Non-Vibrio cholera: a current overview

David R. Nalin, MD
Cholera Research Laboratory and the Johns Hopkins Center for Medical Research and Training, Dacca, Bangladesh

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Non-Vibrio cholera is defined as cholera-like disease in the absence of the *Vibrio*. This entity, like cholera, consists of severe dehydration due to profuse watery diarrhoea; but stool cultures for *V. cholerae* are negative and there is no rise in vibriocidal antibody titres. Non-Vibrio cholera differs from cholera clinically in its shorter mean duration and lower mean total stool volume. Due to overlap in clinical parameters, however, differentiation from cholera on clinical grounds is not possible. Lindenbaum *et al.* (1965) found no difference between patients with cholera and non-Vibrio cholera in respect of symptoms of watery diarrhoea, vomiting, muscle cramps, hoarseness, oliguria, fever, or pre-admission duration. Abdominal pain was reported slightly less frequently in the cholera group. Duration and volume of diarrhoea were 4.7 days on the average (2.7–6.3 range) and 30.8 (5.2–69.1) litres for cholera and 1.5 (0–4.5) days and 3.7 (0–17.9) litres for non-Vibrio cholera respectively. Fortunately aetiological differentiation is not necessary for effective therapy.

TREATMENT

The therapy of both Vibrio cholera and non-Vibrio cholera consists of rapid, total replacement of water and electrolyte losses before hospital admission, followed by measurement and replacement of subsequent losses as they occur. Intravenous and oral solutions developed for cholera therapy are satisfactory for treatment of non-Vibrio cholera because the small differences in stool electrolyte composition in the two disorders are not clinically important (Table 1).

Patients in the state of shock due to severe dehydration have weak or absent radial pulse and require immediate, rapid intravenous infusion of rehydration fluids equivalent to 10% of body weight. For example, a 50 kg patient of this type would require 5 kg, or 5 litres of IV rehydration fluids. A pulseless dehydrated child weighing 10 kg would require 1 litre, and so on. These fluids must be given at the rate of 1 litre per 15 minutes until the full amount is infused. Patients with moderate dehydration require IV equivalent of 5% of body weight, and those with mild dehydration require only oral glucose-saline therapy.

The goal of post-rehydration maintenance therapy is to keep the patient in fluid- and electrolyte-balance. The essential equipment for this second phase of therapy is the canvas and wood-frame Watten cot and a bucket calibrated in litres. The patient lies so that the buttocks are positioned over a hole in the cot. A plastic or rubber sheet lies between the patient and the canvas and the liquid stool passes by way of a sleeve in the sheet through the hole and into the calibrated bucket below. Maintenance IV fluids are given as needed to match the level of diarrhoea fluids in the bucket.

Maintenance therapy can be carried out more cheaply by matching losses with *oral* glucose-saline solution (Table 1). Patients admitted in shock are first given IV rehydration according to the "10% of weight" rule. Immediately thereafter oral glucose-saline therapy is started *without delay*. Since there may be a gap between IV rehydration and resumption of diarrhoea, it is necessary to begin oral therapy with 750 ml per hour in adults and 250 ml per hour in children. These amounts can later be adjusted up or down to match actual measured losses of stool and vomitus. Vomitus is rarely voluminous or frequent enough to affect balance significantly because most patients in shock stop vomiting after initial IV rehydration. Small amounts of vomitus should be measured as with stool and replaced with equivalent additional oral solution.

The IV and oral solutions used must match the composition of the fluids lost (Table 1). The optional addition of 110 mg per litre of glycine will further enhance the beneficial effect of the glucose in the solution on intestinal salt and water absorption. Sucrose has been tested and has *not* been found to be a very satisfactory alternative to glucose in this type of oral solution.

All patients should be allowed oral diet and extra fluids as soon as desired after rehydration. Two per cent glucose should be added to IV solutions for treatment of children, since some children with non-Vibrio cholera develop potentially fatal hypoglycaemia.

Tetracycline is given orally to cholera patients to shorten the duration and volume of diarrhoea by eliminating *Vibrios;* it has also been given empirically to patients with non-Vibrio cholera. The dose used is 250 mg every six hours for adults, or 125 mg six-hourly for children. Alternatively furazolidone can be given to pregnant women or children to avoid potentially harmful effects of tetracycline. The dose is 100 mg by mouth six-hourly for adults and 50 mg

six-hourly for children. A controlled trial of antibiotics has not been carried out in non-Vibrio cholera but they are probably useful as an adjunct to vital fluid replacement. This statement is based on recent studies at the Dacca Cholera Research Hospital which implicate certain *Escherichia coli* strains as the likely cause of non-Vibrio cholera. In Dacca such strains are still sensitive to tetracycline and furazolidone.

Table 1. Composition of stool, intravenous and oral solutions (mMols/litre)

	Stool	*IV*	*Oral*
Na	139	133	120
K	24	15	25
HCO_3	49	48	48
Cl	106	100	97
Glucose	—	110*	110

*2% glucose added for paediatric cases.

PATHOPHYSIOLOGY

The association of *E. coli* strains with watery diarrhoea in man has long been known, but recent advances in pathophysiology are based on veterinary microbiological research. Smith and Gyles (1970) showed that faecal *E. coli* from animals with diarrhoea produces a thermostable and a thermolabile enterotoxin, and that the latter is neutralized by cholera antitoxin. Enterotoxicity, genetically governed by extrachromosomal plasmids, is transferred during mating to toxin-negative strains, including strains of other bacterial species.

Recent work at the Cholera Research Laboratory (CRL) extends these observations to *E. coli* strains from patients with non-Vibrio cholera. When cell-free culture filtrates from these human strains are injected into dog jejunal loops for 10 minutes and then rinsed out they rapidly cause fluid accumulation; this effect ends after rinsing the filtrate out of the loops and is not destroyed by pre-boiling filtrates. Hence this rapid effect is due to a thermostable enterotoxin.

Unheated filtrates contain a second (thermolabile) *E. coli* enterotoxin which resembles cholera toxin that (1) causes fluid accumulation after a gap of four hours; (2) causes prolonged fluid accumulation (24 hours); (3) this effect is not prevented by rinsing loops after a 10-minute exposure to the toxin because toxin binds rapidly to cells; (4) the resulting fluid has a composition identical to cholera diarrhoea; (5) pre-treatment of loops with natural cholera toxoid blocks the effect of thermolabile (but not thermostable) *E. coli* enterotoxin, which suggests a common cell binding site for the two toxins.

All known strains which can produce the thermolabile enterotoxin can also produce the thermostable one. The reverse is not true. Some veterinary strains produce the thermostable toxin alone; similar human strains have recently been identified at CRL. There is as yet no simple assay for the thermostable toxin. The brevity of the effect of the thermostable toxin on low enterotoxin output by *E. coli* compared with cholera may account for the relatively short mean duration of the illness noted in many patients.

Most enterotoxigenic *E. coli* do not conform to classic enteropathogenic serotypes. While there is as yet no simple way to identify which *E. coli* colonies on a plate are enterotoxigenic, sensitive assays can identify strains producing the thermolabile enterotoxin. One such assay is based on enterotoxin-induced changes in shape of Chinese hamster ovarian (CHO) cells. These changes are mediated by increases in cell adenyl cyclase activity induced by the toxin. Such increases have been found in intestinal cells exposed to either the *E. coli* thermolabile enterotoxin or cholera toxin, and are thought to cause the diarrhoea. The CHO cell assay has led to identification of thermolabile toxin-producing strains isolated from infants with diarrhoea, from patients with disabling tourist diarrhoeas, and from a high percentage of adults treated at diarrhoea hospitals in endemic cholera areas.

While cholera antitoxin does not affect the thermostable *E. coli* enterotoxin, the fact that it can neutralize the thermolabile toxin indicates that cholera toxin and the thermolabile *E. coli* toxin are very similar or identical. This suggests the idea, as yet unproven, that a genetic transfer of toxigenicity may occur in nature between *E. coli* and *V. cholerae* or other enterotoxigenic bacteria associated with diarrhoea.

A possible practical implication of toxin cross-neutralization was discovered at CRL when a cholera toxoid tested in volunteers was found to increase serum antitoxin to both cholera and *E. coli* (thermolabile) toxins. A toxoid vaccine, if it protects against clinical cholera, may therefore protect against non-Vibrio cholera as well. Unfortunately, toxoid subjected to field trial has not been as potent an antigen as was the original toxoid, so the answer is still awaited. This answer is potentially of great importance not only in the practical sense but also because of the great epidemiological significance such evidence of cross-immunity would have.

REFERENCES

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