U N I V E R S I T Y O F B E R G E N

Department of Philosophy

Ethical issues in international collaborative research: the standard of care debate

Reidar K. Lie, MD, PhD

Head of Department/Professor

Issues in international research

- Issues of different ethical standards and regulatory requirements
- What types of trials can one do in resource poor settings?
  - Post trial access to intervention studies
- Are researchers obligated to provide additional care to trial subjects?
  - Ancillary care
- **What is the appropriate standard of care for the control group in a clinical trial?**

Helsinki, 2013, article 33

The benefits, risks, burdens and effectiveness of a new intervention must be tested against **those of the best proven intervention(s),** except in the following circumstances:

- Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; **or**
- Where for compelling and ***scientifically sound methodological reasons*** the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention **and** the patients who receive any intervention less effective than the best proven one, placebo, or no intervention ***will not be subject to additional risks of serious or irreversible harm*** as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Scientific necessity criterion

- Cases where we do not know what the “no treatment effect is” and it varies among populations
  - If we compare
    - Established intervention against new intervention with the following results
      - Established intervention prevents 30 deaths
      - New intervention prevents 20 deaths
      - No treatment previously at 10 deaths
  - We cannot conclude that new intervention is effective without a placebo group

Scientific necessity criterion

- Cases where we do not know what the “no treatment effect is” and it varies among populations
  - If we compare
    - Established intervention against new intervention with the following results
      - Established intervention prevents 30 deaths
      - New intervention prevents **20 deaths**
      - No treatment in this population is at **20 deaths**
  - We cannot conclude that new intervention is effective without a placebo group

No serious harm criterion

- Clinical trial of an anti-histamine against runny nose
- Minor elevations of blood pressure
- Depression – Perhaps controversial
- Psychosis - Controversial
- Death – Definitely prohibited

The perinatal HIV transmission studies

- It had been shown that a long course of AZT treatment reduced transmission from around 30% to less than 10%
- This intervention was expensive and logistically difficult in resource poor settings
- Urgent need to develop a more suitable intervention
- A number of short course trials initiated. All but one tested against placebo
- It was argued that the design was scientifically necessary

Helsinki criteria satisfied?

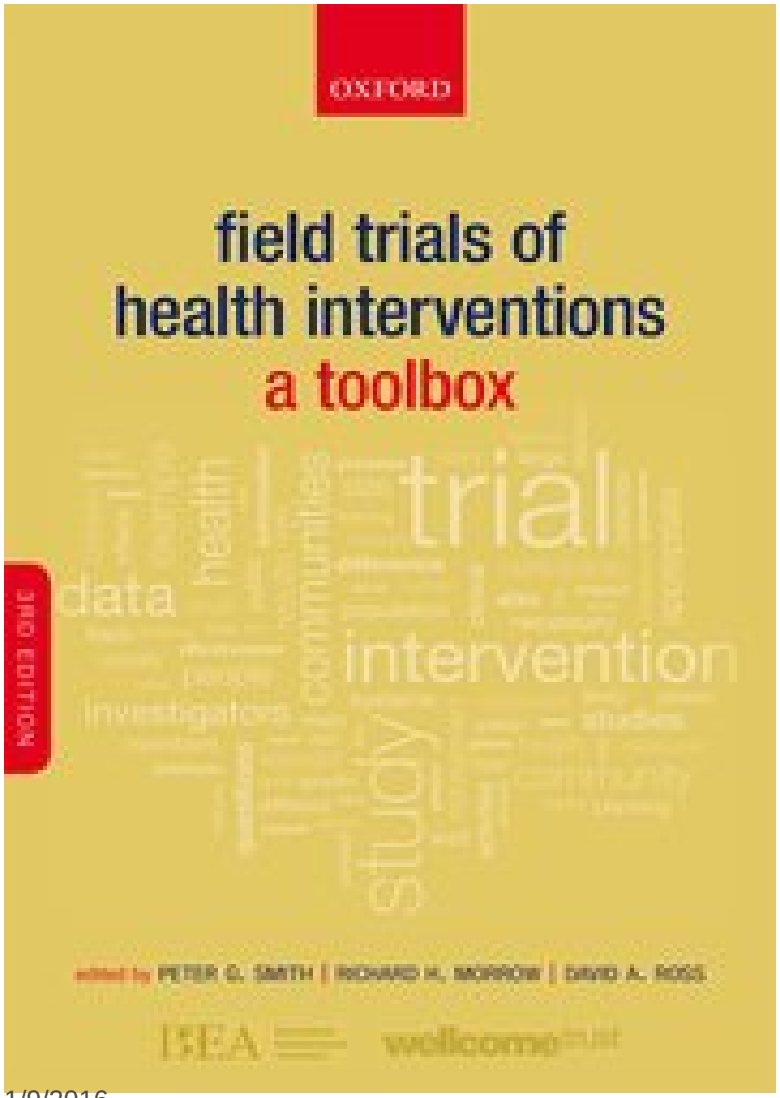
- Was a placebo controlled trial scientifically necessary?
  - There was variability in the no intervention transmission rate
- There was a “best proven intervention” demonstrating reduction in HIV-infection from 30% to below 10%
  - HIV infection is serious harm

Helsinki criteria satisfied?

- Was a placebo controlled trial scientifically necessary?
  - There was variability in the no intervention transmission rate
- There was a “best proven intervention” demonstrating reduction in HIV-infection from 30% to below 10%
  - HIV infection is serious harm
- BUT this intervention is not implementable in resource poor settings

Dilemma

- There is a known effective intervention against a major health problem in a resource poor setting
- This intervention cannot be made available in the foreseeable future
- It is desirable/necessary to introduce cheaper alternatives
- But testing these involves violating international research ethics regulations
  - Or the ethical principle “do no harm”



- Peter Smith, Richard Morrow, David Ross. Field trials of health interventions. A toolbox, 3rd ed. Oxford University Press, 2015
- https://global.oup.com/academic/product/field-trials-of-health-interventions-9780198732860?cc=no&lang=en&

This principle of comparing a new intervention with the best current proven intervention seems reasonable at first sight, but it has given rise to much controversy. The controversy has centered on global ‘best’ interventions that are neither currently available nor likely to become available to the population in which the trial is being conducted, either because of their cost or because of the feasibility of implementing the intervention (for example, radiotherapy for conditions in countries in which there is little or no provision for such treatment). **The ‘purists’** hold that, if the global ‘best’ intervention is not included as the control arm, then the trial is unethical and should not be conducted. **The pragmatists**, who often have experience of conducting trials in LMICs, hold that this position is itself ‘unethical’, as it prevents research investigations that may lead to important public health benefits in deprived populations.

Example: prevent HIV infection after delivery

- Interventions such as nevirapine dramatically reduced transmission during pregnancy and delivery
- But transmission still can occur after delivery if mother breastfeeds baby
- In rich countries: Hiv positive mothers should not breastfeed babies, but use bottle feeding. This eliminates transmission after birth
- In resource poor settings: recommendation is still that HIV mothers breastfeed
  - Overall this is best for the children
    - Lack of clean water

How to prevent infection in Low income countries?

- Best proven intervention is bottle feeding
- According to the Declaration of Helsinki this intervention should be provided in the control group
- Let us say we have a drug that might prevent infection. We should then have the following design
  - The intervention group is a breastfeeding group with the drug
  - The control group is bottle fed

Problems

- Will this design provide results that are useful for Low income countries?
  - We want to know whether drug treatment is better than breast feeding, not how much worse drug treatment is compared with bottle feeding

- The intervention group also receives sub-optimal care: breast feeding with a drug intervention. There is no reason to believe that this overall is as good as bottle-feeding (even within the context of the clinical trial).

Challenge

- According to the Declaration of Helsinki, we are not allowed to do this research, even if it could lead to dramatic health improvements in low income countries.
  - Nevirapine trial in fact did do so

CIOMS

Placebos permitted

- If scientifically necessary for trivial conditions
  - Hair loss
  - Nasal congestion
- If scientifically necessary and if causing temporary harm or non serious harm
  - Migraine headaches
  - Minor elevations of blood pressure

CIOMS

An exception to the general rule is applicable in some studies designed to develop a therapeutic, preventive or diagnostic intervention for use in a country or community in which an established effective intervention is not available and unlikely in the foreseeable future to become available, usually for economic or logistic reasons. The purpose of such a study is to make available to the population of the country or community an effective alternative to an established effective intervention that is locally unavailable.

CIOMS, II

Also, the scientific and ethical review committees must be satisfied that the established effective intervention cannot be used as comparator because its use would not yield scientifically reliable results that would be relevant to the health needs of the study population. In these circumstances an ethical review committee can approve a clinical trial in which the comparator is other than an established effective intervention, such as placebo or no treatment or a local remedy

3 conditions for exception

1. The results of the trial will be relevant to the study population/country in which the study is carried out *or*

There is a reasonable likelihood that the new intervention will be implemented

   – AND

2. No alternative designs are possible AND

3. Participants are not denied treatment they would ordinarily receive

- The view of the pragmatists, including ourselves, is that, if an effective intervention is known, but its cost is beyond that which would make it feasible to introduce it into the local health care system (and there is little prospect that the cost can be reduced by means such as shifting production of pharmaceuticals to generic manufacturers), then it may well be acceptable to exclude it from consideration as a possible comparison intervention in a trial. In some circumstances, **it may be acceptable to try to test a new intervention that might be, at best, equivalent to an existing intervention or may even be inferior to it** if, for example, it is cheaper or simpler to apply, or more stable, or associated with fewer adverse reactions, or is more acceptable to the community than the existing intervention. In such circumstances, the purpose of the trial might be to show that the efficacy of the intervention was 'equally good or not much worse than' the existing intervention.
  - Field trials of health interventions. A toolbox

Case: Pertussis vaccine trials in Sweden/Italy

- Previously vaccine used based on whole killed bacterium
- Various side effects, relatively low protective effect
- Acellular vaccine developed in the early 1990s.
  - Test design: placebo controlled trial
  - Deemed unethical in the US
- NIH funded placebo controlled trial carried out in Italy and Sweden (four armed trial, with 10% of children in the placebo group).
  - Sponsor argued placebo group is necessary
  - Sweden and Italy had discontinued their whole cell vaccination program. 10% of infants vaccinated in Sweden, 40% in Italy

Two unresolved issues

- Sweden had used a locally produced whole cell vaccine previously that was known to be inferior to the one used in the US
- Many pediatricians in Sweden disagreed with the official government position of no whole cell pertussis vaccine
  - Lots of pertussis cases in Sweden after discontinuation of vaccination
  - Experts advising government likely be the same who had an interest in participating in the US sponsored clinical trial

- The low level of vaccination in the two countries is an important factor in designing an ethically acceptable trial, said Dr. Mark Siegler, director of the Center for Clinical Medical Ethics at the University of Chicago. "Since only 4 in 10 Italian children are immunized, it seems that any trial that assured 9 out of 10 participants were likely to receive a safe and effective pertussis immunization is an ethically appropriate trial," he said.
- But Dr. Siegler said to avoid all criticism, the best approach would be to offer all parents interviewed for the study a chance to get the recommended vaccinations first, and then try to enroll those who declined.

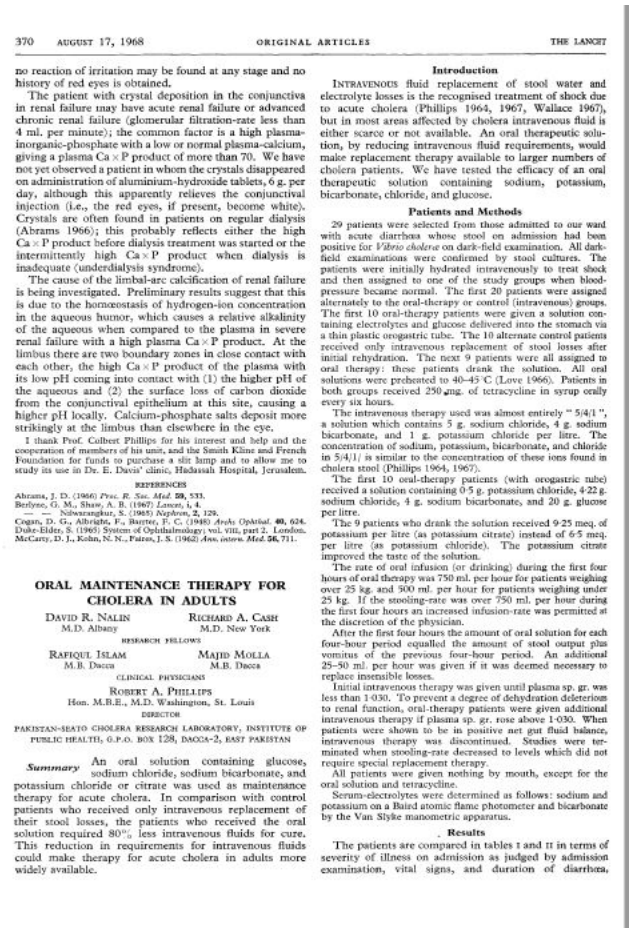
Case: oral rehydration

- In the late 1960s standard intervention for cholera in adults and diarrhea in children was intravenous liquid
  - Perception was that oral rehydration was useles, even dangerous, because liquids could not be absorbed from the gut
- Intravenous administration difficult in resource poor settings, war situations, and epidemics
- A number of researchers in Bangladesh and India started research that led to the current standard, oral rehydration, which has saved millions of lives
- Control group?
- Is any study acceptable?

Key trials

- Beginning of 1960s: 30-40% mortality of mortality in villages. Hospital intravenous fluids, around 1%
- Basic studies of roles of Sodium and sugar in transport of fluids from intestines in cholera patients
- 1967 Richard Cash and David Nalin, two US physicians arrive in Dacca. Both are interns/residents, 26 year old. September 1967 cholera epidemic. Failed oral rehydration trial in field conditions. No deaths, but not adequate rehydration.
- Second protocol carried out in hospital in Dacca

1968 Lancet publication



370 AUGUST 17, 1968 ORIGINAL ARTICLES THE LANCET

no reaction of irritation may be found at any stage and no history of red eyes is obtained.

The patient with crystal deposition in the conjunctiva in renal failure may have acute renal failure or advanced chronic renal failure (glomerular filtration-rate less than 4 ml. per minute); the common factor is a high plasma-inorganic-phosphate with a low or normal plasma-calcium, giving a plasma Ca × P product of more than 70. We have not yet observed a patient in whom the crystals disappeared on administration of aluminium-hydroxide tablets, 6 g. per day, although this apparently relieves the conjunctival injection (i.e., the red eyes, if present, become white). Crystals are often found in patients on regular dialysis (Abrams 1966); this probably reflects either the high Ca × P product before dialysis treatment was started or the intermittently high Ca × P product when dialysis is inadequate (underdialysis syndrome).

The cause of the limbal-arc calcification of renal failure is being investigated. Preliminary results suggest that this is due to the homœostasis of hydrogen-ion concentration in the aqueous humor, which causes a relative alkalinity of the aqueous when compared to the plasma in severe renal failure with a high plasma Ca × P product. At the limbus there are two boundary zones in close contact with each other, the high Ca × P product of the plasma with its low pH coming into contact with (1) the higher pH of the aqueous and (2) the surface loss of carbon dioxide from the conjunctival epithelium at this site, causing a higher pH locally. Calcium-phosphate salts deposit more strikingly at the limbus than elsewhere in the eye.

I thank Prof. Colbert Phillips for his interest and help and the cooperation of members of his unit, and the Smith Kline and French Foundation for funds to purchase a slit lamp and to allow me to study its use in Dr. E. Davis' clinic, Hadassah Hospital, Jerusalem.

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ORAL MAINTENANCE THERAPY FOR CHOLERA IN ADULTS

DAVID R. NALIN, M.D. Albany — RICHARD A. CASH, M.D. New York
RESEARCH FELLOWS
RAFIQUL ISLAM, M.B. Dacca — MAJID MOLLA, M.B. Dacca
CLINICAL PHYSICIANS
ROBERT A. PHILLIPS, Hon. M.B.E., M.D. Washington, St. Louis
DIRECTOR
PAKISTAN-SEATO CHOLERA RESEARCH LABORATORY, INSTITUTE OF PUBLIC HEALTH, G.P.O. BOX 128, DACCA-2, EAST PAKISTAN

Summary An oral solution containing glucose, sodium chloride, sodium bicarbonate, and potassium chloride or citrate was used as maintenance therapy for acute cholera. In comparison with control patients who received only intravenous replacement of their stool losses, the patients who received the oral solution required 80% less intravenous fluids for cure. This reduction in requirements for intravenous fluids could make therapy for acute cholera in adults more widely available.

Introduction

INTRAVENOUS fluid replacement of stool water and electrolyte losses is the recognised treatment of shock due to acute cholera (Phillips 1964, 1967, Wallace 1967), but in most areas affected by cholera intravenous fluid is either scarce or not available. An oral therapeutic solution, by reducing intravenous fluid requirements, would make replacement therapy available to larger numbers of cholera patients. We have tested the efficacy of an oral therapeutic solution containing sodium, potassium, bicarbonate, chloride, and glucose.

Patients and Methods

29 patients were selected from those admitted to our ward with acute diarrhœa whose stool on admission had been positive for *Vibrio cholerae* on dark-field examination. All dark-field examinations were confirmed by stool cultures. The patients were initially hydrated intravenously to treat shock and then assigned to one of the study groups when blood-pressure became normal. The first 20 patients were assigned alternately to the oral-therapy or control (intravenous) groups. The first 10 oral-therapy patients were given a solution containing electrolytes and glucose delivered into the stomach via a thin plastic orogastric tube. The 10 alternate control patients received only intravenous replacement of stool losses after initial rehydration. The next 9 patients were all assigned to oral therapy: these patients drank the solution. All oral solutions were preheated to 40–43° C (Love 1966). Patients in both groups received 250 mg. of tetracycline in syrup orally every six hours.

The intravenous therapy used was almost entirely "5/4/1", a solution which contains 5 g. sodium chloride, 4 g. sodium bicarbonate, and 1 g. potassium chloride per litre. The concentration of sodium, potassium, bicarbonate, and chloride in 5/4/1/ is similar to the concentration of these ions found in cholera stool (Phillips 1964, 1967).

The first 10 oral-therapy patients (with orogastric tube) received a solution containing 0·5 g. potassium chloride, 4·22 g. sodium chloride, 4 g. sodium bicarbonate, and 20 g. glucose per litre.

The 9 patients who drank the solution received 9·25 meq. of potassium per litre (as potassium citrate) instead of 6·5 meq. per litre (as potassium chloride). The potassium citrate improved the taste of the solution.

The rate of oral infusion (or drinking) during the first four hours of oral therapy was 750 ml. per hour for patients weighing over 25 kg. and 500 ml. per hour for patients weighing under 25 kg. If the stooling-rate was over 750 ml. per hour during the first four hours an increased infusion-rate was permitted at the discretion of the physician.

After the first four hours the amount of oral solution for each four-hour period equalled the amount of stool output plus vomitus of the previous four-hour period. An additional 25–50 ml. per hour was given if it was deemed necessary to replace insensible losses.

Initial intravenous therapy was given until plasma sp. gr. was less than 1·030. To prevent a degree of dehydration deleterious to renal function, oral-therapy patients were given additional intravenous therapy if plasma sp. gr. rose above 1·030. When patients were shown to be in positive net gut fluid balance, intravenous therapy was discontinued. Studies were terminated when stooling-rate decreased to levels which did not require special replacement therapy.

All patients were given nothing by mouth, except for the oral solution and tetracycline.

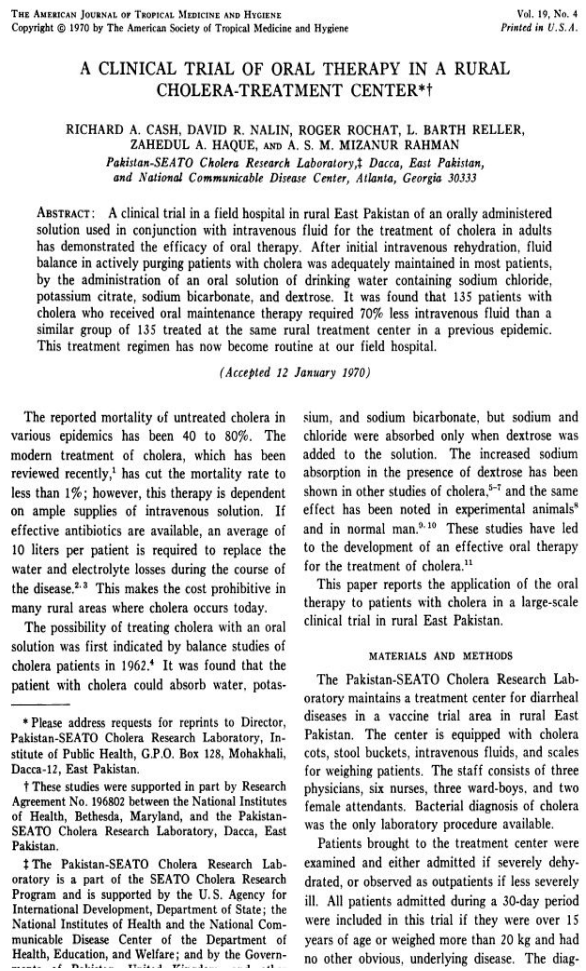
Serum-electrolytes were determined as follows: sodium and potassium on a Baird atomic flame photometer and bicarbonate by the Van Slyke manometric apparatus.

Results

The patients are compared in tables I and II in terms of severity of illness on admission as judged by admission examination, vital signs, and duration of diarrhœa,

- Adults
- Sickest patients selected
- First stabilized intravenously
- Then maintained on oral fluids
  - Some wanted to continue iv fluids
- Safeguards of hospital setting

Field trial in rural East Pakistan



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A CLINICAL TRIAL OF ORAL THERAPY IN A RURAL CHOLERA-TREATMENT CENTER*†

RICHARD A. CASH, DAVID R. NALIN, ROGER ROCHAT, L. BARTH RELLER, ZAHEDUL A. HAQUE, AND A. S. M. MIZANUR RAHMAN
Pakistan-SEATO Cholera Research Laboratory,‡ Dacca, East Pakistan, and National Communicable Disease Center, Atlanta, Georgia 30333

ABSTRACT: A clinical trial in a field hospital in rural East Pakistan of an orally administered solution used in conjunction with intravenous fluid for the treatment of cholera in adults has demonstrated the efficacy of oral therapy. After initial intravenous rehydration, fluid balance in actively purging patients with cholera was adequately maintained in most patients, by the administration of an oral solution of drinking water containing sodium chloride, potassium citrate, sodium bicarbonate, and dextrose. It was found that 135 patients with cholera who received oral maintenance therapy required 70% less intravenous fluid than a similar group of 135 treated at the same rural treatment center in a previous epidemic. This treatment regimen has now become routine at our field hospital.

(Accepted 12 January 1970)

The reported mortality of untreated cholera in various epidemics has been 40 to 80%. The modern treatment of cholera, which has been reviewed recently,[1] has cut the mortality rate to less than 1%; however, this therapy is dependent on ample supplies of intravenous solution. If effective antibiotics are available, an average of 10 liters per patient is required to replace the water and electrolyte losses during the course of the disease.[2,3] This makes the cost prohibitive in many rural areas where cholera occurs today.

The possibility of treating cholera with an oral solution was first indicated by balance studies of cholera patients in 1962.[4] It was found that the patient with cholera could absorb water, potassium, and sodium bicarbonate, but sodium and chloride were absorbed only when dextrose was added to the solution. The increased sodium absorption in the presence of dextrose has been shown in other studies of cholera,[5-7] and the same effect has been noted in experimental animals[8] and in normal man.[9,10] These studies have led to the development of an effective oral therapy for the treatment of cholera.[11]

This paper reports the application of the oral therapy to patients with cholera in a large-scale clinical trial in rural East Pakistan.

MATERIALS AND METHODS

The Pakistan-SEATO Cholera Research Laboratory maintains a treatment center for diarrheal diseases in a vaccine trial area in rural East Pakistan. The center is equipped with cholera cots, stool buckets, intravenous fluids, and scales for weighing patients. The staff consists of three physicians, six nurses, three ward-boys, and two female attendants. Bacterial diagnosis of cholera was the only laboratory procedure available.

Patients brought to the treatment center were examined and either admitted if severely dehydrated, or observed as outpatients if less severely ill. All patients admitted during a 30-day period were included in this trial if they were over 15 years of age or weighed more than 20 kg and had no other obvious, underlying disease. The diag-

* Please address requests for reprints to Director, Pakistan-SEATO Cholera Research Laboratory, Institute of Public Health, G.P.O. Box 128, Mohakhali, Dacca-12, East Pakistan.

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- Treatment center
- Stabilized on IV
- Then maintained on oral fluids
- Next trial (from Calcutta group) using ORT in refugee camp during war.

D. MAHALANABIS, R. B. SACK, B. JACOBS, A. MONDAL AND J. THOMAS

Use of an Oral Glucose-Electrolyte Solution in the Treatment of Paediatric Cholera—A controlled study

by D. MAHALANABIS, M.B.B.S., R. B. SACK, M.D., SC.D., B. JACOBS, M.B.B.S., A. MONDAL, M.B., CH.B., AND J. THOMAS, M.A.

From the Johns Hopkins International Centre for Medical Research and Training, and the Infectious Disease Hospital, Calcutta, India

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Abstract

A controlled trial of oral glucose-electrolyte therapy in children with cholera was performed in Calcutta, India. Fifteen children were treated by standard intravenous methods and 17 by a combination of intravenous and oral glucose-electrolyte fluids. Oral fluid replacement was found to be effective maintenance therapy in spite of large stool losses (up to 9·5 ml. per kg./hr.). Persistent vomiting was the main problem encountered during oral therapy, but this occurred almost exclusively in children with the most severe diarrhoea whose initial deficits were only partially corrected intravenously. Oral fluid replacement was shown to be a useful additional form of therapy in paediatric cholera, although it was uniformly successful only when initial deficits had been completely corrected intravenously.

Oral glucose-electrolyte solutions have been used successfully to treat cholera in adults, both in hospital and in field conditions[1–4]. The main advantages of oral therapy are a marked reduction in the need for intravenous fluids to the extent of 80 per cent in severe cases[1], and thereby a reduced need for trained personnel to administer therapy under difficult field conditions.

Lack of intravenous fluid and lack of trained personnel are major handicaps to successful cholera therapy in many parts of the world. The use of oral hydration in children would be an important addition to the treatment of paediatric cholera under such circumstances. Studies on the efficacy of oral replacement in paediatric cholera, however, are few[5,6] and as yet no controlled study in children has been reported. Intraperitoneal fluids have been shown by us in previous studies[7] to be satisfactory therapy for most pediatric patients. Oral therapy, however, would further obviate the need for needle punctures and restraints, and sterile pyrogen-free fluids.

This study was undertaken (1) to evaluate the use of an oral glucose-electrolyte solution in replacing part of the initial fluid deficit and virtually all of the subsequent stool losses, and (2) to define the practical problems involved in carrying out such treatment in infants and children with cholera.

Materials and Methods

Patients

The study was conducted in Calcutta during the "cholera season", April through July, 1970. Male children age six years and under, with a history of watery diarrhoea of less than 24 hours' duration, with no history of antibiotic medication, and presenting with dehydration estimated by clinical assessment to be approximately 10 per cent of body weight were admitted to the study. Each child was then randomly assigned to either a control or oral therapy group. All studies were performed on metabolic beds for accurate stool and urine collections.

The control group was initially hydrated intravenously (IV) with a hypotonic electrolyte solution in 5 per cent dextrose (Na^+ 106, Cl^- 74, and HCO^-_3, 32 mEq./litre)[8], 100 ml./kg. body weight given over the first 8 hours. The same solution was used to replace, on a volume-for-volume basis, all stool losses occurring after admission. To meet the obligatory water needs, 5 per cent glucose water was given *ad libitum* by mouth.

Children in the oral therapy group were initially partially rehydrated with IV Ringer's lactate solution, 50 ml./kg. body weight, over a 3-hour period, at which time the IV was discontinued and oral glucose-electrolyte (GE) solution started (Group A) to complete the initial calculated deficit

Acknowledgements

We thank Dr. P. M. Manji, Superintendent of the Infectious Diseases Hospital, Calcutta, for making

- Trial in children in 1970 in Calcutta
- IV group as control
- Intervention group initially rehydrated with iv solution, then maintained on oral rehydration
- If oral rehydration failed, iv rehydration resumed