- In the time it takes to distribute and administer the drug and wait for the chemoprophylaxis to take effect, the infection has spread.
- The effect of the antibiotic lasts for only a few days.
- In order to avoid reinfection, the entire population of an area under surveillance must be treated at the same time and then kept isolated.
- People who are presumably infected but have no symptoms are often reluctant to take the treatment.

Mass chemoprophylaxis not only has failed to prevent the spread of cholera but has also diverted attention and taken up resources that could be used for more effective measures. In addition, in several of the countries it has contributed to the development of antibiotic resistance, thus depriving critically ill patients of a valuable form of treatment.

The *selective treatment* of family members who have shared food and lodging with a cholera patient can be useful. As a matter of fact, secondary cases are not very common in communities affected by El Tor cholera. In societies where intimate social relations and the exchange of food among families are common, it is difficult to determine who is a close contact. Most people who are infected with *V. cholerae* 01 El Tor have only mild cases of the disease, and as a result they and their close contacts escape detection and treatment.

When treatment is being given for preventive reasons, it is necessary to recommend the drug and corresponding dosage. Doxycycline is the drug of choice, since only one dose is needed.

Vaccination

The vaccines currently available do not help to control cholera for the following reasons:

- They are not sufficiently effective;
- It is often shown that they do not have the required potency;
- The immunity that they confer lasts for only 3 to 6 months;
- Vaccination does not reduce the rate of asymptomatic infection.

Even more important, vaccination produces a false sense of security not only for those who are vaccinated but also for health authorities, and more effective measures may fail to be applied. Moreover, vaccination campaigns divert resources, care, and personnel from more effective activities.

Vaccination campaigns for controlling cholera not only waste resources but can also introduce health hazards that are much more serious. When inoculation practices are not very safe, as is frequently the case in mass vaccination campaigns, they have been followed by cases of serum hepatitis, and in recent years the risk of HIV infection has become a serious threat to health.

In view of these limitations, the Twentieth-sixth World Health Assembly abolished the requirement under the International Health Regulations for a certificate of vaccination against cholera.

(*Source:* Health Situation and Trend Assessment Program, PAHO.)

Clinical Diagnosis and Treatment of Cholera Cases

Cholera is an acute bacterial enteric disease with sudden onset, profuse painless watery stools, occasional vomiting, rapid dehydration, acidosis and circulatory collapse.

Many cases of cholera are mild and cannot be distinguished clinically from other types of diarrhea; they can only be recognized from positive fecal cultures. These cases are epidemiologically important because the bacillus continues to circulate in the community.

Serious cholera usually has an abrupt onset, with voluminous stool, but it can also begin slowly, with mild diarrhea during the first 24-36 hours. Vomiting can be copious; it occurs in most patients and can be present before or after the onset of diarrhea. The peak fecal loss usually takes place during the first 24 hours. The stool have a *rice water* appearance, and the volume exceeds 1 liter per hour in adults and 8 to 10 ml/kg/hour in small children.

After the first 24 hours the rate of elimination declines. Diarrhea can end spontaneously in 1 to 6 days, and many patients improve without antibiotics if the electrolytes and water lost are adequately replaced. The total volume of feces during the course of the disease may be as much as 50% or more of bodyweight.

The metabolic disorders associated with cholera are caused by the rapid loss of water and electrolytes. This has clinical importance because of hypovolemia due to the loss of isotonic fluids, acidosis due to rapid loss of bicarbonate, and depletion of potassium.

Biochemical studies done before the initiation of treatment have revealed a high specific density of

plasma and a drop in arterial pH and serum bicarbonate. The plasma concentration of sodium is normal.

Although there is depletion of potassium, the serum concentration is usually normal. However, it can also be low. If the base deficit is corrected, it is not necessary to replace the deficit in potassium.

Glucose concentration is moderately elevated in adults, but small children may occasionally develop serious hypoglycemia. The vomiting and diarrhea that occur with cholera give an indication of how much isotonic fluid is lost, ranging over a period of 4 hours to 1 or 2 days.

The first symptom is thirst, which begins to occur when water loss reaches 20-30 ml/kg. A loss of 50-80 ml/kg causes weakness, lethargy, and signs of postural hypotension such as fainting or syncope with inability to remain standing. If the deficit goes beyond 80 ml/kg, the thirst becomes more intense and renal flow diminishes, resulting in oliguria followed by anuria.

There are muscle cramps and pains in the limbs, as well as distal cyanosis. The voice weakens, and some patients develop aphonia. If fluid loss exceeds 100-120 ml/kg, the disease is usually fatal.

The physical findings in cholera are also related to the fluid deficit. A deficit of 50 ml/kg causes only a reduction in skin turgor and moderate tachycardia. Additional signs of hypovolemia will develop quickly if the losses exceed 80 ml/kg to 100-120 ml/kg.

If the heart rate reaches 100 beats per minute, the radial pulse weakens and becomes undetectable. At the same time, diastolic pressure falls, breathing becomes more rapid, turgor decreases, the nails become cyanotic, the skin of the fingers begins to shrivel and give the appearance of *washerwoman's hands*, the eyes become sunken, and in very young children the anterior fontanelle is depressed.

The abdomen is soft, the rectus abdominus muscle can be spastic and give the impression of abdominal defense, and intestinal sounds are diminished.

Some adult patients become stuporous, although usually they are aware. Coma occurs in one-fourth of the critically dehydrated cases.

Diagnosis is confirmed by culturing *vibrio cholerae* of the serogroup 01 from feces. The *vibrio cholerae* serogroup 01 includes two biovans (biotypes) cholerae (classical) and El Tor, each of which includes organisms of Inaba and Ogawa serotypes. A similar enterotoxia is elaborated by these organisms so that the clinical pictures are similar. In any single epidemic, one particular type tends to be dormant. Presently the El Tor biotype is predominant. People are the only known reservoir.

The mode of transmission is primarily through ingestion of water contaminated with feces or vomitus of patients, or to a lesser extent, feces of carriers or ingestion of unrefrigerated food which has been contaminated by dirty water, feces, soiled hands, or perhaps flies.

The incubation period is usually 2 to 3 days and the period of communicability for the duration of the stool-positive stage, usually only a few days after recovery.

Susceptibility and resistance are variable; gastric achlorhydria increases risk of disease and breastfed infants are protected. Clinical cholera usually is confined to the lowest socio-economic groups. Even in severe epidemics, attack rates rarely exceed 2%. Infection results in a rise in agglutinating, vitriocidal, and antitoxic antibodies, and increased resistance to reinfection which lasts longer against the homologous serotype. In endemic areas, most persons acquire antibodies by early adulthood.

Treatment

Without treatment, the case-fatality rate due to serious cholera can reach 50%. With adequate treatment, mortality goes down to 1%.

Management of the disease focuses on replacing the fluids and electrolytes lost in feces and preventing serious dehydration.

Physiological Basis for Oral Rehydration Therapy (ORT)

Studies of intestinal absorption of fluid have clearly shown that during secretory diarrhea induced by enterotoxins some of the mechanisms of intestinal absorption are inhibited. However, the mechanism for absorbing glucose and other mediate carriers for the absorption of sodium remains intact, even in patients with serious cholera. Citrate (or bicarbonate) and potassium are absorbed separately from glucose. Moreover, the absorption of citrate (or bicarbonate) appears to increase the absorption of sodium and chlorine. Numerous clinical studies have shown conclusively that the loss of fluids and electrolytes in cases of acute diarrhea and cholera can be adequately replaced by mouth using glucose-electrolyte solutions when these ingredients are in optimum concentration. For the adequate absorption of orally administered electrolytes, the following conditions are necessary:

- The concentration of glucose should be 20-30 g (111-165 mmol/l) in order to achieve maximum absorption of sodium and water. A higher concentration can cause osmotic diarrhea because the unabsorbed glucose is fermented by the intestinal bacteria, resulting in osmotically active products that attract water to the intestine. A lower glucose concentration, on the other hand, can cause insufficient absorption of sodium and water.

- The nearer the concentration of sodium in the oral solution to the concentration of sodium in plasma, the faster and higher will be its net absorption.
- The ratio of sodium concentration to glucose concentration should be within an approximate range of 1:1 to 1:1.4.
- Potassium losses due to acute diarrhea are higher in children under 1 year of age and can be especially dangerous in undernourished children. A potassium concentration of 20 mmol/l is well tolerated and is sufficient to replacing the losses.
- A citrate concentration of 10 mmol/l, or a bicarbonate concentration of 30 mmol/l, is optimum for correcting the base deficit in cases of acidosis. Trisodium citrate, dihydrate, is used as the base instead of sodium bicarbonate, since the use of citrate salt yields a pharmaceutical product with a longer shelf life and has a good biological effect.

Oral Rehydration Therapy

Treatment should be started at once, without waiting for laboratory confirmation. The patients should immediately be given large amounts of liquid by mouth. The formula for oral rehydration salts (ORS) that has been successfully used for oral administration and has been recommended by the World Health Organization (WHO) is as follows (per liter of water):

	grams/l
Sodium chloride	3.5
Trisodium citrate* (dihydrate)	2.9
Potassium chloride	1.5
Glucose (anhydride)	20.0
	mmol/l
Sodium	90
Chlorine	80
Potassium	20
Citrate	10
Glucose	111

*Trisodium citrate can be substituted for sodium bicarbonate 2.5 g/l (which yields 30 mmol/l of bicarbonate).

Also, ORS packets already prepared for mixing can be added to 5 or 10 liters of water. These are prepared in hospital pharmacies where large amounts are consumed on a daily basis.

In dehydrated children there is a cumulative deficit of sodium. From studies of fluid and electrolyte balance carried out in cases of serious dehydration it has been estimated that this deficit is approximately 8-12 mmol of sodium/100 ml of water. Use of the ORS solution with 90 mmol of sodium/liter of water is adequate for rehydration in these cases. During the maintenance phase, when the ORS solution is used to replace steady losses, the risk of hypernatremia is not a problem because breast milk or cow's milk, water, or some other liquid is also being provided at the same time, depending on the age of the child, especially in children under 1 year of age. The ORS solution has been used in this way to treat millions of cases of diarrhea of various etiologies and in persons of all ages, and it has been shown to be safe and effective. When the ORS are given orally, it is not necessary to calculate the amount of liquid to be administered because the patient's thirst regulates the quantity that should be taken.

Rapid Endovenous Therapy

Patients with serious dehydration, hypovolemic shock (unconscious or in coma, weak or imperceptible pulse, capillary perfusion longer than 10 seconds), uncontrollable vomiting, fecal output in excess of intake capacity, inability to drink, or other serious complications usually require rapid intravenous therapy at first in order to achieve rehydration.

Children who are critically dehydrated and in shock should receive 30 ml/kg of Ringer's solution or a polyelectrolyte solution infused intravenously over a period of 1 hour, followed by 40 ml/kg for the next 2 hours. If the child has improved after this 3-hour treatment, then the ORS solution should be offered, and if the child tolerates it, he or she should be given 40 ml/kg for the next 3 hours and the intravenous therapy should be suspended.

Older children and adults should receive 110 ml/kg of Ringer's solution or a polyelectrolyte solution intravenously over a period of 3 to 4 hours, as rapidly as needed, and then switched to ORS if they have improved.

If there is no Ringer's solution available, it is possible to use a polyelectrolyte solution or salt composed of 3.5 g sodium chloride, 1.5 g potassium chloride, 4,082 g monosodium acetate (trihydrate), and 20.0 g dextrose. Simple glucose in water is ineffective and should not be used.

Progress with the rehydration therapy should be evaluated after 1 hour and then every 1 to 2 hours. It is important to pay attention to the number and volume of evacuations, the amount of vomiting, the presence of any signs of dehydration and any change in these, and whether or not adequate amounts of the rehydration solution (intravenous at first and oral thereafter) have been given.

The administration of ORS is begun as soon as is possible, especially when normal saline is used

intravenously to give the patient bicarbonate and potassium.

If the signs of dehydration get worse or remain unchanged, it is may be necessary to speed up administration of the solution being used.

The ORS can be administered via nasogastric tube to a patient who is *not* in shock but who cannot drink (due to fatigue, sleepiness, or other reasons) at a rate of 20 ml/kg per hour if there are personnel available who have been trained to do this. In children who are in shock, this procedure should be used only when it is not possible to give the solution intravenously.

Antibiotics

Antibiotics are very important in the treatment of cholera because they reduce the duration of diarrhea and the shedding of vibrios within 2 or 3 days.

Oral tetracycline is the antibiotic of choice: 500 mg should be given 4 times/day for 3 days. Doxycycline (300 mg), a form of long-acting tetracycline that is given only once, is preferred when it is available. Other alternatives, when the strains are resistant, are furazolidone and trimetroprim-sulfamethoxazole.

No other antidiarrheal, antiemetic, antispasmodic, cardiotonic, or corticosteroid products should be used.

Maintenance Therapy

After the initial fluid and electrolyte imbalance has been corrected and the signs of dehydration have disappeared, it is important to replace the abnormal losses due to diarrhea or vomiting and, in addition, to meet the normal daily requirement for liquids until the diarrhea ends. During maintenance therapy the ORS should be used after every evacuation (1/2 to 1 cup depending on the patient's age). Maintenance therapy also includes continued feeding throughout the course of the disease.

References

American Public Health Association. *Control of Communicable Diseases in Man.* Abram S. Benenson (editor), Washington, D.C., 15th edition, 1990.

(*Source*: Diarrheal Disease Control Program, PAHO.)

Laboratory Diagnosis of Cholera

A request for laboratory diagnosis is most important upon an initial suspicion of cholera based on the recognition of the typical clinical features and the appropriate epidemiologic setting. Because most bacterial diarrheas are self-limited, stool cultures are generally limited to cases with severe symptoms requiring hospitalization, persistent or recurrent and dysentery-like clinical presentation.

The clinical or public health laboratory is usually organized to process the specimens following an algorithm designed to identify a list of enteric pathogens prevalent in the Region. Most laboratories may not inoculate media suitable for the isolation of vibrios unless specifically requested to do so. *Vibrio cholerae* is not the only organism to cause watery diarrhea or *rice water* stools, although it produces the most severe disease. The approach adopted by a particular laboratory for the isolation of vibrios will depend on the frequency anticipated, and the cost-effectiveness of incorporating agar thiosulfate-citrate-bile salt-sucrose (TCBS) medium on a routine basis. Vibrios may be isolated in other plating media, but a particular search may need to identify *V. cholerae* or to screen for Gram negative bacilli, oxidase-positive colonies.

Stool specimens should be collected early in the disease and preferably within the first 24 hours of illness, and before the patient has received any antimicrobial agents. Rectal swabs are probably highly efficient in the acute phase of illness, but less satisfactory for convalescent patients or transiently infected asymptomatic persons. Specimens should be inoculated onto isolation plates with minimun delay. The viability of vibrio species is well maintained in an alkaline pH of *rice water* stool but is unpredictable in formed stools. Vibrios are very susceptible to desiccation; hence, specimens must not be allowed to dry. When there will be a delay in plating a culture, the rectal swabs or fecal material should be placed in the semisolid transport medium of Cary and Blair, which maintains the viability of vibrio cultures for up to 4 weeks. Buffered glycerol-saline, often used in enteric bacteriology, is an unsatisfactory transport medium even for short periods. In the absence of available suitable transport media, strips of blotting paper may be soaked in liquid stool and inserted into airtight plastic bags to prevent drying, and the organism will remain viable for up to 5 weeks. Specimens in transport medium may be shipped to the laboratory without refrigeration.