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POSITION PAPER ON THE CONTROL AND TREATMENT OF DIARRHOEAL DISEASE 1982

Diarrhoeal illness is one of the most important causes of morbidity and mortality in developing countries. A rapid increase in interest in this subject have resulted in an increasing volume of literature both formal and informal. To keep abreast, it is necessary to know how to procure information. This is particularly difficult when working in developing countries. For this reason ICDDR,B is establishing a diarrhoea information service and documentation centre (DISC) which will be able to rapidly provide not only bibliographic information and abstracts but also full copies of papers when required.

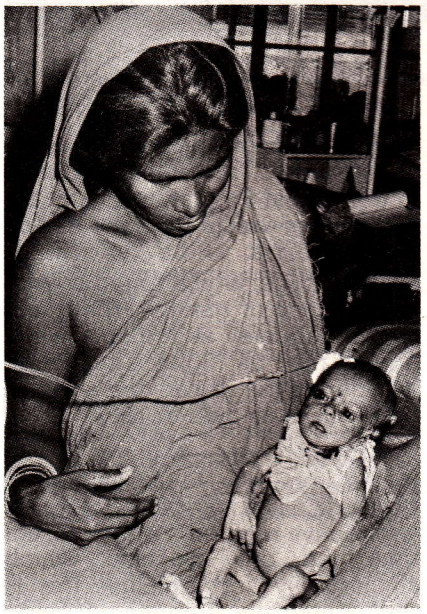
ESTABLISHED KNOWLEDGE

Causative Agents

The etiology of almost all cases of acute watery diarrhoea can now be confirmed if appropriate technology is applied. Table 1 lists many of these agents. This cannot be said for the general group of diseases listed under the term 'dysentery', particularly in milder cases or when acute diarrhoea continues beyond a week to ten days.

Pathogenesis of Diarrhoea

There is rather complete knowledge about the mechanisms of action of cholera and related enterotoxin such as *E. coli* heat labile and heat stable enterotoxins. These operate through the second messenger systems (cyclic nucleide systems) and induce an aberrant, excessive response of a normal function of the intestinal tract. Knowledge is much less complete with respect to the factors which determine adhesion of bacteria or viruses to gut epithelium or to the process of invasion by salmonella, shigella and related species.



Diarrhoeal illness is one of the most important causes of morbidity and mortality in the developing countries; children often caught up in the vicious cycle of diarrhoea and malnutrition are the worst sufferers.

Treatment

The treatment of diarrhoeal diseases has been greatly simplified since 1970. In all diarrhoeal illnesses the replacement of salts and water is fundamental, now this can be given by mouth. The currently World Health Organization recommended composition has been generally accepted as safe for all ages. There is some debate whether the salt content of the WHO solution may be too high in mild diarrhoea and this remains to be settled by future research. The basic principles are extremely simple i.e. to replace in quantity the total volume lost from the body in the diarrhoeal stool and to approximate the composition of this loss replacing the specific constituents of the diarrhoeal stool. For acute watery diarrhoea due to enterotoxin producing bacteria such as *Vibrio cholerae* or *E. coli* intravenous and/or oral rehydration is sufficient to cure the patient, however, in cholera since the volume loss may be prolonged an antibiotic may be used to shorten the disease and reduce the total volume lost. Choice of an effective antibiotic is now difficult due to multiple antibiotic resistant strains of *Vibrio cholerae.*

The treatment for viral diarrhoea is only replacement as there are no effective antiviral agents.

The treatment for invasive diarrhoeas in the dysentery group include antibiotics, the selection of antibiotics depends on the resistance of the organism in the area where the treatment is given. This

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cannot be predicted as multiple antibiotic resistance varies from area to area and one time of the year to another. Thus for adequate treatment of shigella and salmonella it is necessary to know what the pattern of antibiotic resistance is in the bacteria causing disease in the particular community at the particular time.

Finally, for diarrhoea caused by *E. histolytica* or giardia the standard recommended treatments are applicable and useful.

Many of the diarrhoeal diseases are water borne, lack of knowledge on proper sanitation, importance of using safe water and simple hygeinic practices result in wide incidences of the disease in the rural areas.

Prevention and Control

Though the control of diarrhoeal diseases may seem extremely simple, in fact it is very complex and difficult. In order to prevent diarrhoeal diseases it is only necessary to make sure that none of viruses, bacteria or parasites which can cause diarrhoeal disease are taken into the mouth with food, water or by contact. In a country such as Bangladesh the approach suggested is to improve sanitation through water purification and disposal of human wastes. These are thwarted by the extraordinary flood plain on which the country is situated. It is doubtful if even with the best modern technology, a system for guaranteed germ free water and satisfactory separation of human faeces could be achieved. Some very simple measures however are highly successful in controlling the spread of diarrhoeal disease. These are principally measures which can be implemented in households independent of the contamination of the surrounding environment. The most effective method is simply washing hands with soap and water before eating and after defaecating. The only sure way of water purification at present in rural Bangladesh is boiling. This however involves fuel which is dear and very scarce. The next is use of protected tubewells exclusively, without any use of river, ditch or tank water.

Certain natural phenomena that existed in the past could be used, for instance, certain tanks or ponds are more or less protected from human wastes; if a system was devised by community action for fully protecting tanks from human waste this might provide a source of safe water. From the experience in the Teknaf Project most successful human waste disposal device so far seems to be the water-sealed latrine, which together with the practice of hand washing and use of tubewell as the sole water source may be highly effective in preventing the spread of diarrhoea. This will be known in 1982.

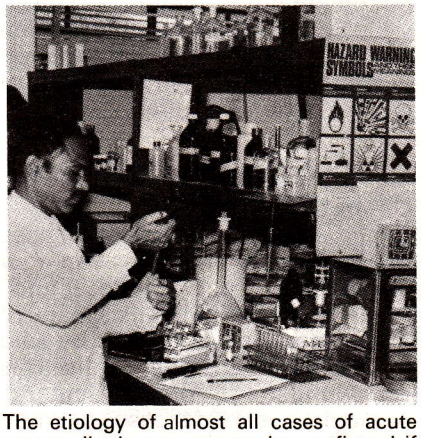
Artificial increase in an individual's immunity to specific diarrhoeal diseases is another potentially effective method. At the present time the only vaccine which successfully accomplishes this is the genetically engineered living strain of Salmonella typhi of the Swiss Serum Institute. This is a highly successful living oral vaccine, a prototype of the kind of vaccine which may also be applied successfully in the future to such diseases as cholera, enterotoxigenic *E. coli,* shigellosis, etc. It is also hoped that an effective vaccine against rotavirus and other viruses causing diarrhoea in young children can be evolved over the next decade. The use of antibiotics is expensive and not likely to succeed due to the problem of resistance.

SPECULATION ON FUTURE DEVELOPMENTS IN CONTROL AND TREATMENT OF DIARRHOEAL DISEASE

It is expected that over the next decade more will be discovered about the currently known agents which cause diarrhoea. New agents will be found which will allow 100% identification of the causes of every instance of diarrhoeal disease. It is likely that more enterotoxigenic bacteria will be discovered and that possibly some new enterotoxins with different mechanisms of action will also be identified in addition to adenylate cyclase activating toxins.

The mechanism of action of different causative agents will be better understood. Receptor sites for adhesion of microbes to intestinal epithelium will be discovered and characterized. It is also expected that the receptors for specific toxins will be fully defined.

Treatment is likely to be simplified further. Most probably starches of all varieties will replace sugars in oral rehydration solutions. This will become a method of home treatment for which no medical personnel will be required. The main process of implementation will be one of education and marketing. Drugs will be developed, which will limit the loss of fluid to such an extent that virtually no intravenous hydration will be required. Agents will also be discovered that will block receptors therefore reducing the severity of the disease or even preventing



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disease. It is hoped that agents will be discovered which can block the spread of plasmids from one bacteria to another or cause plasmids to be lost by pathogenic bacteria such that they can be killed by available antibiotics.

Innovative methods of water purification and waste disposal or recycling will eventually be evolved particularly through space-age technology concerned with the task of recycline human wastes in closed environments such as space stations. In the meantime, simple health measures such as hand washing and adequate separation of food, water and human wastes must take place by currently known technology.

We can anticipate with the advent of genetic engineering the rapid expanse in vaccine technology. With the advent of new vaccines providing protection against the agents which now cause diarrhoeal disease. In addition we may see the advent of some innovative agents which will block receptors, preventing bacteria and their noxious agents from exerting any effect on the target organs. This is an area of embryonic research efforts which I expect in future will replace a number of current strategies for combating infectious diseases. The best example of this is the use of the B Subunit of cholera toxin to block gut receptors for this toxin, thereby preventing the disease and generating immunity.

There will of course be other measures developed from basic research now carried out on diarrhoeal diseases. Significant advances can be made to reduce morbidity and mortality from these diseases to an insignificant level.

TABLE I
PREDOMINANT CAUSES OF DIARRHOEA

Chemicals	Muscarinic alkaloids
	Arsenic
Hormones	Gastrin
	VIP
	Prostaglandins
Viruses	Rotavirus
	Reoviruses
	Adenoviruses
Bacteria	Vibrios
	Campylobacter
	E. Coli
	Shigellae
	Salmonellae
	Clostridia
	Staphylococci
Protozoae	E. Histolytica
	Giardia
Helminths	Strongyloides
Other	Fungi
	Algae

PUBLICATIONS

Demographic Surveillance System-Matlab. Volume Seven. Vital Events and Migration—1978/*Mridul K Chowdhury, Stan Becker, Abdur Razzaque, A M Sarder, Kashem Shaikh, Lincoln C. Chen.* May1981. *(Scientific Report No.* 47*)*

This is the seventh volume in a series of scientific reports produced by the International Centre for Diarrhoeal Disease Research, Bangladesh (former Cholera Research Laboratory) presenting basic tabulations from the registration of births, deaths, marriages, divorces and migrations in the Demographic Surveillance System of the Matlab Field Station. The present volume presents results for the calendar year 1978 for the reduced surveillance area.

Determinants of Natural Fertility Study. Volume One. Methods and Descriptive Tables for the Prospective Study 1975-1978/ *A K M Alauddin Chowdhury, Stan Becker.* May1981. *(Scientific Report No.* 48*)*

The reproductive events of approximately 2000 women were recorded prospectively from 1975 to 1978. Checks of data quality revealed quite accurate data. In addition the population studied was similar to the general population of Matlab, Comilla district and Bangladesh as a whole with respect to age, sex and marital status distributions. The study women were largely muslims and had a low level of education.

The high fertility of the population was revealed by both the age-parity distribution and the rates of birth events in the prospective period. A mere three percent of the study women reported any practice of contraception.

Over sixty percent the women were breastfeeding at any point in time during the study. The long duration of breastfeeding as documented previously in this population, explains the 15-month median length of postpartum amenorrhoea found. The mean delay from resumption of menstruation to conception was five months.

With regard to nutritional and morbidity status of the women, reported illness was quite low in the population.

The anthropometric measurements revealed very few differences between women according to reproductive status. Differences were apparent between age groups, however, with older women having lower weight, height and arm circumference than younger women.

Efficacy of Short Course Antibiotic Prophylaxis in Controlling Cholera in Contacts During Epidemic/*Moslemuddin Khan.* June1981. *(Scientific Report No.* 49*)*

During an epidemic of cholera, vaccination has limited applicability in controlling its spread. It has been seen that one out of every 5-10 *V. cholerae* infected people develop diarrhoea severe enough to require hospital treatment. Most health authorities are concerned with this severely ill group in whom majority of deaths occur.

During the cholera epidemic of 1975 in Dacca two doses of tetracycline were administered to all family contacts of index cases. Contacts in the control group of cholera cases did not receive the drug. The families were re-visited after 10-12 days and history of any diarrhoea and hospitalization was obtained.

It was found that the subsequent diarrhoea or cholera cases occurring among the cholera contacts within 10-12 days were not different between the treated (13.5%) and the untreated (14.4%) groups. The occurrence of severe cases requiring hospitalization was however, significantly reduced in the treated group (8.0% to 4.5%).

In view of the emergence of *V. cholerae* strains resistant to tetracycline, antibiotic sensitivity testing of epidemic strains would be needed before use of tetracycline for protecting cholera contacts as an immediate control measure.

DIRECT NUTRIENT LOSS IN DIARRHOEA

The loss of protein in the gut occurs in many diseases, in diarrhoea it has been established beyond doubt. Using the standard Kjeldahl method protein loss can be estimated from the stool; but there are several drawbacks. Normally after protein is lost in the gut, it is degraded or reabsorbed later. When the loss in the gastrointestinal tract exceeds the capacity of the gut to reabsorb it is manifested in the stool. From the stool examination only the final loss of protein can be detected, it is also difficult to determine the exact site of the loss. Radioisotopes such as I^{131} albumin, I^{131} polyvinylpyrolidone (PVP),^{59} Fe-dextran, and ^{51}Cr, are used to measure protein loss,but these methods are difficult, time consuming and costly. This study examines the new methodology using α_1-antitrypsin for detecting and measuring the loss of protein in the stool. This method is also used to quantitate the loss.

α_1-antitrypsin is an inhibitor of proteolytic enzymes, and is present in measurable quantities in the serum. Once secreted in the gut, it is resistant to further breakdown, the quantity of the α_1-antitrypsin can be calculated by radial immunodiffusion technique using hyperimmune sera against purified α_1-antitrypsin. The quantity of the protein lost in the gut can be calculated from the ratio of the concentration of the α_1-antitrypsin in the faeces and the serum. In all healthy subjects this ratio has been found to be less than 1, this is also true for disease without protein-losing enteropathy. The amount of protein lost in the gut can be estimated from the total amount of stool passed.

RESULTS

In an earlier study[1] the ratio of α_1-antitrypsin has been found to be very high in patients with symptoms of dysentery or pus/red blood cells in the stool, excessive protein-losing enteropathy was demonstrated in 67 percent patients with enterotoxigenic *E. coli* (ETEC) and 40 percent with rotavirus.

Protein loss was seen in 88 percent patients with WBC & RBC, 63 percent with only WBC in the stool. Patients with shigellosis lost an equivalent of about 100 ml to 500 ml of serum in the faeces in 24 hours. Antibiotic therapy helped to reduce this loss.

DISCUSSION

A number of factors possibly contribute to the quick development of hypoproteinaemia in dysentery patients. Serum protein is lost through the ulcerated and inflamed colonic mucosa; circulating endotoxemia, which is a frequent feature in shigellosis, may interfere with the normal function of the liver thereby interrupting the synthesis of the plasma protein, mainly albumin; food intake is reduced after an attack of diarrhoea; inflammatory process in the body also increases breakdown of body protein through catabolism.

Rotavirus, which is perhaps the main cause of diarrhoea in the weaning period **i.e.** between the ages six months to two years, damages patches of mucosa in the upper intestine. In rotavirus diarrhoeas, protein is lost in the gut not only through the exudation in the intestine, but also perhaps due to shedding of the mucosal epithelium. Protein-losing enteropathy is a major problem in rotavirus diarrhoea. It has been seen that it takes days, and sometimes weeks to recover the full absorptive capacity of the intestine after rotavirus diarrhoea.

THE MECHANISM

The phenomena of protein loss in diarrhoeas caused by enterotoxigenic *E. coli* bacteria is not yet fully understood. The heat-labile toxin (LT) behaves like the cholera toxin, **i.e.** insignificant protein loss in the stool, the heat-stable toxin's (ST) activities in the small intestine is not clear, does it cause epithelial damage as seen in rotavirus? What would be the explanation for the excessive loss of protein in the stool in about 67 percent of the cases with diarrhoea caused by ETEC. Since the large majority of the ETEC strains in Bangladesh produce ST or ST/LT toxins, the loss of significant amount of protein in case of diarrhoea caused by ETEC may be due to the presence of ST. In a study conducted by Dr. Molla and others in ICDDR,B[2] it has been found that the absorbtive capacity of the intestine does not return to normal even after two-weeks of recovery in diarrhoea caused by ETEC.

CONCLUSION

α_1-antitrypsin has been found to be a simple and useful quantitative marker for estimating the loss of protein into the gut in diarrhoeal diseases. The method also provides a reasonably satisfactory answer to some of the theoretical objections raised in carrying out studies involving estimation of protein loss. α_1-antitrypsin seems to offer some theoretical advantages over the time honoured radio-isotope method.

1 Wahed MA, Rahaman MM, Gilman RH *et al.* Protein-losing enteropathy in diarrhoea: application of α_1-antitrypsin assay. Dacca, International Centre for Dirrhoeal Disease Research, Bangladesh, 1981. (Working paper no. 22)

2 Molla A, Molla AM, Sarker SA, Khatoon M, Rahaman MM. Effects of diarrhoea on absorption of macronutrients during acute stage and after recovery. Dacca, International Centre for Diarrhoeal Disease Research, Bangladesh, 1981. (Working paper no. 19)

This paper was jointly authored by Dr. Mujibur Rahaman and Mr. M A Wahed and presented at the workshop on INTERACTIONS OF DIARRHOEA AND MALNUTRITION PATHOPHYSIOLOGY, EPIDEMIOLOGY AND INTERVENTIONS held in Bellagio, Italy, from 11-15 May, 1981. The workshop was sponsored jointly by
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