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Epidemiology of Cholera in India and its Treatment and Control

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Epidemiology

Brief History

Cholera has been endemic in Ganges and Brahmaputra deltas of eastern India and Bangladesh since the beginning of recorded history. Epidemics from this area have spread almost every year during fairs and festivals, flood and famine, wars and other human catastrophes and killed thousands of people. This Asian pestilence 'Cholera Asiatica' moved out of its homeland in 1817 and spread to Europe and America in a pandemic form causing widespread death and devastation. The world witnessed six such pandemics upto 1923 and subsequently it was confined to its original homeland. Since cholera was not a notifiable disease in earlier years, there is hardly any reliable data available regarding the incidence of the disease in India. However, according to available statistics, cholera accounted for 793743 deaths in 1900[1] but a declining trend in cholera deaths was noticed over the decades from 1900 to 1980.

Due to partial improvement of water supply and sanitation the incidence of cholera declined steadily and by the 1960s many scientists in the field felt that cholera would die a natural death. But they were proved to be wrong as a focus of origin of the current 7th pandemic spread due to *ElTor* cholera had already appeared by then in the Celebes island of Indonesia. In 1961, this new variety of cholera vibrio, haemolytic *ElTor*, started its march towards Philippines and Hong Kong (1962), Burma and Bangladesh (1963), India (1964), Pakistan, Afghanistan, Iran, Iraq, south of USSR (1965–66) and finally to Europe and Africa (1970). It has now established innumerable endemic foci in over 80 developing countries in Asia and Africa but has not taken hold in Japan, USA, France, Britain etc., obviously because of the prevalent high standard of sanitation and personal hygiene in the latter countries. A declining trend in cholera admission in the Infectious Diseases Hospital, Calcutta, has recently been reported over a period of 1982–88 (personal communication). Only time will tell whether this signifies the beginning of the end of the 7th Pandemic. However, India still contributed 10.4% (5026) of the total of 48403 cholera cases reported all over the world during 1989[2].

Change Over to ElTor Infection

Soon after its introduction in India, cholera *ElTor* spread to all parts of the country and by 1966, the age old classical cholera vibrio was totally replaced[3]. This total replacement of a pathogen in such a short time is still an epidemiological curiosity. The classical *V. cholerae* was reintroduced in West Bengal (India) in 1970–71 by the Bangladeshi refugees but for reasons not very clear, did not get its foothold[4]. However, occasional isolations of classical *V. cholerae* strains were reported from Calcutta, Assam and Orissa[5].

Special Epidemiological Features

There is a marked epidemiological difference between *ElTor* and classical cholera[6]. The number of endemic foci have been greatly increased and most of the city slums have been reporting high incidence of cholera every year. This endemicity is maintained by a cycle of transmission from man to man through their micro-environment[7]. A large number of healthy

carriers in the endemic areas facilitate the maintenance of *ElTor* infection in the community. The rates of severe cases to mild or inapparent infections has been shown to be about 1 : 5 to 1 : 10 for classical cholera and about 1 : 25 to 1 : 100 for *ElTor* cholera[8]. Studies carried out during 1966–67 have shown that 1.5 percent of the slumdwellers in Calcutta were healthy cholera carriers[7], without any known contact with a cholera patient. The above study also demonstrated that cholera carriers could act as reservoirs of infection in between two cholera seasons. The household contacts of cholera patients showed a higher (20.0%) incidence of carriers[9].

Cholera has a characteristic *seasonal pattern*. In northern India, cholera peaks during the hot dry months of May to June, whereas in southern India its incidence is greatest during the colder months of December and January; in Bangladesh it follows the monsoon rains and in Philippines it is right during the rainy season. In Calcutta, the original seasonality of May–June has dramatically changed to autumn since 1976[10]. The cause of this variation in seasonality is unknown.

In highly endemic areas children are highly *susceptible* to this disease. The infection rate is low below 2 years of age, maximal at 2–4 years and then falls steadily with increasing age. In one study conducted in Calcutta during 1975–77 the incidence of cholera was found to be three times more in those aged below 5 years as compared to older age group[11]. By early adulthood, individuals have been exposed to the organisms many times and have acquired an effective immunity. Secondary cases are rare within households. In a newly invaded area, however, the disease affects adults more often than children, because of increased risk of exposure to infection due to greater mobility. However, there is no difference in susceptibility so far as sex is concerned. Cholera is usually a disease of the lower socio-economic groups living in slums with poor sanitary conditions[12]. There are no recognised nutritional factors that predispose to cholera infection[13]. However, gastric acidity has been shown to play a definite protective role against cholera[14].

Humans are the only known natural *reservoir* of cholera. An acute case of cholera usually excretes 10^6 to 10^8 vibrios/ml in faeces, which contaminates its immediate environment. Asymptomatic and convalescent carriers also may contaminate the environment. *V. cholerae* 01 probably depends on the human intestinal tract as its primary multiplication site, but the possibility of an extra-human reservoir cannot be ruled out. Since 1977, *ElTor* Inaba vibrios have been isolated repeatedly from 5 free-flowing rivers in Australia without known human contamination.

Transmission

Spread of cholera infection mainly occurs through consumption of contaminated water and food. In a study conducted in a Calcutta slum, a highly endemic area, it was shown that contamination of water and food often takes place by the fingers of cholera carriers[15]. Contamination of underground water sources and damaged pipe lines often results in explosive outbreaks of cholera, especially in urban settings, where water logging aggravates the situation further as was seen in Delhi and Ahmedabad[16] in 1988. In urban agglomerations low lying areas usually get water-logged due to improper drainage facilities. This accumulated water gets easily contaminated due to indiscriminate defaecation or overflow of the clogged sewerage system. Leaking water pipes or shallow tubewells without proper superstructures thus get infected, leading to explosive epidemics.

In endemic areas, however, it is more common to find a protracted pattern of outbreak in which a few cases occur per day or week for a period of several weeks and then decline slowly. In these outbreaks, the mode of transmission may reflect person to person spread in addition to contaminated food and water.

Treatment

There has been a tremendous development in our knowledge of pathophysiology and treatment of cholera and the introduction of oral rehydration therapy (ORT) has so much simplified the treatment that now most cases of cholera can be treated at the village home even by uneducated mothers[17].

Pathophysiology

After ingestion of *Vibrio cholerae*, the organisms multiply in the small intestine and produce a potent enterotoxin. The enterotoxin binds to the G_{M1} ganglioside of the epithelial cells of the small intestine and stimulates the adenylate cyclase which in turn causes an increase in intracellular cyclic AMP. As a result, there is outpouring of huge amounts of isotonic fluid into the bowel lumen and when this small intestinal secretion exceeds the absorptive capacity of the colon, watery diarrhoea starts. This loss of fluid and electrolytes from the body leads to dehydration which is the main cause of death in cholera. If the fluid loss can be replenished adequately in proper time, virtually the life of all cholera patients can be saved.

Intravenous Fluid Therapy

Although intravenous administration of a saline solution was first attempted in Russia and Scotland in the early 1830s, it was Sir Leonardo Roger who introduced intravenous hypertonic saline in Calcutta in the 1890s and thereby reduced the mortality of hospitalised cholera cases from 61% to 33%[18]. Later on further improvement of the intravenous solution was made by Andrew[19] in 1909 by adding bicarbonate and in the 1940s by Daniel Darrow[20] and colleagues who added potassium to the saline. Subsequently hypertonic saline was largely replaced by isotonic saline which resulted in a dramatic reduction of the death rate amongst hospitalised cholera cases to less than 1%[21].

Development of Oral Rehydration Therapy

However, the I.V. method of treatment is beyond the reach of the vast majority of the people living in the rural community as this therapy can only be given in a hospital setting by trained personnel. Therefore, attempts were made to develop a simplified form of therapy, culminating in the development of oral rehydration therapy.

Two important early observations which formed the basis of this epoch making discovery need to be mentioned. A group of physiologists[22-25] observed that glucose enhances the absorption of sodium and water across the intestinal brush border membrane of experimental animals. The second observation was that there are no morphologic changes in the gut epithelium of cholera patients[26]. Taking a lead from the above observations, Captain Phillips of the U.S. Army in 1964 first successfully tried oral glucose-saline in cholera patients[27]. Subsequently, scientists working at the Cholera Research Laboratory, Dhaka and the Infectious Diseases Hospital, Calcutta, largely contributed to the development of modern oral rehydration salt (ORS) solution. The efficacy of standard ORS was first demonstrated by Pierce *et al*[28] and others[29-31]. However, it was observed that ORS was not effective in children because of excessive vomiting. Therefore, no serious attempts were made for its routine use in the hospitals. Then a team of workers from the Cholera Research Centre, Calcutta, in 1974 demonstrated, for the first time, that if ORS is given in small quantities and at regular intervals, vomiting can be avoided and thus ORS was shown to be effective even in 92% of children with diarrhoea including cholera[32]. Encouraged by the results of the above study, the Infectious Diseases Hospital, Calcutta, became the first hospital in the world to switch over from traditional intravenous therapy to ORT[33] and thus saved a large sum of money due to reduction in the use of I.V. fluids. Soon this safe and simple method of treatment was accepted by the doctors, nurses and the patients[34].

Types of Rehydration Fluids with Dosage

The treatment of cholera is essentially replacement of gastro-intestinal losses of fluid and electrolytes. This should be done by oral or intravenous routes depending upon the degree of dehydration. Most cases of cholera with mild and moderate degrees of dehydration can be successfully rehydrated with oral rehydration salt (ORS) solution alone. The WHO recommended ORS contains Glucose (20g), sodium chloride (3.5g), Trisodium citrate, dihydrate (2.9g) or sodium bicarbonate (2.5g) and potassium chloride (1.5g) dissolved in one litre of drinking water. ORS should be given with a spoon or cup at 50–100 ml/kg within 4 hours and maintenance should be done with ORS at 100 ml/kg/d till diarrhoea stops. However, cases of cholera with severe dehydration require prompt administration of intravenous fluids till a strong radial pulse is palpable. Ringer's Lactate solution is the best commercially available fluid for intravenous infusion. Older children and adults are given 100 ml/kg of Ringer's Lactate within 4 hours, while infants require 70 ml/kg of the fluid within 3 hours. Even in severe cholera after correction of initial dehydration with Ringer's Lactate, maintenance may be done with ORS except in a few instances where due to continuing severe purging intravenous infusion may have to be given again.

Antibiotics in Cholera

Although virtually all cholera cases can be managed successfully with fluid therapy alone, a marked reduction of stool output, duration of diarrhoea and vibrio excretion in stool may be achieved in severely dehydrated cases of cholera by antibiotic therapy as an adjunct to fluid replacement. The drug of choice is oral tetracycline[35] 500mg 6 hourly for 48 hours; furazolidone[36] 5mg/kg/d in 4 divided doses is of value, but appears to be less effective than tetracycline. However, in view of the reported emergence of tetracycline resistant strains of *V. cholerae* in some areas, doxycycline[37] and norfloxacin[38], a 4-quinolone, have been found to be effective alternatives in such situations.

Role of Other Drugs

Anti-diarrhoeal agents and other drugs like kaolin, pectin, activated charcoal, opium and diphenoxylate with atropine, steroids, stimulants and antiemetics are not indicated in the treatment of cholera patients[39].

Feeding in Cholera Management

Maintenance of nutrition during an attack of cholera is also essential. Mothers should be instructed to continue uninterrupted breast feeding; formula-fed infants should be given half-strength initially. Adults need energy-rich, high potassium containing non-fibrous foods as soon as they desire.

Home Available Fluids in Cholera

Since many cases of cholera in the community are mild and have no dehydration, they may be managed by mothers at home with adequate amounts of home-available fluids (HAF), such as salt-sugar solution (Sarbat), butter milk (Lassi), rice water (Kanji), soup (Dal), green coconut water, breast milk and many similar fluids having carbohydrate and sodium chloride in them. These should be easily available at home, safe and acceptable to the community. A community based study on about 10,000 rural population near Calcutta has shown that about 50% of diarrhoeal children who were initially managed with HAF by mothers, did not require any further rehydration with ORS[40]

Control

Cholera control received prime individual attention till late seventies, when it was realised that cholera being one of the components of the entire spectrum of diarrhoeal diseases, needed only an integrated control approach under the diarrhoeal diseases control programme.

While planning the earlier cholera control activities, four principles were considered[41]. These were –

1. Isolation and treatment of cases mainly with the idea of preventing spread of infection.
2. Management of contacts of cases for preventing dissemination of infection.
3. Anti-cholera immunization.
4. Improvement of environmental sanitation.

When integrated with the diarrhoeal diseases control programme, though some of the above principles were retained, others were either modified or replaced. Attempts are made in the following sections to briefly discuss the various strategies of cholera control.

Isolation and Treatment of Patients

The above strategy was meant for early detection of cholera patients, their isolation and treatment with appropriate antibiotics to render them non-infectious. Though theoretically very sound, this was not considered feasible in developing countries because of poorly developed surveillance systems and lack of resources[42]. Moreover, the idea of rendering all bacteriologically proven cholera patients non-infectious by treating them with antibiotics in an endemic area has also been challenged by the observations of a Calcutta study[9]. The results showed that 34.8% of 23 cholera patients who though treated with antibiotics in the hospital, were re-excreting *V. cholerae* within 5–26 days of their leaving the hospital. A cholera patient during and after the period of convalescence is not usually considered an extra risk for an endemic community where the infection already exists.

However, early detection of diarrhoea cases including cholera and treating them with oral rehydration therapy (ORT) for prevention of dehydration and death, still remain the major strategy in the current diarrhoeal diseases control programme.

Management of Contacts of Cholera Patients

In *ElTor* cholera the healthy carriers are known to be responsible for spreading the infection within the community as well as across the country. The incidence of carrier is highest amongst contacts of cholera patients. Therefore, attempts were made to find an effective strategy for their control. Detection and isolation of all the carriers in the community was not considered a feasible proposition[43]. A number of chemoprophylaxis field trials were conducted in Calcutta and in Dhaka during the late sixties and early seventies. In the Dhaka trial tetracycline given for 5 days, either in single or divided doses, successfully brought down the incidence of carriers amongst contacts of cholera cases[44]. However, the drug required multiple administrations for a longer period which was considered inconvenient and impracticable for routine use. A similar trial conducted in Calcutta, but with two doses of tetracycline (1 gm daily) and for a period of three days, also succeeded in bringing down the number of vibrio excretors amongst contacts from the 2nd day onwards. How-

ever, soon after withdrawal of the drug, the number of carriers rose again to the original level[45]. Though the frequency of administration could be reduced in this study still six doses had to be administered which was not very practicable.

Controlled studies carried out in collaboration with WHO in Calcutta with single dose therapy of sulfadoxin[46] and doxycycline (300 mg)[47], showed that these were as effective as multiple doses of tetracycline. However, all the above Calcutta studies showed that the incidence of contact carriers went up within 3–5 days of stoppage of the drugs. It was, therefore, concluded that chemoprophylaxis has a very limited role in the control of cholera carriers in endemic areas. However, it is felt that it could still be used in a limited way in non-endemic areas or in closed communities like jails, hostels, ships etc. after detection of cholera infection.

Anti-cholera Immunization

Amongst the bacterial vaccines the cholera vaccine is one of the most extensively used prophylactic agents. Being the first bacterial vaccine to be introduced against a communicable disease, cholera vaccine has, however, been greatly overrated for its efficacy. This impression was generated on the basis of several earlier trials conducted without proper controls[48].

Several controlled field trials with the conventional cholera vaccines carried out in Calcutta, Bangladesh and Philippines during the sixties have yielded some valuable information. (a) The current vaccine offers partial protection of 40–50%; (b) duration of protection is only 3–6 months; (c) vaccination does not affect carrier state; (d) young children who are the main victims in endemic areas, are poorly protected; (e) it does not modify the severity of illness; (f) increasing the antigenic content of the vaccine as well as frequency of administration did not enhance the protection; (g) vaccines made of classical biotype strains are capable of protecting against *ElTor* biotype infection[49].

The search for a more potent cholera vaccine has subsequently led to the development of aluminium adjuvant vaccines and a whole cell/B-subunit vaccine. Two aluminium compound adsorbed vaccines, one with aluminium hydroxide and the other with aluminium phosphate, were given field trials during the early seventies. The former tried in Indonesia offered a protection of 88% for a period of 6 months and about 50% between 11 and 14 months in the under-5 year age group[50]. The latter vaccine (aluminium phosphate adsorbed) showed a protection of 91.7% for 18 months amongst the under-5 age group in Calcutta[11]. The whole-cell/B-subunit vaccine which was given a trial in Bangladesh recently, provided a protection of 85% in all ages during the first 4–6 months[51]. However, this higher protection did not last even for one year. This vaccine also afforded very little protection in the age group below 5 years.

The available information on the efficacy of different cholera vaccines, suggests a need for a cautious approach to their use. The validity of routine cholera vaccination as an alternative to well organised treatment facilities, has been questioned[49]. The cost-benefit analysis also puts it behind treatment and sanitational improvement. The requirement for cholera vaccinations during fairs and festivals like "Kumbh Melas" has been discontinued in the country since 1986 with no reported adverse effects.

However, it is felt that still there is scope for judicious use of cholera vaccines in the face of epidemics, in a selected population group with high risk, when existing environmental control measures are inadequate. This might help in protecting about 50% of the vaccinated population for a period of 3–6 months, by which time the epidemic is expected to be over.

Environmental Sanitation and Personal Hygiene

There is a general agreement over the point that improvement of environmental sanitation coupled with that of personal hygiene can effectively reduce or even eradicate cholera. Experiences during the current 7th pandemic of cholera have shown that high sanitational and personal hygiene standards have made certain countries non-receptive to cholera infection[52]. Though repeatedly introduced, the infection failed to establish a foothold in countries like U.K., France, Sweden, Australia and Japan[53].

The principles of control measure should include provision of sanitary excreta disposal, safe water supply, domestic and food hygiene, disinfection of infected materials etc. The improvement of environmental sanitation is considered economical in the long run[54]. However, deployment of a substantial amount of resources at the initial period still remains a major constraint in developing countries like India.

The improvement of both sanitational conditions and personal hygiene should go side by side in order to achieve the goal. Isolated implementation of one component is not likely to give the desired result. In a study on transmission of cholera infection in Calcutta slums, it was found that the infection was transmitted through tubewell or piped water and left over cooked food. In slums, safe drinking water is usually

stored unhygienically in open buckets and subsequently contaminated by dipping infected fingers while drawing water[15]. Similarly, stored cooked food was found to be contaminated in cholera infected houses. A subsequent intervention study designed to prevent contamination of drinking water by storing in "Sorai" revealed that the transmission of cholera infection amongst the contacts of cholera cases was significantly reduced[55]. This particular strategy of preventing contamination of stored water has now found a place amongst the WHO strategies for the prevention of diarrhoeal diseases[56].

It would, therefore, appear that appropriate training of health workers and education of mothers on various control measures hold the key to the success of programmes for cholera and diarrhoeal diseases control.

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