214 Vibrio cholerae

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Cholera is a historically feared epidemic diarrheal disease that still affects different regions of the world, imposing significant economic constraints on already impoverished developing countries. More recent epidemics are the Latin American extension of the seventh pandemic of cholera at the beginning of 1991, the epidemic of cholera in Zaire in 1994, and the epidemic of cholera caused by *Vibrio cholerae* O139 in 1992 in Asia (Fig. 214-1). These epidemics show that it is still not possible to predict when and where a new epidemic of cholera will start, that appropriate therapy may reduce the mortality to values below 1%, and that changes in the cause of this ancient disease are still taking place.

The term *cholera* has ancient origins and is derived from Greek words meaning "a flow of bile."[1] Thomas Sydenham was the first to distinguish cholera, the disease, from cholera, the state of anger.[1] He proposed the term *cholera morbus* for the disease. Because earlier descriptions of the disease confused cholera with other diarrheal diseases, the modern history of cholera began with Sydenham's description in 1817.

The modern era of cholera is characterized by seven pandemics. The first six occurred between 1817 and 1923. These pandemics were most likely caused by *V. cholerae* O1 of the classic biotype and largely originated in Asia, usually the Indian subcontinent, with subsequent extension to Europe and the Americas. Filippo Pacini published his observations on the discovery of a curved bacillus in the stools of victims of cholera in Italy in 1854. He coined the name *Vibrio cholerae.*[2] In 1883, Robert Koch made the same discovery. Transmission of the disease was recognized only after the brilliant work of John Snow during the second pandemic affecting London in 1849, even before knowing the cause of the disease. He reduced the transmission of cholera by blocking access to contaminated water in one area of London.

The seventh pandemic of cholera differed from the prior six. This pandemic was caused by the biotype El Tor of *V. cholerae* O1, a biotype that had been isolated for the first time in Egypt at the beginning of the century and was associated with sporadic cases until 1961. In 1961, the pandemic originated in the Celebes Islands, Indonesia, instead of the Indian subcontinent. This pandemic has been the longest lasting and has affected more countries and continents than the other six. The last extension of this pandemic in Latin America occurred in 1991, where it caused higher attack rates than those seen during the last century but the lowest case-fatality rates.[3] The pandemic is still going on in many countries—for example, 632 outbreaks were reported to ProMED between 1995 and 2005, and 66% of them were reported from Africa.[4] Fifty-three countries officially reported 177,963 cases to the World Health Organization in 2007, with 4031 deaths; 94% of these cases were reported from Africa. However, it is estimated that only 1% of the actual number of cases is officially reported.[5] Epidemic cholera was mostly restricted to Africa during 2007, with 34 reporting countries and five countries (Angola, Ethiopia, Democratic Republic of the Congo, Somalia, and Sudan) accounting for 76% of the total number of cases and fatalities. Social disruption, poverty, poor sanitary and hygienic conditions, and poor access to health care explain the high prevalence and mortality rates still observed in Africa.[6]

Finally, in October 1992, a totally unexpected epidemic of a cholera-like disease was observed in Madras, India, with subsequent cases being reported along the Bay of Bengal.[7] *V. cholerae* of the new serogroup O139 was responsible for this epidemic, the first non–O1 *Vibrio* to do so. The epidemic was widespread in the Asiatic continent, with imported cases reported from developed countries.[8-10] Some regarded this as the eighth cholera pandemic,[11] although the epidemic has remained confined to Bangladesh and India. The O139 serogroup today coexists with O1 *V. cholerae,* being responsible for continuous epidemics in Bangladesh.[12]

Microbiology

V. cholerae is a curved gram-negative bacillus varying in size from 1 to 3 μm in length by 0.5 to 0.8 μm in diameter. It belongs to the family Vibrionaceae and shares common characteristics with the family Enterobacteriaceae. The bacterium has a single polar flagellum that confers the erratic movement on microscopy. The antigenic structure of *V. cholerae* is similar to that of other members of the family Enterobacteriaceae, with a flagellar H antigen and a somatic O antigen. The O antigen is used to classify *V. cholerae* further, into serogroups O1 and non-O1. Approximately 206 serogroups of *V. cholerae* have been identified to date, but only the serogroups O1 and O139 are associated with clinical cholera and have pandemic potential.

V. cholerae O1 can be classified into three serotypes according to the presence of somatic antigens and into two biotypes according to specific phenotypic characteristics. Serotype Inaba carries the O antigens A and C, serotype Ogawa carries the antigens A and B, and serotype Hikojima carries the three antigens A, B, and C. No evidence of different clinical spectra among these three serotypes of *V. cholerae* has ever been presented. During epidemics, a shift from one serotype to another may occur.[13,14] A serotype-cycling behavior has been reported from Bangladesh; the predominance of one serotype over others depends on the immunity level of the population.[15] The differences between the two biotypes of *V. cholerae* O1 are remarkable. The classic biotype, probably responsible for the first six pandemics of cholera, causes an approximately equal number of symptomatic and asymptomatic cases. In contrast, the El Tor biotype causes more asymptomatic infections, with a ratio between 20 and 100 asymptomatic infections to 1 symptomatic case. The classic biotype is confined to the south of Bangladesh, whereas the El Tor biotype is responsible for the current pandemic. These two biotypes are not derived from each other, but rather from environmental nontoxigenic strains.[16] They have coexisted for decades in their natural environment, possibly interacting genetically to produce hybrids, as has been reported recently from patients in Bangladesh and Mozambique.[17] The persistence of the classic biotype has suggested the possible need for the development of multivalent vaccines. The O139 serogroup is composed of a variety of genetically diverse strains, both toxigenic and nontoxigenic, with at least nine different ribotypes identified.[18] This novel serogroup is genetically closer to El Tor *V. cholerae,* and might have been originated from it, acquiring distinctive features from a nonidentified donor, likely a non-O1 vibrio, through recombination of genetic material.[18]

ISOLATION AND IDENTIFICATION

V. cholerae O1 or O139 can easily be observed under darkfield examination. The chaotic movements and high numbers of bacteria seen in a stool sample from patients with clinical disease are characteristic of

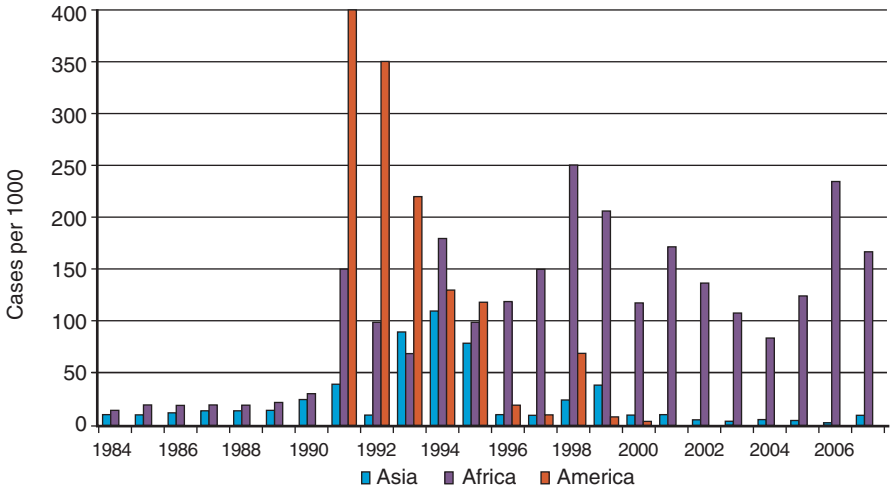

Figure 214-1 Cholera cases reported to the World Health Organization from 1984 to 2007. A substantial increase in the number of cases has been observed since 1990. This is the result of large epidemics of cholera caused by *V. cholerae* O1 in America and Africa, and the appearance of a new serogroup, O139, in Asia. At present, cholera is restricted to Africa. *(Adapted from World Health Organization. Cholera.* Wkly Epidemiol Rec. *2008;83:269-284.)*

V. cholerae infection. The use of specific antisera against the serotype blocks the movement of these vibrios and allows confirmation of the diagnosis. However, under epidemic conditions, the presence of bacteria with darting movements under darkfield microscopy in a stool sample from patients highly suspected of having cholera is sufficient to make the diagnosis, but definitive confirmation still requires isolation of the bacteria in culture. A specific medium is needed to isolate *V. cholerae* from stool. The two media most commonly used are thiosulfate citrate bile salts sucrose agar and tellurite taurocholate gelatin agar. These two media are equally sensitive to isolate either O1 or O139 *V. cholerae.* Enrichment media or the addition of antibiotics to culture medium may be used when the number of bacteria in the stool is small or when environmental samples are evaluated for the presence of *Vibrio.*[19] High sensitivity and specificity have been reported more recently using polymerase chain reaction (PCR) assay and real-time nucleic acid sequence-based amplification assays for detecting vibrios in stool and environmental samples.[20-22] A rapid diagnosis of cholera can be made in the field using a highly sensitive and specific immunochromatographic dipstick test applied to fresh stools.[23]

Pathophysiology

V. cholerae O1 and O139 cause clinical disease by secreting an enterotoxin that promotes secretion of fluids and electrolytes by the small intestine. The infectious dose of bacteria varies with the vehicle. When water is the vehicle, more bacteria (10^3 to 10^6) are needed to cause disease, but when the vehicle is food, the amount needed is lower (10^2 to 10^4).[24] Conditions that reduce gastric acidity, such as the use of antacids or histamine receptor blockers, gastrectomy, or chronic gastritis induced by *Helicobacter pylori,* increase the risk of getting the disease and predispose the patient to more severe clinical forms. Toxin is produced, but *V. cholerae* does not invade the intestinal wall and few neutrophils are found in the stool. The incubation period varies with the infectious dose and gastric acidity and lasts 12 to 72 hours.

Both Koch and Snow suspected that a toxin was responsible for some of the disease manifestations, but it was not until 1959 that De and Dutta and colleagues, working in different laboratories, showed that *V. cholerae* promoted intestinal secretion in animal models.[25,26] The toxin was finally purified by Finkelstein and LoSpalluto in 1969.[27] The toxin has five B subunits and two A subunits. The B subunits allow binding of the toxin to a specific receptor, a ganglioside (GM_1) located on the surface of the cells lining the mucosa along the intestine of humans and certain suckling mammals. The active, or A, subunit has two components, A1 and A2, linked by a disulfide bond. Activation of the A1 component by adenylate cyclase results in a net increase in cyclic adenosine monophosphate, which blocks the absorption of sodium and chloride by microvilli and promotes the secretion of chloride and water by crypt cells. The result of these events is the production of watery diarrhea with electrolyte concentrations similar to those of plasma, as shown in Table 214-1.

The complete genomic sequence of *V. cholerae* O1 El Tor is well known today. The genetic material consists of two circular chromosomes, with the larger containing 3 megabases, and the smaller containing 1.07 megabases.[28] The main virulence genes are *ctx*A and *ctx*B, which encode for cholera toxin subunits A and B, respectively, and *tcp*A, which codes for toxin-coregulated pilus. The regulation of the expression of these genes is complex. Environmental factors, such as sunlight and possibly others, may influence the expression of genes encoding for cholera toxin.[29]

Epidemiology

Cholera has unique epidemiologic features. Perhaps the most intriguing are the predisposition to cause epidemics with pandemic potential and the ability to remain endemic in all affected areas.[30] These two epidemiologic patterns, the epidemic and endemic patterns, are summarized in Table 214-2. Recognizing the different age groups at risk, depending on the epidemiologic pattern, is useful in designing preventive measures.

New insights into the life cycle of *V. cholerae* have allowed a better understanding of cholera transmission. *V. cholerae* lives in aquatic environments, which are their natural reservoirs.[31] Both O1 and non-O1 strains coexist in these environments, with non-O1 and non-

TABLE 214-1 Electrolyte Concentration of Cholera Stools and Common Solutions Used for Treatment

	Electrolyte and Glucose Concentration (mmol/L)				
	Na^+	Cl^-	K^+	HCO_3^-	Glucose
Cholera stool					
Adults	130	100	20	44	
Children	100	90	33	30	
Intravenous solutions					
Ringer's lactate	130	109	4	28*	0
Dhaka	133	98	13	48	0
Normal saline	154	154	0	0	0
Peru polyelectrolyte	90	80	20	30	111
Reduced osmolarity WHO ORS	75	65	20	10†	75

*Ringer's lactate solution does not contain HCO_3^-; it contains lactate instead.
†Bicarbonate is replaced by trisodium citrate, which persists longer than bicarbonate in sachets.
WHO ORS, World Health Organization oral rehydration solution.

TABLE 214-2 Epidemiologic Patterns of Cholera

Epidemiologic Features	*Epidemic Pattern*	*Endemic Pattern*
Age at greatest risk	All ages	Children, 2-15 yr
Modes of transmission	Single introduction with fecal-oral spread	Multiple modes of introduction—water, food, fecal-oral spread
Reservoir	None	Aquatic reservoir
Asymptomatic infections	Less common	Asymptomatic people more common
Immune status of the population	No preexisting immunity	Preexisting immunity; evidence of infection increases with age
Secondary spread	High	Variable

Adapted from Glass RI, Black RE. The epidemiology of cholera. In: Barua D, Greenough WB III. eds. *Cholera*. New York: Plenum Press; 1992:129-154.

toxigenic O1 strains predominating over toxigenic O1 strains.[32] In its natural environment, *V. cholerae* lives attached to a particular type of algae or attached to crustacean shells and copepods (zooplankton), which coexist in a symbiotic manner (Fig. 214-2).[33,34] When conditions in the environment such as temperature, salinity, and availability of nutrients are suitable, *V. cholerae* multiplies and can survive for years in a free-living cycle without the intervention of humans. Otherwise, when conditions are not suitable for its growth, *V. cholerae* switches from a metabolically active state to a dormant state.[32] In this dormant state, *V. cholerae* cannot be cultured from the water on standard or enrichment media but appears to survive under difficult environmental conditions. Immunofluorescent techniques using monoclonal antibodies have been used to detect dormant *V. cholerae.*[35] Experimentally, the switch from a nonculturable to culturable state has been attained in the laboratory, as well as in human volunteers.[36] *V. cholerae* may also persist in the environment and adopts a rugose form visible on a special agar, Luria agar.[37] Recently, it has been shown that *V. cholerae* can form biofilms, surface-associated communities of bacteria with enhanced survival under negative conditions, that can switch to active bacteria and induce epidemics.[38] Humans infected by *V. cholerae* may shed the bacteria for a long time, sometimes for months or years. Recent evidence has suggested that *V. cholerae* can upregulate certain genes in the intestine of humans, resulting in a short-time hyperinfectious state.[39] Interestingly, households in contact with acutely ill patients who shed large amounts of *V. cholerae* O1 Inaba El Tor in their stools are more likely to develop cholera than those in contact with

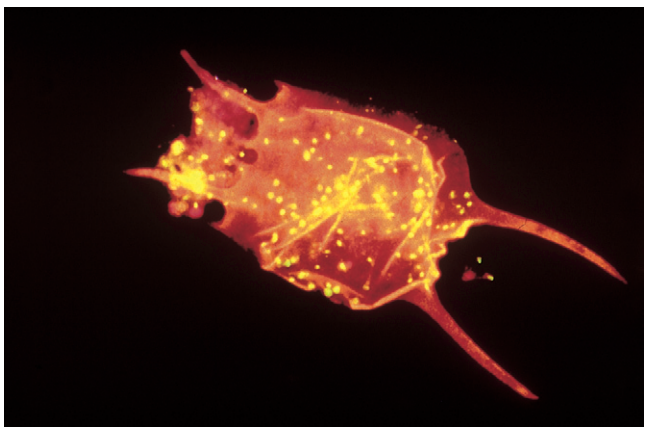

Figure 214-2 *Vibrio cholerae* attached to a copepod (stained with fluorescent techniques). *(Courtesy of Dr. Rita Colwell and Dr. Anwarul Huq, University of Maryland, College Park, Md.)*

environmental strains. Also, the abundance of *V. cholerae* O1 in the intestine of cholera patients is in part determined by the presence of lytic phages.[40]

From its aquatic environment, *V. cholerae* is introduced to humans through contamination of water sources and contamination of food. The cycle of transmission is closed when infected humans shed the bacteria into the environment and contaminate water sources and food. Once humans are infected, incredibly high attack rates may ensue, especially in previously nonexposed populations. Additional evidence of very high household transmission rates exists, as occurred during the last Latin American epidemic or, more recently, during the epidemic in Zaire in 1994.[41,42] Transmission via contaminated water and food has been recognized for years.[43] During the Latin American epidemic and more recent epidemics in Africa, acquisition of the disease by drinking contaminated water from rivers, ponds, lakes, and even tube well sources has been documented.[6,44,45] Contamination of municipal water was the main route of transmission of cholera in Trujillo, Peru, during the epidemic of 1991.[46] Drinking unboiled water, introducing hands into containers used to store drinking water, drinking beverages from street vendors, drinking beverages when contaminated ice had been added, and drinking water outside the home are recognized risk factors to acquire cholera. On the other hand, drinking boiled water, acidic beverages, and carbonated water, as well as using narrow-necked vessels for storing water, are protective.[47] *V. cholerae* survives for up to 14 days in some foods, especially when contamination occurs after preparation of the food.[48] Cooking and heating the food eliminate the bacteria. Epidemics of cholera associated with the ingestion of leftover rice, raw fish, cooked crabs, seafood, raw oysters, and fresh vegetables and fruits have been documented.

Transmission of cholera during funerals in Africa has been reported. Risk factors identified included eating at the funeral with a nondisinfected corpse and touching the body.[49] Eating rice at the funeral was the main risk factor for the acquisition of cholera in one study.[50] Person-to-person transmission is less likely to occur because a large inoculum is necessary to transmit disease. However, anecdotal reports exist in the literature.[51-53] Careful evaluation of these reports shows that other potential risk factors might have been implicated in the transmission. Other vehicles of transmission such as insects and fomites have been incriminated, but are less likely to be important in epidemic situations.

Seasonality is another typical characteristic of cholera. Epidemics tend to occur during the hot seasons, and countries with more than one hot season per year may also have more than one epidemic, such as seen in Bangladesh.[54] Data from the epidemic of cholera in Peru from 1991 to 1995 also confirmed that outbreaks are associated with the warmest months of the year.[55] A recent evaluation of data reported to the World Health Organization has suggested that countries located near the equator have more constant outbreaks not related to seasonal variations; in contrast, countries far from the equator have less intense outbreaks clearly associated to seasonal variations.[56] Climate change and climate variability may affect the incidence of certain infectious diseases.[57] The El Niño–Southern Oscillation (ENSO), a periodic phenomenon representative of global climate variability, has been studied in relation to its effect on the transmission of cholera and vector-borne diseases. A strong association between ENSO and cholera has been observed in Bangladesh and also proposed for Latin America, with studies suggesting that this relationship may be even more intense in future years.[58-61] ENSO causes warming of normally cool waters on the Pacific coastline of Peru, promoting phytoplankton bloom, which in turn promotes zooplankton bloom and *V. cholerae* proliferation. Lipp and associates[57] have elegantly described the complex associations among various climatic, seasonal, bacterial, and human factors acting on cholera transmission in a hierarchical model (Fig. 214-3). Interestingly, as noted previously, environmental conditions modulate vibrio abundance and may affect the expression of virulence genes of *V. cholerae,*[29,57,62,63] thus promoting the beginning of epidemics, as might have been the situation in Peru during 1991.[64] In addition, abundance of lytic phages in the environment inversely correlate with the burden

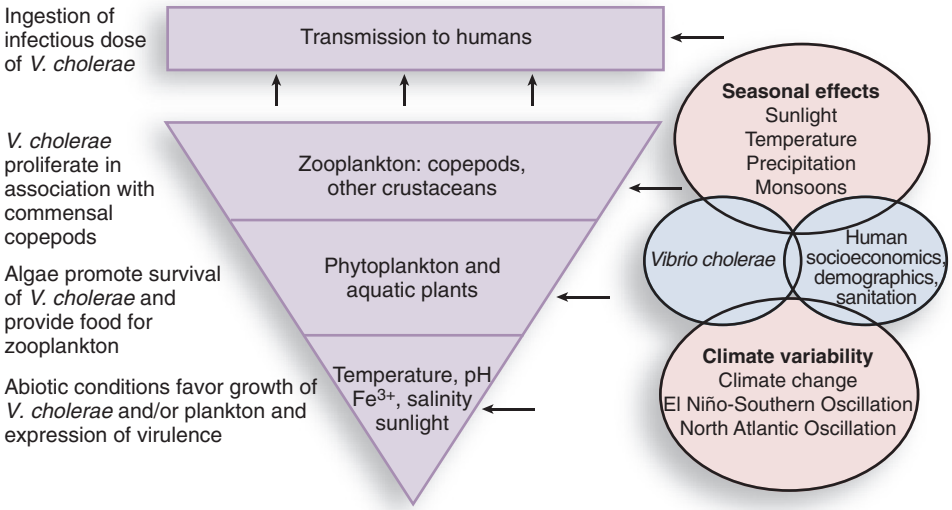

Figure 214-3 A hierarchical model for cholera transmission. *(From Lipp EK, Huq A, Colwell RR. Effects of global climate on infectious disease: The cholera model.* Clin Microbiol Rev. *2002;15:757-770.)*

of vibrio and may influence transmission to humans.[65] Drastic climatic events such as floods and droughts also influence cholera transmission.[66]

Some host factors are important in the transmission of cholera. Among them, infection by *H. pylori,* the effect of the O blood group, and the protective effect of breast milk deserve special consideration. Data from Bangladesh have shown that people infected by *H. pylori* are at higher risk of acquiring cholera than those not infected by *H. pylori.*[67] Additionally, the risk of acquiring severe cholera in people infected by *H. pylori* was higher in patients without previous contact with *V. cholerae,* as measured by the absence of vibriocidal antibodies in the serum.[68] *H. pylori* causes a chronic gastritis that induces hypochlorhydria, which in turn reduces the ability of the stomach to contain the *Vibrio* invasion. The impact of the association of these two infections is particularly interesting because *H. pylori* infection is very common in persons of all ages in developing countries.[68] In support of these previous observations, endoscopic findings in patients with severe cholera and mixed infection with *H. pylori* in Peru have revealed hypochlorhydria, chronic atrophic gastritis, and intestinal metaplasia.[69] Patients carrying the O blood group have a higher risk of developing severe cholera caused by O1 or O139 *V. cholerae* and disclose higher purging volumes of diarrhea, but have a lower risk of acquiring infection by *V. cholerae* O1.[70] Higher affinity of the cholera toxin to the ganglioside receptor in patients with O blood group and lower affinity in patients of A, B, and AB blood groups explains this association. Finally, the protective effect of breast milk has been reported, and it is linked to higher concentrations of IgA anti–cholera toxin.[71]

Although mainly countries with poor sanitary conditions are affected by cholera, a few developed countries such as the United States, Canada, and Australia have reported indigenous cases. Two different *V. cholerae* O1 strains have been isolated from these regions, and these vibrios differ from the strain responsible for the seventh pandemic.[72-74] Sporadic cases are reported periodically from these areas. Surveillance of cholera is needed to detect future epidemics and to identify current trends in serogroup predominance and susceptibility to antimicrobial agents in endemic areas. A 4-year surveillance study in four rural areas of Bangladesh has shown that noncholera pathogens predominated as a cause of diarrhea in children younger than 2 years, O1 *V. cholerae* predominated in young children, and O139 *V. cholerae* was observed in people of all ages but especially in older adults, suggesting that this new serogroup is still not endemic in the area.[75] Identifying areas of high transmission is desirable to focus prevention on a more local level. Integration of socioeconomic, behavioral, and biologic factors is needed to achieve that goal.[76]

Clinical Manifestations and Laboratory Abnormalities

The hallmark of cholera is the production of watery diarrhea, with varying degrees of dehydration ranging from none to severe and life-threatening diarrhea. Patients with mild to moderate dehydration secondary to cholera are difficult to differentiate from those infected by other enteric pathogens, such as enterotoxigenic *Escherichia coli* or rotavirus. Patients with severe dehydration from cholera are easy to identify because no other clinical illness produces such severe dehydration in a matter of a few hours as cholera. Onset of the disease is abrupt and characterized by the production of watery diarrhea without strain, tenesmus, or prominent abdominal pain, rapidly followed or sometimes preceded by vomiting. As the diarrhea continues, other symptoms of severe dehydration are manifest, such as generalized cramps and oliguria. Physical examination will show an alert patient most of the time, despite the fact that the pulse is nonpalpable and blood pressure cannot be measured. Fever is observed in less than 5% of cases. Patients look anxious and restless or sometimes obtunded, the eyes are very sunken, mucous membranes are dry, the skin has lost its elasticity and when pinched retracts very slowly, the voice is almost nonaudible, and the intestinal sounds are prominent. Patients in this condition are difficult to confuse with patients with other medical conditions. Figure 214-4 shows a typical patient with severe cholera. Table 214-3 shows the clinical manifestations according to the degree of dehydration as a guide to the proper administration of fluids. Although watery diarrhea is the hallmark of cholera, some patients do not have diarrhea but instead have abdominal distention and ileus, a relatively rare type of cholera called cholera "sicca."[77] Management of these patients is particularly difficult because evaluation of the degree of dehydration is overshadowed by the accumulation of fluid in the intestinal lumen.

Laboratory abnormalities reflect the isotonic dehydration characteristic of cholera. Increases in packed cell volume, serum specific gravity, and total protein are typically seen in patients with moderate to severe dehydration. Although abnormal results of these tests correlate with the degree of dehydration on arrival at a health center, they are less useful for monitoring rehydration status. Biochemical and acid-base laboratory abnormalities typical of severe dehydration are prerenal azotemia, metabolic acidosis with a high anion gap, normal or low serum potassium levels, and normal or slightly low sodium and chloride levels. The calcium and magnesium content in plasma is also high as a result of hemoconcentration. The white blood cell count is high in patients with severe cholera. Hyperglycemia caused by high concen-

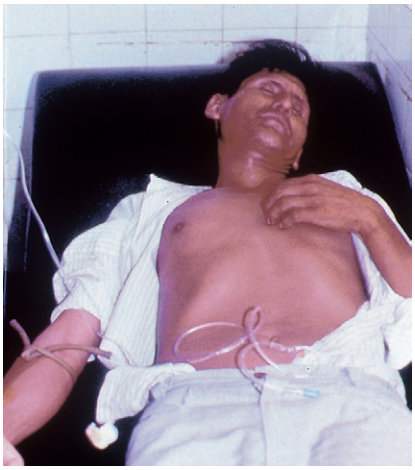

Figure 214-4 A Peruvian patient with severe cholera. Sunken eyes and washer woman's hands are typical of patients with severe dehydration.

trations of epinephrine, glucagon, and cortisol stimulated by hypovolemia is more commonly seen than hypoglycemia, but hypoglycemic children have a higher risk of dying than nonhypoglycemic children.[78] Acute renal failure is the most severe complication of cholera. Incidence rates of 10.6 cases/1000 were reported in Peru during the first months of the epidemic in 1991.[41] Patients with acute renal failure had a history of improper rehydration. All age groups were equally affected, and the mortality rate in this group of patients was extremely high (18%), particularly in older patients.[41]

The clinical manifestation of cholera in children is similar to that in adults. However, hypoglycemia, seizures, fever, and mental alteration are more common in children.[79] Cholera in pregnant women carries a bad prognosis and portends more severe clinical illness, especially when the disease is acquired at the end of the pregnancy.[80] Fetal loss occurs in as many as 50% of these pregnancies. Cholera in older patients also carries a bad prognosis because of more complications, particularly acute renal failure, severe metabolic acidosis, and pulmonary edema.[41] Proper hydration may correct all electrolyte and acid-base abnormalities in older patients.[81] Recent observations have suggested that HIV infection in Africa is associated with an increased risk for cholera.[82]

TABLE 214-3 Clinical Findings According to Degree of Dehydration

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Treatment

The goal of therapy is to restore the fluid losses caused by diarrhea and vomiting. Although treatment of patients without severe dehydration is easy, treatment of patients with severe dehydration requires experience and proper training. Basic training in how to recognize the degree of dehydration, select the proper intravenous solution, and rapidly rehydrate the patient is crucial. Recent experience during the epidemic in Zaire, in which untrained people played a negative role, cannot be overemphasized. Conversely, well-trained staff provided with adequate supplies can successfully treat patients, even under epidemic situations.[42,83,84] Guidelines to rehydrate cholera patients have been written and reviewed elsewhere.[85-87] The IV route should be restricted to patients with moderate dehydration who do not tolerate the oral route, those who purge more than 10 to 20 mL/kg/hr, and patients with severe dehydration. Rehydration should be accomplished in two phases, the rehydration phase and the maintenance phase. The purpose of the rehydration phase is to restore normal hydration status, and it should last no longer than 4 hours. IV fluids should be infused at a rate of 50 to 100 mL/kg/hr in severely dehydrated patients. Ringer's lactate solution is the most frequently recommended solution, but other solutions may also be used, as shown in Table 214-1. Normal saline solution is not recommended because it does not correct the metabolic acidosis. When IV access proves difficult, nasogastric tubes or intraosseous catheters can be used, although problems with IV access were not common during the last cholera epidemic in Peru.[55]

After finishing the rehydration phase, all signs of dehydration should have abated and the patient should pass urine at a rate of 0.5 mL/kg/hr or higher. The maintenance phase then begins. During this phase, the objective is to maintain normal hydration status by replacing ongoing losses. The oral route is preferred during this phase, and the use of oral rehydration solutions at a rate of 500 to 1000 mL/hr is highly recommended. Oral rehydration therapy uses the principle of common transportation of solutes, electrolytes, and water by the portion of the intestine not affected by the cholera toxin. People with diarrhea can undergo successful rehydration with simple solutions containing glucose and electrolytes that may be prepared at home. In 2002, the World Health Organization recommended the use of oral rehydration solutions with lower osmolarity (250 mOsm/L) than previously recommended in 1978 (311 mOsm/L).[88] The recommendation was based on a meta-analysis showing a lesser need to use IV fluids during treatment, and lower volumes of diarrhea and vomiting in children treated with the reduced osmolarity solution compared with the standard solution.[89] These results are also applicable to adults. Symptomatic hyponatremia in children in Bangladesh was lower with the reduced osmolarity solution compared with the standard rehydration solution.[90] Substitution of glucose for rice, amino acids, or amylase-resistant starch seems to improve the efficacy of the oral salts reducing further the volume and duration of diarrhea.[91,92] Evaluation of rehydration status and accurate recording of intake and output volumes are essential. Patients without severe dehydration who tolerate the oral route can be rehydrated with oral rehydration solutions exclusively and discharged promptly from the health center. Practical guidelines[87] are summarized in Table 214-4.

Discharging patients from health centers, particularly those with severe dehydration, is a critical issue, especially during epidemics. No significant readmission of patients was observed in Peru during the epidemic in 1991 when the following criteria were used to discharge patients: urine volume higher than 40 mL/hr, diarrhea output below 400 mL/hr, and oral ingestion of rehydration solutions between 600 and 800 mL/hr.[41] Adequate organization of health centers to accommodate and properly treat hundreds of patients, and proper allocation of available resources are critical under epidemic situations. Examples of successful use of resources during the O139 cholera epidemic of 1993 in Dhaka, Bangladesh, and during the O1 epidemic in Peru of 1991 are shown in Figures 214-5 and 214-6, respectively. The case-fatality rate during epidemics may be reduced to below 1%, even in disaster situations, provided that adequate access to health care centers

TABLE 214-4 Practical Guidelines for the Treatment of Cholera

1. Evaluate the degree of dehydration on arrival.
2. Rehydrate the patients in two phases:
   - Rehydration phase: Lasts 2-4 hr
   - Maintenance phase: Lasts until diarrhea abates
3. Register output and intake volumes in predesigned charts and periodically review the data.
4. Use the intravenous route only for:
   - Severely dehydrated patients during the rehydration phase, in whom an infusion rate of 50-100 mL/kg/hr is advised
   - Moderately dehydrated patients who do not tolerate the oral route
   - High stool volume (>10 mL/kg/hr) during the maintenance phase
5. Use ORS for patients during the maintenance phase at a rate of 800-1000 mL/hr, matching ongoing losses with ORS.
6. Discharge patients to the treatment center if the following conditions are fulfilled:
   - Oral tolerance ≥1000 mL/hr
   - Urine volume ≥40 mL/hr
   - Stool volume ≤400 mL/hr

ORS, Oral rehydration solution.

From Seas C, Dupont HL, Valdez LM, et al. Practical guidelines for the treatment of cholera. *Drugs*. 1996;51:966-973.

and proper management of patients can be ensured.[41,84] A case-fatality rate of 3.7% among hospitalized patients was reported from a specialized center in Dhaka, Bangladesh, in 1996.[93] In this setting, the overall case-fatality rate was 0.14%, and pneumonia was the leading cause of death. In contrast, figures as high as 10% have been reported in epidemic settings when patients had no access to health care or received improper treatment.[94] Treatment of cholera caused by O139 *V. cholerae* is the same. No significant differences in clinical manifestations of the disease caused by these two agents have been found.[95]

Antimicrobial agents play a secondary role in the treatment of cholera. Clinical trials have shown that when patients with severe dehydration are given antibiotics, the duration of diarrhea is decreased and the volume of stool is reduced by almost 50%.[96] Early discharge and lessened hydration decrease hospital expense. These benefits are critical in epidemic conditions. Oral tetracycline and doxycycline are the agents of choice in areas of the globe where sensitive strains predominate. A single dose of doxycycline (300 mg) is the preferred regimen.[97] Tetracyclines are not safe in children younger than 7 years, and alternatives such as trimethoprim-sulfamethoxazole, erythromycin, and furazolidone are preferred over tetracyclines. Pregnant women can be treated with erythromycin or furazolidone. Currently recommended regimens are presented in Table 214-5.

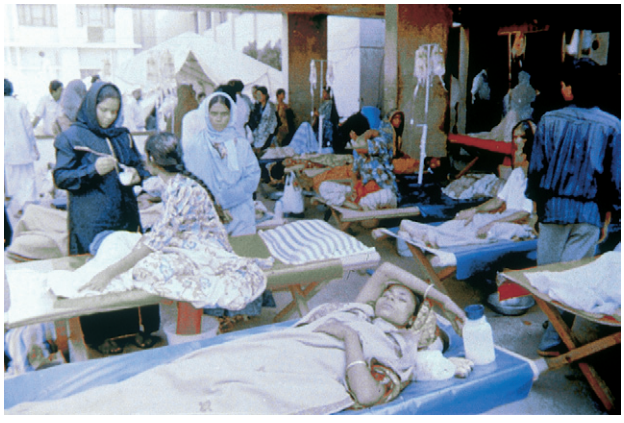

Figure 214-5 Patients with cholera caused by the O139 serogroup of *V. cholerae*. In this photograph, patients were being treated in the parking lot of the International Center for Diarrhoeal Disease Research, Dhaka, Bangladesh. Use of cholera cots, rehydration by the intravenous route of severely dehydrated patients, and rehydration by the oral route with oral rehydration therapy are shown. *(Courtesy of Dr. Wasif Ali Khan, International Center for Diarrhoeal Disease Research, Dhaka, Bangladesh.)*

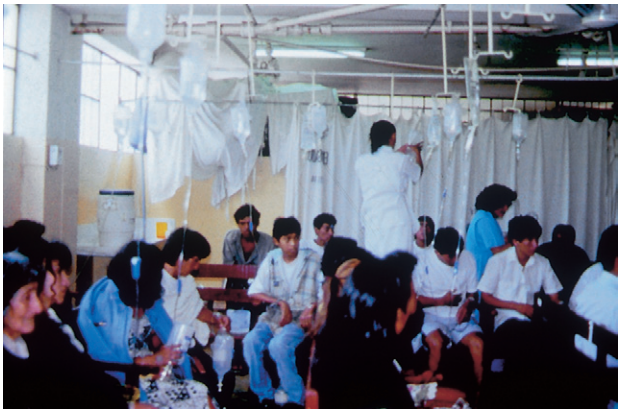

Figure 214-6 Patients with cholera caused by El Tor *V. cholerae* O1. In this photograph, patients were being treated in the Rehydration Unit at Hospital Nacional Cayetano Heredia, Lima, Peru. Cholera chairs instead of cholera cots were successfully used during the large epidemic of 1991. *(Courtesy of Dr. Eduardo Salazar, Department of Pediatrics, Hospital Nacional Cayetano Heredia, Lima, Peru.)*

Selection of an adequate antimicrobial in certain parts of the world has been complicated by the appearance of strains resistant to tetracyclines and other antimicrobial agents.[98,99] New agents have been tested in endemic and epidemic areas, with quinolones being the most effective.[100] Ciprofloxacin has been more extensively studied than other quinolones, showing at least similar if not better results than comparators in adults and children with severe cholera caused by O1 or O139 *V. cholerae* in single- or multiple-dose oral regimens.[101-103] However, single-dose regimens have shown lower clearance of the pathogen in the stools. More recently, strains resistant to quinolones have been reported from India.[104,105] The high cost and concern about cartilage damage in young children are drawbacks to large-scale quinolone use. Azithromycin has arisen as an alternative for the treatment of certain diarrheal diseases of bacterial origin. A single dose of azithromycin (20 mg/kg) in children with severe cholera in Bangladesh has shown clinical and bacteriologic results comparable to a 3-day regimen with erythromycin.[106] Better clinical and bacteriologic results were observed with single-dose azithromycin in adult patients with severe cholera compared with single-dose ciprofloxacin at the same institution.[107] Advantages of single-dose regimens like this are not only assurance of

TABLE 214-5 Antimicrobial Regimens for the Treatment of Cholera

	Dose	
Drug	*Adult*	*Children*
Tetracycline	500 mg qid for 3 days	50 mg/kg of body weight qid for 3 days
Doxycycline	300 mg as a single dose	Not evaluated
Furazolidone	100 mg qid for 3 days	5 mg/kg/day in four divided doses for 3 days or 7 mg/kg as a single dose
Cotrimoxazole	160 mg of trimethoprim/800 mg of sulfamethoxazole bid for 3 days	8 mg of trimethoprim/40 mg of sulfamethoxazole/kg divided in two doses for 3 days
Norfloxacin	400 mg bid for 3 days	Not recommended
Ciprofloxacin	1 g as a single dose	20 mg/kg of body weight as a single dose
	250 mg/day for 3 days	Dosing regimen not evaluated in children
Azithromycin	1 g as a single dose	20 mg/kg of body weight as a single dose

From Seas C, DuPont HL, Valdez LM, et al. Practical guidelines for the treatment of cholera. *Drugs*. 1996;51:966-973.

compliance, but also the potential reduction of resistance and the appeal for using them under extreme epidemic situations. The use of other drugs, such as antimotility agents (e.g., loperamide, diphenoxylate), adsorbents, analgesics, and antiemetics, is not recommended. The addition of oral zinc (30 mg/day) to an erythromycin regimen in children with cholera in Bangladesh resulted in a 12% reduction in the duration of diarrhea and an 11% decrease in the volume of stools compared with placebo; its incorporation into daily practice was recommended.[108] Chemoprophylaxis of household contacts of cholera cases has been proposed. However, published data do not support this concept.[5,109,110] Moreover, when transmission of the disease is low, as occurs in endemic areas, the usefulness of chemoprophylaxis is not significant.[111] Prophylaxis with antibiotics might be considered in situations in which the rate of transmission of the disease is high, along with other measures to curtail transmission.

Prevention and the Role of Vaccines

John Snow was the first scientist to show that transmission of cholera may be significantly reduced when uncontaminated water is provided to the population. Providing potable water and ensuring proper management of excreta to avoid contamination of other water sources are important measures to reduce cholera transmission. The limited number of indigenous cases reported from the United States and Australia, despite the fact that *Vibrio* is isolated from the environment in these countries, provides further evidence that hygiene and sanitation contain cholera transmission. However, the experience with continuing epidemics in developing countries shows that these simple measures are almost impossible to implement.

Alternative ways to prevent cholera transmission are necessary. Water can be made safer to drink by boiling or adding chlorine. Both methods are expensive and difficult to implement under epidemic situations. Exposing water to sunlight has also been considered, but its implementation is again not feasible in developing countries. Education of the population at risk about appropriate hygienic practices is always recommended, but the impact of massive educational campaigns on the reduction of cholera transmission is questionable. Identification of local customs that place people at risk may help in eliminating such practices. A simple preventive measure derived from better knowledge of the ecologic basis for disease transmission has been proposed by Colwell and colleagues.[112] Sari cloth, a traditional cloth of India and Bangladesh made of cotton, was folded eight times to retain particles larger than 20 µm, including copepods to which *V. cholerae* is attached, and was used to filter water for drinking purposes in the field. A marked reduction in cholera incidence in rural Bangladesh was observed by using this method. Simple measures such as this may be implemented in developing countries, with potential impact on transmission. Predicting the onset of an epidemic may have a tremendous impact on prevention. Searching for *V. cholerae* O1 from municipal sewage and environmental samples in endemic areas is a warning signal of future epidemics, because its detection precedes the occurrence of human cases.[113] The possibility of predicting an epidemic by monitoring the movement of plankton by satellite seems attractive, but more data are needed to support this method.

An inability to implement these measures to curtail cholera transmission has necessitated a search for vaccines. An ideal vaccine against cholera should elicit a fast and long-lasting immune response, with minimal side effects. Additionally, the vaccine should be locally produced and, to increase compliance, a single dose is highly desirable.

The parenteral vaccine once available in the United States had poor efficacy and required boosting every 6 months. That vaccine is no longer available. The disappointing experience with parenteral vaccines and the improved knowledge of the immune response to natural infection that has accumulated during recent years clearly show that an oral route for administering the vaccine is preferred. The ideal vaccine is still not available, but significant progress has been made. Two oral vaccines have been studied in epidemic and endemic settings. The oral inactivated vaccine WC-BS (whole cell plus B subunit) has been more extensively evaluated. Short- and long-term data from a large field trial conducted in Matlab, Bangladesh, have shown protective efficacy of 85% after 6 months, declining to 50% after 3 and 5 years.[114,115] Significant drawbacks were the need of two doses to confer protection, less protection against the El Tor biotype, less protection in children, and less protection in persons with blood group O. Benefits of THS vaccine, apart from its moderate direct protection, are indirect protection (herd immunity) of young infants and other residents in endemic areas,[116-118] and excellent protective efficacy (estimated to be 78%) after mass vaccination in field conditions in Africa, including refugee settings.[119,120] A vaccine with inactivated whole cells of four strains plus recombinant B subunit is available in some countries for adults and children 2 years of age or older, marketed as Dukoral. It is given as two doses 10 to 14 days apart. The vaccine does not reach maximal efficacy until 10 days after the second dose. A killed oral whole-cell cholera vaccine (without the B-subunit component), containing initially only O1 and more recently a reformulated bivalent vaccine (containing both O1 and O139 serogroups, biv-WC), has been produced and used in a national vaccination program in Vietnam[121,122] and has been tested in Kolkata, India.[123]

Another group of oral cholera vaccines is the live attenuated vaccines, especially the third-generation CVD 103–HgR. A live attenuated vaccine derived from reference strain 569B (classic 01, Inaba) is licensed in several countries as Orochol-E. Protective efficacy was achieved after 8 days in a volunteer study. Promising results with this vaccine, even in those with O blood group, were not confirmed when a large field trial was conducted in Jakarta, Indonesia.[124] The field trial showed no benefit from administration of the vaccine.

New vaccine candidates are currently being evaluated, including the live attenuated vaccine Peru-15, which contains El Tor vibrio.[116,125] Potential usefulness of cholera vaccines include use for high-risk persons in endemic areas, vulnerable populations under emergency situations, outbreaks if rapid implementation is feasible, and travelers.[126] A mathematical model has shown that by using the killed whole-cell vaccine, WC-BS, and covering 50% to 70% of the population, it is possible to achieve 89% reduction in cholera incidence in an endemic area.[127] An expert panel convened by the World Health Organization in 2005 recommended the use of oral cholera vaccines for certain endemic situations.[128] More recent statements consider the vaccines as promising strategies, in addition to known public health measures.[5] Current challenges are how to predict new epidemics, detect the appearance of new strains in the environment that may cause epidemics early, and induce lasting protective immunity, irrespective of age and blood group, with a single dose of an oral vaccine. Our understanding of this ancient scourge has improved significantly since the time of John Snow, but the solution remains the same.[129]

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