and treated as has been described by Wallace (1968). Blood was drawn from the femoral artery for bedside determination of pH, bicarbonate content and plasma specific gravity. Standard techniques, previously described by Pierce et al. (1968), were used for subsequent determinations of the osmolality of the chloride, sodium and potassium contents of the blood plasma and the stool samples taken upon admission, and for determining the total protein content of the blood plasma.

Stool specimens were obtained upon admission by means of a sterile rectal catheter and daily thereafter either by catheter or by rectal swab if no liquid stool was obtained. All specimens were streaked immediately on desoxycholate-citrate agar, salmonella-shigella agar, bile-salt agar, and either gelatin-taurocholate-tellurite agar or meat-extract agar. Six-hour-enrichment cultures from alkaline peptone water were also streaked on the same media. Plates were examined by the stereoscopic microscope technique of Finkelstein & Gomez (1963) for the presence of colonies morphologically typical of *V. cholerae*. Isolates were verified by specific sugar fermentation and slide agglutination tests, using both group antisera and specific Ogawa and Inaba antisera. *V. cholerae*, biotype El Tor, was characterized by resistance to lysis with Mukerjee's phage type IV, by resistance to polymyxin B (50-IU disc), by haemagglutination of chick red blood cells and by formation of a pellicle in brain-heart infusion broth at 18 hours. Haemolysis tests were negative when performed by the usual tube and plate techniques. Haemolysis by El Tor vibrios, however, was demonstrated by culture on sheep-blood agar incubated anaerobically, and in tubes of brain-heart infusion broth, with glycerol (Barua & Mukherjee, 1964).

All patients were observed in a study ward for at least 7 days and no patient was discharged until at least 3 consecutive daily stool cultures were negative for *V. cholerae*. In 24 patients the duodenum was intubated approximately 7 days after the last vibrio-positive stool culture, and the aspirate was cultured following an intravenous injection of 50–100 Ivy-dog units of cholecystokinin. Of these 24 patients, 20 were also purged with magnesium sulfate, usually the day after intubation, but the interval ranged from immediately after intubation to 7 days later. Eleven patients were purged without having had duodenal intubation. The resultant diarrhoeal stools after purging were cultured for *V. cholerae* as described above. The distribution of the tested patients among the treatment regimens is summarized in Table 1. Specific techniques and results of these attempts to determine possible gall-bladder infection have been reported (Wallace et al., 1967).

### RESULTS

There were 66 patients positive for *Vibrio cholerae* who met our criteria for inclusion in this study. Of these patients 60 were infected with *V. cholerae*,

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Intubated and purged</th>
<th>Intubated only</th>
<th>Purged only</th>
<th>Total patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1965 Treatments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Tetracycline 3 g</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Tetracycline 4 g</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1966 Treatments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>4</td>
<td>0</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Tetracycline 4 g</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Chloramphenicol 6 g</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Sulfaguanidine 42 g</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Total patients</td>
<td>20</td>
<td>11</td>
<td></td>
<td>35</td>
</tr>
</tbody>
</table>

*All patients had infection with *V. cholerae*, serotype Ogawa, biotype El Tor, except the one patient treated with 3 g tetracycline, who was infected with a classical *V. cholerae* of Inaba serotype.*
serotype Ogawa, biotype El Tor. Of the 1965 group 6 were infected with classical V. cholerae (5 serotype Inaba and 1 Ogawa). Infection with classical organisms was not observed in Calcutta during 1966. Of the patients infected by classical organisms 2 were in the 1965 control group receiving no antibiotics, 1 was in the 4-g tetracycline treatment group, and 3 were in the 3-g tetracycline treatment group. Table 2 shows the general similarity in the results of the laboratory tests upon admission of the patients in each treatment group.

All patients responded to intravenous fluid replacement with rapid return to normal blood-pressure and tolerated well the administration of oral antibiotics and green coconut (dab) water. After initial rehydration and early correction of the acidosis, vomiting ceased and therefore did not interfere with the oral antibiotic treatment.

The effects of the various regimens on the duration of diarrhoea are compared in Fig. 1. The 2 control groups were similar. Diarrhoea was of significantly shorter duration in all the antibiotic treatment groups than in both groups of control patients. The duration of diarrhoea of patients in the sulfaguanidine-treated group did not differ significantly from that of the 1965 control group. This sulfaguanidine group did, however, have a shorter duration of diarrhoea than the control group of the same year.

Fig. 2 shows the range and mean total volume of diarrhoea for the 7 groups during the period of

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>1965 Treatments</th>
<th>1966 Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Tetracycline (4 g)</td>
</tr>
<tr>
<td>No. of patients</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Age (years)</td>
<td>38.3 ±15.7</td>
<td>36.0 ±14.4</td>
</tr>
<tr>
<td>Body-weight (kg)</td>
<td>40.4 ±5.4</td>
<td>41.5 ±9.9</td>
</tr>
<tr>
<td>Onset of diarrhoea prior to admission (hours)</td>
<td>11.7 ±8.9</td>
<td>8.6 ±3.4</td>
</tr>
<tr>
<td>Systolic blood-pressure (mm Hg)</td>
<td>38.8 ±33.3</td>
<td>20.9 ±30.5</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.09 ±0.12</td>
<td>7.09 ±0.21</td>
</tr>
<tr>
<td>Total protein (g/100 ml plasma)</td>
<td>12.3 ±1.8</td>
<td>12.5 ±1.9</td>
</tr>
<tr>
<td>Plasma specific gravity</td>
<td>1.041 ±0.004</td>
<td>1.040 ±0.005</td>
</tr>
<tr>
<td>Plasma sodium (mEq/l)</td>
<td>149.5 ±6.4</td>
<td>150.7 ±12.2</td>
</tr>
<tr>
<td>Plasma potassium (mEq/l)</td>
<td>5.4 ±0.7</td>
<td>6.3 ±1.5</td>
</tr>
<tr>
<td>Plasma chloride (mEq/l)</td>
<td>108.1 ±7.3</td>
<td>112.0 ±4.7</td>
</tr>
<tr>
<td>Plasma bicarbonate (mEq/l)</td>
<td>17.5 ±7.7</td>
<td>11.5 ±6.2</td>
</tr>
<tr>
<td>Plasma osmolality (m osmol/l)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Stool sodium (mEq/l)</td>
<td>135.1 ±9.2</td>
<td>131.0 ±11.2</td>
</tr>
<tr>
<td>Stool potassium (mEq/l)</td>
<td>21.0 ±10.8</td>
<td>20.0 ±5.8</td>
</tr>
<tr>
<td>Stool chloride (mEq/l)</td>
<td>107.9 ±13.7</td>
<td>88.8 ±18.3</td>
</tr>
<tr>
<td>Stool osmolality (mosmol/l)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

a Mean values ± standard deviations.  
b Single value.  
c 2 values.
hospitalization. Only in the 3 tetracycline-treated groups was the total diarrhoeal output significantly decreased in comparison with the 2 control groups. The total output was not significantly decreased in the chloramphenicol- and sulfaguanidine-treated groups. Fig. 3 shows a comparison of the mean relative diarrhoeal losses of patients in the various treatment groups during the first two 12-hour periods and the total volume of diarrhoeal output. In the tetracycline- and the chloramphenicol-treated groups, more than two-thirds of the total diarrhoea occurred in the first 24 hours of hospitalization, with a significant diminution in volume between the first and second 12-hour periods. The total quantity of intravenous fluid required to maintain physiological hydration, as confirmed by normal plasma specific gravity determinations, ranged from 2 to 4 litres more than the total measured diarrhoeal output.

The mean duration and time range of vibrio excretion (as determined by routine stool-culture techniques) are presented in Fig. 4. There was no difference between the 3 tetracycline regimens, in all of which the duration of excretion was significantly
FIG. 3
MEAN VOLUME OF TOTAL DIARRHOEAL LOSSES

shorter than in the untreated control, chloramphenicol- and sulfaguanidine-treated groups. Chloramphenicol- and sulfaguanidine-treated patients both had a significantly shorter duration of excretion when compared with control patients of the same year (1966), but not when compared with the control patients of 1965.

Of the 35 patients who underwent duodenal intubation with cholecystokinin stimulation and magne-

sium sulfate purgation, or magnesium sulfate purga-
tion alone, after routine stool cultures had become consistently negative, only 2 had vibrios in subse-
quent stool cultures. Both of these patients were in
the 1966 control group. One of them had positive
stool cultures for V. cholerae after each of 7 purg-
ings with magnesium sulfate over a 23-week period,
starting 9 days after his last positive rectal-swab
culture obtained without purging. During the 23-
week period all stool cultures were negative except
after purging. The second patient was first intubat-
ed on the fourth day after his last positive, unpurged
stool culture. On 2 occasions over a 2-week con-
valvescent period V. cholerae were present in the
cultured duodenal aspirate but only after the patient
had been given intravenous cholecystokinin. After
both duodenal aspirations, purges by magnesium
sulfate also yielded vibrio-positive stools. Subse-
quent specimens following intubation and purging,
on 4 occasions over a 5-month period, were negative
for vibrios.

FIG. 4
DURATION OF VIBRIO CHOLERA EXCRETION
BY STOOL CULTURE

Our data clearly indicate favourable clinical and
bacteriological responses to a total dose of 3 g or 4 g
of tetracycline in each of the 3 schedules used.
Tetracycline was consistently effective in reducing
the total amount of diarrhoea, the duration of
diarrhoea and the duration of V. cholerae excretion.
The present data also demonstrate a favourable
response to antibiotic therapy after the first 12 hours
of hospitalization in patients receiving either tetra-
cycline or chloramphenicol (Fig. 3). In view of the
possible occurrence of chloramphenicol-associated
blood dyscrasias and as tetracycline is an equally
satisfactory (if not superior) therapeutic adjunct, we
believe that tetracycline is the antibiotic of choice in
cholera.

Our findings in Calcutta are similar to those
recently reported by Lindenbaum et al. (1967a,
1967b) from Pakistan, which demonstrated a more
favourable response to tetracycline than other treat-
ment regimens. Lindenbaum and his group did
find, in contrast to the present series, that chloram-
phenicol was equally as effective as tetracycline.
There may be several reasons for this. The Pakistan
group (Lindenbaum et al., 1967a) was dealing with
66 patients whose mean age was 23.6 years and
mean body-weight was 37.4 kg—a larger popula-
tion, somewhat younger, and much lighter than our
7 patients. Their patients were individuals infected
by classical \textit{V. cholerae}, while the majority of our
patients were infected by the biotype El Tor. The
Pakistan group included all bacteriologically con-
"irmed cholera patients admitted to their centre,
while we included only severely affected adult
males. Our series was selectively small because we
wished to study a uniform group of patients to
"ompare control and study groups over a period of
several years. Our chloramphenicol-treated group
was significantly heavier in body-weight than each
of our other antibiotic-treated groups, which implies
a reduced drug dose per kg of body-weight. It
might be argued that this mean body-weight differ-
ce would explain our findings that neither the
duration of excretion of vibrios nor the total diar-
rhoeal output was significantly reduced by chloram-
phenicol. Our chloramphenicol-treated patients,
however, were not significantly heavier than our
1966 control group. Moreover, in a companion
paper Lindenbaum et al. (1967b) do report that
chloramphenicol in the form of the p"omitate syrup
is not as effective as tetracycline in treating children
with cholera.

There is no question that the commonly used
regimen of sulfaguanidine is a more complicated
one, and we found little support for its purported
efficacy as an adjunct in the treatment of cholera.

It has been our experience in treating cholera
patients that 500 mg of tetracycline every 6 hours
for 8 doses is an easy and most practical regimen to
administer. We recommend this as a standard
tetracycline regimen in treating adult cholera
patients at the present time. A schedule of 2 g upon
admission and again after 24 hours was equally
effective. In an epidemic situation, the convenience
of giving medication on only 2 occasions might be
helpful.

The fact that we had no bacteriological or clinical
relapses (in contrast to the experience of Linden-
baum and his group) might be due to the fact, as
Lindenbaum et al. suggested, that we were only
dealing with severely and acutely ill adult males.
Also, as stated above, we were primarily dealing
with individuals infected with \textit{V. cholerae}, biotype
El Tor, and it has been suggested that these organ-
isms may respond differently from \textit{V. cholerae} to
antibiotic therapy. However, we have demonstrated
a vibrio-eradicating effect with tetracycline and a
predictable clinical response as compared with ap-
propriate controls. The treatment of rarely diag-
nosed, insidious \textit{V. cholerae} infection and of chronic
carriers has not been satisfactorily studied. It is
appreciated that a larger series of tests in Calcutta
with a longer follow-up period might demonstrate a
clinical or bacteriological relapse with the present
tetracycline recommendations.

There is a continuing need for clinical evaluations
of drug usage in various locations and under vary-
ing circumstances. Certainly a search for an even
more effective oral adjunct in cholera is indicated.
Vibrio-sensitivity studies, especially in areas where
cholera is endemic, must be continued to anticipate
the possible development of vibrios resistant to any
specific antibiotic regimen (Lewis, 1967). Finally it
must be re-emphasized that, although antibiotics are
very useful adjuncts in the treatment of cholera,
adequate intravenous fluid and electrolyte replace-
ment remains the basis of successful management.

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of this study.

Dr Helen Abbey, Associate Professor of Biostatistics, The Johns Hopkins University School of Hygiene and
Public Health, was especially helpful in planning and executing the statistical analysis of the data.

RÉSUMÉ

Le traitement réhydratant reste la base d'une thé-
raputique efficace du choléra, mais il n'en est pas moins
nécessaire de poursuivre l'étude clinique de schémas
médicamenteux, dans des conditions et des endroits
divers, pour tenter notamment de prévenir l'apparition
d'une résistance des vibrios aux antibiotiques.

Les essais décrits dans le présent article ont porté
sur 66 malades de sexe masculin, âgés de plus de 15 ans,
admis en 1965 et 1966 à l’hôpital de Calcutta, Inde, pour choléra avéré. Tous présentaient une diarrhée aqueuse et de l’hypotension. Certains patients ont été traités par la tetracycline, à la dose totale de 3-4 g, administrée en 2, 8 ou 12 prises, d’autres par le chloramphénicol (dose totale: 6 g en 12 prises) ou par la sulfaguanidine (dose totale: 42 g en 21 prises). Deux groupes témoins n’ont pas reçu d’antibiotiques.

L’antibiothérapie a eu un effet favorable sur l’évolution de l’infection cholérique, réduisant l’intensité et la durée de la diarrhée et abrégeant la période d’élimination de Vibrio cholerae. Les meilleurs résultats ont été obtenus avec la tetracycline. Le chloramphénicol et la sulfaguanidine se sont montrés moins actifs. Sept jours après l’obtention des dernières cultures positives, on a pratiqué chez 35 malades un tubage duodénal et on leur a administré une purgation par le sulfate de magnésium et, dans certains cas, une injection de cholécystokinine. Chez deux d’entre eux seulement, appartenant aux groupes témoins, des vibrons cholériques ont été découverts.

Pour les auteurs, l’administration de 8 doses de 500 mg de tetracycline à intervalles de 6 heures est le traitement de choix du choléra chez l’adulte.

REFERENCES

Lewis, G. W. (1967) In: Johns Hopkins CMRT (1965-66) [Progress Report, Johns Hopkins University Center for Medical Research and Training], Baltimore, Md., p. 58