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CHOLERA

method of
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Cholera is an acute watery diarrhea caused by infection of the small intestine with *Vibrio cholerae*. Although sporadic cases of cholera have been reported in communities along the Gulf Coast of the United States as well as in other industrialized countries, the disease is most common in developing countries where fecal contamination of water supplies is widespread.

PATHOGENESIS

The port of entry for the vibrio is the mouth; spread occurs fecal-orally. Severity of disease depends on the inoculum ingested; 10^6 bacilli are more likely than a low inoculum to cause severe illness. Vibrios are acid sensitive, but once past the gastric barrier and in the small intestine, they colonize the mucosa—a process that is facilitated by specific colonization factors—and release cholera toxin. This toxin is a protein, consisting of an active (A) subunit and five binding (B) subunits, that attaches to the G_{M1} ganglioside receptor at the lining of the mucosal cells. It triggers a cascade of reactions involving the release of neurotransmitters including cyclic adenosine monophosphate, prostaglandins, serotonin, and calmodulin. The ensuing increase in intestinal chloride secretion and decrease in sodium chloride absorption are accompanied by water excretion that leads to diarrhea when the volume of fluid secreted by the small intestine surpasses the absorptive capacity of the colon. The volume typically exceeds 1 liter per hour in adults and 10 mL per kg per hour in children. It is intriguing that cholera results from infection yet is not accompanied by systemic manifestations of a cytokine-induced acute phase reaction. Electron microscopic studies of the small intestinal mucosa show prominent widening of intercellular spaces and alteration of apical junctional complexes in the villus epithelium, whereas blebbing of microvillus border and mitochondrial changes are more prominent in the crypt epithelium. Changes that correlate with clinical severity include degranulation of argentaffin cells, mucosal mast cells, and eosinophils; an increase in neutrophil polymorphs; and changes in the enteric nerve fibers and microvasculature. It is suggested that morphologic change of the gut in the recently emerged non-O1 *V. cholerae* infection is more severe than in infection caused by *V. cholerae* O1.

TABLE 1. **Classification of Dehydration and Fluid Deficit Based on Clinical Signs and Symptoms**

Sign or Symptom	Sign or Symptom for Degree of Dehydration		
	Mild or None	*Moderate*	*Severe*
Approximate absolute fluid deficit (%)	≤50 mL/kg (<5%)	51–90 mL/kg (5–7%)	>90 mL/kg (10%)
Mentation	Alert	Restless or lethargic	Infants or young children may be comatose; older children and adults are apprehensive
Voice	Normal	High pitched	Absent (aphonia)
Thirst	Present	Present	Present
Radial pulse	Normal	Rapid	Rapid and feeble or impalpable
Respiratory pattern	Normal	Tachypneic	Tachypneic, labored (Kussmaul's)
Blood pressure	Normal	Normal	Low or absent (shock)
Mucous membranes	Moist	Dry	Dry
Elasticity of subcutaneous tissue	Pinch retracts immediately	Pinch retracts slowly	Pinch retracts slowly; washerwoman's fingers
Eyes	Normal	Sunken	Sunken
Urine flow	Normal	Scant and dark	Scant or absent

CLINICAL SYMPTOMS

The spectrum of illness varies from mild disease with no or hardly any symptoms to severe disease (cholera gravis) when the voluminous painless watery diarrhea leads to dehydration and even death within a few hours (Table 1). Associated symptoms include nausea, vomiting (especially early in the illness), and muscle cramps followed by signs of hypovolemic shock, such as a weak radial pulse, undetectable blood pressure, depressed mental status, and ultimately coma. As a result of the metabolic acidosis, hyperventilation (Kussmaul's breathing) may occur. The case-fatality rate for untreated cholera gravis is 50%. Cholera is in principle a self-limited disease if the dehydration is sufficiently remedied.

Cholera stool is not malodorous and is often described as rice-water stool because of small flecks of mucus but little fecal matter; bloody stool is not suggestive of cholera. Because the vibrio does not invade the epithelial lining of the intestine, there is little inflammatory response; hence, the stool contains few if any leukocytes, and patients are afebrile. The stool is isotonic with plasma; the sodium concentration is slightly lower and bicarbonate and potassium concentrations are higher than those found in plasma (Table 2).

Suspicion of cholera increases if there are other cases of cholera in the area, if the patient is from an area of poor sanitation, or if the patient has recently traveled to a cholera-endemic area.

Assessment of Dehydration

The degree of dehydration is assessed on the basis of physical signs (see Table 1) and measurement of stool, vomitus, and urine output. Measurement of stool output is facilitated by the use of a "cholera cot." This plastic-lined jute cot contains a hole in the middle through which stool is collected into a calibrated bucket. Monitoring stool losses every 2 to 4 hours may assist in ensuring that fluid replacement proportional to stool losses is given.

Complications

Complications from cholera are largely due to inadequate rehydration. Acute tubular necrosis with renal failure can result if the rate of rehydration is too low or if the rehydration solution does not contain salts.

Metabolic abnormalities can also occur. Hypokalemia is the result of loss of potassium in the stool but may initially

TABLE 2. **Electrolyte Composition of Cholera Stool in Adults and Children and of Rehydration Solutions (Concentration in mmol/L)**

Cholera Stool	**Na^+**	**K^+**	**Cl^-**	**HCO_3^-**	**Carbohydrate**
Adults	135	15	100	45	—
Children	105	25	90	30	—
Rehydration Fluid	**Na^+**	**K^+**	**Cl^-**	**Citrate**	**Carbohydrate**
Cereal ORS*	90	20	80	10†	20–50
Glucose ORS*	90	20	80	10	111
Lactated Ringer's	131	41	11	29	—
Dhaka solution	133	13	98	48	—
Saline‡	154	—	154	—	—

*Glucose ORS contains (per liter) NaCl 3.5 gm, KCl 1.5 gm, trisodium citrate 2.9 gm, and glucose 20 gm, with a total osmolality of 311 Osm/L. The electrolytes in cereal ORS are the same, but the glucose is replaced by a cereal (e.g., rice) 40–80 gm/L. Cereal (Ceralyte) ORS has a total osmolality of about 220–250 Osm/L.

†Either sodium bicarbonate 2.5 gm (which provides 30 mmol of bicarbonate) or trisodium citrate 2.9 gm (which provides 10 mmol of citrate) can be used as the base. The World Health Organization prefers citrate.

‡Normal saline only should be used for patients in shock when lactated Ringer's solution or another polyelectrolyte solution is not available. ORS is to be started immediately to replace potassium and base, which are not included in saline.

Abbreviation: ORS = oral rehydration solution.

be masked by the concomitant acidosis. The acidosis results from both bicarbonate loss in the stool and increased lactate production due to anaerobic glycolysis. Restoration of the circulation will diminish lactate production, and the bicarbonate contained in the intravenous solution will replenish plasma bicarbonate concentrations. Excess bicarbonate therapy can lead to tetany as a result of a decrease in the proportion of ionized to bound calcium. Halting the bicarbonate infusion will result in the resolution of the tetany. Pulmonary edema may occur if saline rather than lactated Ringer's is used and the metabolic acidosis is not corrected. Generalized edema can occur if excessive intravenous fluids are given. Ileus, paralytic bladder, and cardiac arrhythmias may occur as a result of hypokalemia when the rehydration fluids do not contain sufficient potassium. Cardiac arrhythmias can also result from hyperkalemia if renal failure is not recognized. Shock from cholera can precipitate abortion in pregnant women, although this is less likely to occur if rehydration is prompt. Severe hypoglycemia due to deficient gluconeogenesis can result in seizures and other neurologic abnormalities. Hypoglycemia is most common in malnourished children who have not eaten for several hours and have depleted their glycogen stores.

Hyperglycemia at admission has been found as a common feature in some settings. Septicemia is rare but has been described in a patient concurrently infected by *V. cholerae* O139 Bengal and *Shigella boydii*; as an extraintestinal manifestation, it is ascribed to the fact that *V. cholerae* O139, in contrast to *V. cholerae* O1, contains a capsulated polysaccharide.

MICROBIOLOGY

V. cholerae is a gram-negative, comma-shaped rod (formerly called *Vibrio comma*) belonging to the family Vibrionaceae. The diagnosis is confirmed by identifying *V. cholerae* from a stool culture on special media (thiosulfate citrate bile salts sucrose agar). For rapid diagnosis, dark-field examination of a fresh, unstained stool specimen is highly sensitive and specific; typical is the "shooting star" phenomenon caused by the motility of the vibrio's single polar flagellum. Cholera SMART is a rapid, colorimetric immunodiagnostic kit suitable for the direct detection of the presence of *V. cholerae* O1 in clinical specimens. A new immunochromatographic strip test (QUIX) is claimed to be the most simple, rapid, sensitive, and specific immunochromatographic test currently available for the detection of *V. cholerae*. In advanced settings, serologic tests are available for diagnosis; toxigenic *V. cholerae* serogroup O1 can be subdivided into El Tor and classical biotypes and Ogawa and Inaba serotypes. Two monoclonal antibody–based rapid immunodiagnostic test kits, BengalScreen, a coagglutination test, and Bengal DFA, a direct fluorescent antibody test, have been developed for direct detection of *V. cholerae* O139. For higher yield, rectal swabs are preferred to stool samples for both culture and rapid diagnosis. Other Vibrionaceae can also cause diarrhea, but only toxigenic *V. cholerae* belonging to serogroup O1 or to serogroup O139 has been associated with epidemic cholera. Other serogroups of *V. cholerae* as well as nontoxigenic *V. cholerae* O1 and O139 do not cause epidemic cholera, although they may cause individual cases of diarrhea. In epidemic settings in developing countries, a bacteriologic diagnosis is not indicated in all suspected cases because the management of dehydrating diarrhea is guided by the extent of fluid loss rather than by the nature of the infecting organism. By contrast, in individual cases of suspected cholera in the developed world, the diagnosis should be confirmed with culture and reported to the national health authorities.

EPIDEMIOLOGY

Since 1817, cholera has raged in seven pandemics, with possibly an eighth one emerging superimposed on the seventh. The first six were caused by the classical biotype and originated in cholera's homeland, Bengal; the seventh and current one is caused by the El Tor strain and began in 1961 in Indonesia to gradually affect most of Asia and Africa. In 1991, this pandemic reached South America, where cholera had not been seen for more than 100 years, and has since spread over the whole of Latin America where it is accompanied by an emerging diversity in the vibrio's electrophoretic types. In its wake, hundreds of importations have been reported in the United States. In Latin America, despite the epidemic's rapid spread, well-established case management has kept fatality rates low (about 1%). In contrast, cholera in Africa has been sporadic, and fatality rates tend to be higher (about 10%). In the Rwandan refugee camps in eastern Zaire in 1994, an estimated 50,000 persons died during the first several weeks of an explosive cholera epidemic, in the absence of adequate health facilities and oral rehydration. In 1992, a novel *V. cholerae* variant O139 (synonym Bengal) emerged in southern Asia where marine ecosystems in the Bay of Bengal were experiencing a pandemic of coastal algal blooms, apparently harboring and amplifying the agent, as a reflection of what ecologists refer to as "environmental distress syndrome." Studies using the random amplified polymorphic DNA fingerprinting method have suggested that this *V. cholerae* O139 strain has emerged from a common origin associated with the El Tor strain. This was the first epidemic caused by a serogroup other than O1 and occurring in populations assumed to be largely immune to *V. cholerae* O1. The Bengal strain has potential for pandemic spread because it has now affected areas throughout the Indian subcontinent, neighboring states, and other parts of Asia, with imported cases as far as the United States and Western Europe. It might be illustrative of the relative virulence of the three strains that the El Tor strain nearly completely replaced the classical strain in cholera-endemic Bangladesh during the late 1980s and that, in turn, the Bengal strain has nearly replaced the El Tor strain during the 1990s.

RISK FACTORS

The following risk factors have relevance for the management of patients.

Breast-feeding

Exclusive breast-feeding provides important protection to infants not because of transmission of maternal antibodies but because of the lesser exposure to contaminated food and water. Mothers should be encouraged to continue breast-feeding their children during episodes of cholera.

ABO Blood Type

Persons with blood group O have a higher risk for El Tor cholera than do persons with blood group A, B, or AB.

Strain Biospecificity

V. cholerae El Tor can survive longer in humans and in the environment and is more infectious than classical

strains. An episode of classical cholera protects nearly entirely against recurrent cholera of either biotype; an episode of cholera El Tor does not protect against future attacks. The impact of a *V. cholerae* O139 infection on the risk for a subsequent *V. cholerae* infection, either O1 or non-O1, has not been determined yet.

Gastric Acid Output

Persons with impaired gastric function (e.g., after gastric surgery or while receiving antacid or acid-suppressing medication) have a substantially increased risk because of the loss of the gastric acid barrier. In addition, *Helicobacter pylori* gastritis is associated with a significant increase in the risk for life-threatening cholera but only among persons lacking natural vibriocidal immunity.

Age

Children are more likely to have only subclinical infection or mild diarrhea; adults tend to develop more severe disease and require hospitalization.

TREATMENT

The treatment of cholera patients consists of two components: rehydration, which is critical; and antimicrobial therapy, which is optional and intended to shorten the duration of illness.

Rehydration in the Acute Phase

Depending on the severity of the dehydration (see Table 1), intravenous or oral rehydration is preferred, and the choice of solution and rate of administration are determined. Effective fluid replacement can be expected to reduce mortality to less than 1% of severely affected individuals, compared with 50% or more when no treatment is provided. Return to a status of full hydration must be achieved in 4 hours of the beginning of treatment, with half of the fluid replacement occurring within the first hour. Analysis of the electrolyte loss in cholera stool has provided clues for the composition of rehydration solutions, oral and intravenous (see Table 2). The stool is generally isotonic and has electrolyte concentrations that are similar to those of serum.

Mild and moderately dehydrated patients can be treated with use of oral rehydration solution (ORS), which has three basic components: sugars, salts, and water. The sugar acts physiologically as the vehicle for salts to be absorbed by the mucosal cell, and water follows passively. The World Health Organization (WHO) and the United Nation's Children's Fund promote standard ORS, which comes in packages (see Table 2). Alternative formulations of ORS have also been developed. Solutions in which sugar is substituted by starch decrease the purge rate and the duration of diarrhea significantly. Similarly, studies have suggested that reduced osmolarity ORS may be more effective than standard ORS in reducing stool output. Partial replacement of glucose by the amino acid glutamine has the same effectiveness as standard ORS but has metabolic advantages. Homemade solutions lack the potassium and bicarbonate salts and are often inaccurately prepared ("a fist of sugar and a pinch of salt in a pint of water").

ORS is intended to replace only the stool losses. Patients are therefore encouraged to drink additional fluids such as water. Infants should continue to be breast-fed or use formula, and all patients should resume eating as soon as possible.

Severely dehydrated patients should be treated intravenously. The optimal intravenous fluid is an isotonic, polyelectrolyte solution containing a base and potassium. Commonly available examples include lactated Ringer's and the Dhaka solution* (see Table 2).

Providing rapid rehydration requires one or sometimes multiple intravenous infusions. When intravenous solutions and equipment are not available, severely dehydrated patients may be treated through a nasogastric tube with use of the intravenous rate of rehydration. Subcutaneous and intraperitoneal parenteral fluids should not be used, because absorption from these sites is not sufficiently rapid to restore circulation.

Maintenance Hydration

Once rehydration is achieved, continuous stool losses have to be replaced. Patients receiving intravenous therapy may begin ORS treatment; patients receiving ORS should continue with ORS until the diarrhea stops.

Antimicrobials

Antibiotic treatment is optional and serves to shorten the illness and save rehydration fluids; incomplete courses have contributed to antibiotic resistance. Options are shown in Table 3 and are guided by local sensitivity patterns. Single-dose treatment has higher compliance of patients. Tetracyclines and quinolones are not recommended during pregnancy; at the recommended doses, tetracycline is not harmful to children. During epidemics, prophylactic antibiotics should be used for the immediate family only and be limited to a single-treatment dose.

Other Drugs

Not recommended in cholera are the following drugs: activated charcoal, kaolin, loperamide (Imodium), diphenoxylate (Lomotil), dopamine, norepinephrine, high-dose steroids, and colloid intravenous fluids.

PREVENTION

The persistence and penetrance of the current cholera pandemic serve as a marker for the inadequate sanitation in most of the world for which future prospects are undermined by the impact of international

*Not available in the United States.

TABLE 3. **Antimicrobial Agents Used in the Treatment of Cholera**

Agent	Adult Dose	Dose for Children <12 Years
Doxycycline*	300 mg as a single dose or 100 mg bid × 3 d	Do not use
Tetracycline	500 mg qid × 3 d	12.5 mg/kg qid × 3 d
Furazolidone (Furoxone)†	100 mg qid × 3 d	1.25 mg/kg qid × 3 d
TMP-SMZ (Bactrim, Septra)‡§	TMP 160 mg + SMZ 800 mg bid × 3 d	TMP 5 mg/kg + SMZ 25 mg/kg bid × 3 d
Ciprofloxacin (Cipro)‡‖	500 mg bid × 3 d	Do not use
Erythromycin‡¶	250 mg qid × 3 d	Do not use

* The drug of choice for most situations, because a single dose can be used.
† The drug of choice in pregnant women.
‡ Not FDA approved for this indication.
§ The preferred drug for children.
‖ This fluoroquinolone is the reserve for strains resistant to all other antibiotics.
¶ Next best alternative in case of multiple resistance.
Abbreviation: TMP-SMZ = trimethoprim-sulfamethoxazole.

debt on ailing economies. Because cholera is difficult to eradicate from water, it is likely to remain a serious threat to public health for some time. This holds particularly true for Latin America, where 73% of the population carries the predisposing blood type O. Measures to prevent cholera at the community and household levels include separation of sewage and water systems; disinfection of drinking and cooking water through boiling or addition of alum potash; bucket chlorination at untreated water sources; avoidance of commercial ice used by street vendors; safe food preparation, particularly of seafood (shellfish), using a core temperature of 60°C or 170°F, and of vegetables and fruits; basic sanitation including use of designated defecation areas; hygiene measures such as hand washing with soap; active case finding through community outreach; and effective case management of ill patients with the use of oral rehydration. During epidemics, bodies of persons dying of cholera should be disinfected and rapidly buried, and community leaders should be instructed to discourage the consumption of food served at gatherings including funerals.

Vaccines

The currently licensed, parenteral, killed cholera vaccine is no longer recommended by WHO because of its limited protective effect (50% for about 3 to 6 months) and ensuing false sense of security. To induce mucosal immunity, oral vaccines, both inactivated (WC/BS) and live (CVD103), have been developed and field tested; they show no side effects and have longer lasting protection than the parenteral vaccine. Vaccines that include the toxin's B subunit have been proved to provide cross-protection against traveler's diarrhea due to enterotoxigenic *Escherichia coli*. Before the use of cholera vaccines is recommended for public health purposes, several considerations have to be taken into account. The cost-effectiveness of the vaccine needs to be weighed against the cost-effectiveness of other preventive measures; the safety of live vaccines in populations with human immunodeficiency virus infection is questioned; vaccination may induce a transient state of enhanced susceptibility; and the new oral vaccines still have a delayed onset of protection of a limited level and duration. In light of these considerations, new guidelines need to be developed for the use of cholera vaccines, particularly in emergency settings such as refugee camps established overnight.