Cholera: Clinical features, diagnosis, treatment, and prevention

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INTRODUCTION

Cholera is an acute secretory diarrheal illness caused by toxin-producing strains of the gram-negative bacterium *Vibrio cholerae*. Severe cholera is characterized by profound fluid and electrolyte losses in the stool and the rapid development of hypovolemic shock, often within 24 hours from the initial onset of vomiting and diarrhea. Administration of appropriate rehydration therapy reduces the mortality of severe cholera from over 10 percent to less than 0.5 percent [1].

This topic discusses the epidemiology, clinical manifestations, diagnosis, treatment, and prevention of cholera. The microbiology and pathogenesis of *V. cholerae* and infections caused by non-O1/O139 *V. cholerae* strains are discussed elsewhere. (See "Cholera: Microbiology and pathogenesis" and "Infections due to non-O1/O139 Vibrio cholerae".)

The general approaches to acute diarrhea among adults and children in inadequately resourced settings are also discussed elsewhere. (See "Approach to the adult with acute diarrhea in resource-limited countries" and "Approach to the child with acute diarrhea in resource-limited

countries".)

ETIOLOGIC AGENT

V. cholerae is a diverse species and includes pathogenic and non-pathogenic variants. Only cholera toxin-producing (toxigenic) strains of *V. cholerae* are associated with cholera. *V. cholerae* is classified serologically; of over 200 serological groups identified, only 2 (*V. cholerae* O1 and O139) have caused cholera epidemics. This is discussed in detail elsewhere. (See "Cholera: Microbiology and pathogenesis", section on 'Microbiology'.)

EPIDEMIOLOGY

Cholera is vastly underreported, and precise measurements of the morbidity and mortality attributable to *V. cholerae* infection are lacking. However, there are an estimated 3 million cases of diarrheal illness and approximately 100,000 deaths worldwide caused by *V. cholerae* annually [2].

Global distribution — Cholera primarily occurs in settings where there is inadequate access to clean water and sanitation. Cholera is endemic in approximately 50 countries (defined as having reported cholera cases in at least three of the five past years), mostly in Africa and Asia [2]. In addition, epidemics due to *V. cholerae* have occurred throughout Africa, Asia, the Middle East, South and Central America, and the Caribbean and can be extensive [3]. As an example, the strain implicated in the 2010 outbreak in Haiti was subsequently associated with outbreaks in the neighboring countries of Dominican Republic, Cuba, and Mexico [4].

Cases in resource-rich settings are generally imported from travel to endemic or epidemic settings [5].

Transmission — *V. cholerae* infection is primarily acquired by ingesting contaminated food or water. In endemic regions, *V. cholerae* in the water are an important reservoir of the organism. Because *V. cholerae* can live on chitinous plankton [6], filtration of water through coarse cloth can reduce the incidence of cholera in endemic areas [7]. (See 'Preventing transmission' below.)

While exposure to environmental *V. cholerae* is important, direct person-to-person transmission is also thought to play a role in transmission. Individuals with severe cholera can excrete as many as 10^{10} to 10^{12} organisms per liter of stool. Organisms that were recently shed from infected individuals appear to be transiently more infectious than organisms isolated from the aquatic environment [8]. Mathematical models suggest that person-to-person transmission of human-shed,

hyper-infectious *V. cholerae* is essential for the rapid propagation of cholera that is observed during epidemics [9]. (See "Cholera: Microbiology and pathogenesis", section on 'Hyperinfectivity'.)

Endemic versus epidemic infection — Patterns of cholera transmission and infection differ between historically endemic areas and areas experiencing cholera epidemics.

In areas of high endemicity, the incidence of *V. cholerae* infection follows a seasonal distribution, with peaks before and after rainy seasons [3]. Superimposed epidemics may also occur, and mathematical models suggest these epidemics are dependent on fluctuations in population-based immunity and climate [10]. In areas of high endemicity, the incidence of cholera is highest in children younger than five years, likely reflecting the lack of protective immunity [11].

In areas with more limited immunity in the population, massive epidemics may occur, with similar attack rates in children and adults. The cholera epidemic in Haiti is an example of the consequences of the introduction of *V. cholerae* into a naïve population. A *V. cholerae* O1 variant El Tor strain was introduced into Haiti from South Asia possibly via United Nations stabilization forces [12,13]. Within two years, 604,634 cases of infection, 329,697 hospitalizations, and 7436 deaths from cholera were reported in Haiti [14].

Even in endemic regions, breakdowns in safe water, hygiene, and health services can contribute to epidemic transmission of cholera. In Yemen, where public health and healthcare infrastructure has been devastated by years of warfare, two rapidly sequential outbreaks occurred at the end of 2016 and the middle of 2017. The second of these outbreaks amounts to the world's worst cholera outbreak to date, with approximately 500,000 cases of suspected cholera and 2000 associated fatalities recorded within only four months [15].

Other major outbreaks have occurred in Sierra Leone, the Democratic Republic of Congo (DRC), Nigeria, Angola, Vietnam, Pakistan, and Zimbabwe. Experience from such outbreaks demonstrates that fatality rates in epidemic cholera are consistently higher than 1 percent, particularly in the early stages of an epidemic and in rural areas [16]. As an example, in the 2008 to 2009 cholera outbreak in Zimbabwe, which involved nearly 100,000 people, the case fatality rate was over 4 percent [17].

Risk factors — Cholera is associated with poverty and lack of access to safe food, water, and adequate sanitation [18]. Large cholera epidemics often occur in populations impacted by natural disaster or human conflict [19]. These associations reflect the underlying mode of transmission via contaminated food and water. For example, drinking un-boiled or untreated water is a commonly identified risk factor for cholera, while use of soap is associated with a lower likelihood of infection [20]. In some, primarily foodborne cholera outbreaks, risk factors may include consumption of

specific foods, including rice products, or specific vegetables or fruits [21]. In areas where cholera occurs sporadically, most cases are associated with shellfish consumption.

Other risk factors for *V. cholerae* infection and cholera reflect the biological interaction between the host and pathogen, including blood group O (associated with more severe cholera), hypochlorhydria (lowers the dose needed to cause infection), retinol deficiency [22-26]. Breastfeeding has been consistently shown to be protective against cholera [27,28]. (See "Cholera: Microbiology and pathogenesis", section on 'Host susceptibility'.)

CLINICAL MANIFESTATIONS

Infection with *V. cholerae* results in a spectrum of disease, ranging from asymptomatic intestinal colonization to severe diarrhea [29]. Abdominal discomfort, borborygmi, and vomiting are other common symptoms, particularly in the early phases of disease. Among those with severe disease, most complications are related to the substantial volume and electrolyte loss from diarrhea. Fever is uncommon.

The clinical manifestations of cholera caused by *V. cholerae* O1 versus O139 are indistinguishable.

Incubation period — Cholera has a typical incubation period of one to two days [30-32]. However, the incubation period of cholera varies with host susceptibility and inoculum size and can range from several hours to as long as three to five days.

Diarrhea — While mild cases of *V. cholerae* infection may be clinically indistinguishable from other causes of diarrheal illness, the profound and rapid loss of fluid and electrolytes mark severe cholera as a clinically distinct entity. Cholera stools may contain fecal matter and bile in the early phases of disease [3]. However, the characteristic symptom of severe cholera ("cholera gravis") is the passage of profuse "rice-water" stool, a watery stool with flecks of mucous (picture 1). It typically has a fishy odor. The diarrhea is usually painless, without tenesmus. In adults, stool output can reach as high as 1 liter per hour in the most severe cases. In children, the maximal rate of stool excretion in severe cholera is typically between 10 and 20 cc/kg/hour [33]. This rate of fluid loss is not typically observed in other causes of diarrheal illness.

In addition, compared with other causes of childhood diarrheal illness, stool from cholera patients contains a higher concentration of sodium, as well as significant amounts of potassium and bicarbonate (table 1).

In patients treated with proper rehydration, diarrhea is most severe during the first two days and ends after four to six days [34-36]. The total volume loss over the course of illness may be up to

100 percent of body weight [35].

Other gastrointestinal symptoms — Vomiting, frequently with watery emesis, is common, and may begin either before or after the onset of diarrhea. Patients may have abdominal cramping but typically do not have the frank abdominal pain classically associated with dysentery.

Manifestations of hypovolemia and electrolyte loss — Because of the rapid fluid and electrolyte loss characteristic of diarrhea associated with severe cholera, hypovolemia and electrolyte abnormalities are the most important sequelae. Severe hypovolemia may occur within hours of the onset of symptoms. In the early stages of the cholera epidemic in Haiti, the median time between onset of symptoms and death in individuals who died before presentation to a cholera treatment center was 12 hours [37].

Cholera patients with severe hypovolemia may have sunken eyes, dry mouth, cold clammy skin, decreased skin turgor, or wrinkled hands and feet (also known as "washer woman's hands"). Patients are frequently apathetic and lethargic. Acidosis from loss of stool bicarbonate as well as lactic acidosis from poor perfusion may result in Kussmaul breathing (deep respirations reflecting compensatory hyperventilation). The peripheral pulse is rapid and thready initially, and it may become difficult to palpate as blood pressure drops. Muscle cramping and weakness due to loss of potassium and calcium are common.

Laboratory testing of cholera patients may reveal hypokalemia, hyponatremia or hypernatremia (although cholera is most often associated with isonatremic dehydration), hypocalcemia, and acidosis.

Renal failure with acute tubular necrosis may occur as urine output decreases. In children, depletion of glycogen stores and inadequate gluconeogenesis can lead to symptoms of severe hypoglycemia or even coma.

Additional complications — Pneumonia has been described as a frequent comorbidity among children with cholera, potentially from aspiration in the setting of vomiting, and has been associated with mortality [38]. Blood stream invasion by the organism is rare. Fever is also infrequent, so the presence of an elevated temperature should prompt consideration of a concurrent infection or complication.

"Cholera sicca" is an unusual form of the disease in which fluid accumulates in the intestinal lumen; circulatory collapse and even death can occur in the absence of diarrhea.

In general, there are no long-term complications of cholera when it is appropriately treated. However, like other causes of childhood diarrheal illness, cholera may contribute to the

development of chronic enteropathy and malnutrition in young children.

Mortality — The mortality of cholera in untreated patients may reach 50 to 70 percent [39,40]. Administration of appropriate rehydration therapy can reduce the mortality of severe cholera to less than 0.5 percent [1]. In areas where cholera is endemic, the mortality risk is increased in children (10 times greater than in adults) [41,42]. Although earlier studies had suggested a high risk of fetal death associated with cholera during pregnancy (up to 50 percent during the third trimester), more recent studies have reported a lower, but still elevated, risk (approximately 8 percent) [43,44].

DIAGNOSIS

Most cases of cholera are presumptively diagnosed based on clinical suspicion in patients who present with severe acute watery diarrhea. The diagnosis can be confirmed by isolation of *V. cholerae* from stool cultures performed on specific selective media. Rapid tests such as stool dipsticks or darkfield microscopy can support the diagnosis in settings where stool culture is not readily available. (See 'Diagnostic studies' below.)

However, because of the morbidity of severe cholera, the variable availability of diagnostic testing in endemic and epidemic settings, and the general applicability of fluid resuscitation to other causes of severe watery diarrhea, management of cholera should be initiated on the basis of clinical suspicion. (See 'Treatment' below.)

When to suspect cholera — Cholera is a potential cause of any case of severe watery diarrhea with or without vomiting, especially in patients who develop rapid and severe volume depletion. Whereas many different microbial pathogens can lead to volume-depleting diarrhea in children, *V. cholerae* is the primary etiology in adults with such a presentation.

Specifically, according to the World Health Organization, cholera should always be suspected when a patient five years or older develops severe volume depletion from acute watery diarrhea, even in an area where cholera is not known to be endemic [45]. In endemic areas, cholera should be suspected in patients two years or older with severe acute watery diarrhea.

In resource-rich settings where cholera is rare, epidemiologic clues that might increase the suspicion of *V. cholerae* in a patient with watery diarrhea include travel to endemic areas or areas where cholera outbreaks are occurring or ingestion of undercooked or raw shellfish.

Diagnostic studies

Stool culture — A definitive diagnosis of cholera is based on isolation of the organism from clinical samples, which also permits a determination of the antibiotic susceptibility profile. *V. cholerae* can be isolated from stool using selective media such as thiosulfate citrate bile sucrose (TCBS) agar or taurocholate tellurite gelatin agar (TTGA). Once cultured, *V. cholerae* can be identified by biochemical tests; serogroup and serotype can be assigned by testing with specific antibodies [46]. In settings such as the United States, where cholera is a sporadic illness, the clinical microbiology laboratory should be informed of a suspicion of cholera so that appropriate selective media can be used. These selective media are not routinely used for stool culture.

The recovery of viable *V. cholerae* from clinical specimens can be enhanced by enrichment in alkaline peptone water [46]. *V. cholerae* can also persist in a number of standard transport media, including Cary-Blair media, while being transported to a central laboratory from field settings.

Molecular and rapid tests — Several rapid, antigen detection-based tests are commercially available to diagnose cholera [47]. These include immunochromatographic lateral flow devices (dipsticks), such as Crystal VC, which detect the presence of the O1 or O139 antigen in rice water stool samples, and Cholkit, which detects only the O1 antigen.

These rapid tests are less specific than the gold standard of culture, but this may reflect the lack of sensitivity of culture in individuals who no longer shed viable bacteria in the stool (eg, many individuals are coinfected with lytic bacteriophage or are taking antibiotics that may render the culture negative) [48,49]. Thus, the low specificity of antigen-based dipstick tests may be more reflective of the limits of bacterial culture. Models that account for this suggest that some rapid tests are actually quite accurate. As an example, when the performance of Cholkit, Crystal VC, microbial culture, and polymerase chain reaction (PCR) were estimated using latent class modeling, the sensitivity of Cholkit and Crystal VC were both 98 percent (95% CI 88-100 percent for both), with specificities of 97 percent (95% CI 89-100 percent) and 98 percent (95% CI 92-100 percent) respectively [50].

Accurate molecular testing for *V. cholerae* (eg, PCR), including tests that use dried fecal spots, is also feasible, but the practical use of molecular tests has been primarily limited to epidemiologic research and surveillance [51].

Darkfield microscopy of fresh rice-water stools (at 400x magnification) can also be used to rapidly evaluate for the presence of highly motile Vibrios, whose shooting star-like motion can be inhibited by the subsequent addition of specific antibodies [52]. Darkfield microscopy is quite specific for *V. cholerae* but lacks sufficient sensitivity for it to be used reliably for diagnosis.

ADDITIONAL EVALUATION

Further clinical evaluation of the patient with suspected or confirmed cholera includes an assessment of the degree of volume depletion (table 2), as this determines the management strategy. (See 'Assessment of fluid loss' below.)

Laboratory testing is generally not needed, although serum electrolyte and glucose testing may be helpful to identify extreme abnormalities in patients who have ileus, confusion, seizure, or no urine output in response to fluid replacement. (See "Approach to the adult with acute diarrhea in resource-limited countries", section on 'Clinical assessment' and "Approach to the child with acute diarrhea in resource-limited countries", section on 'Clinical assessment'.)

DIFFERENTIAL DIAGNOSIS

A variety of pathogens can cause acute watery diarrhea (table 3). In resource-limited settings, where cholera most commonly occurs, rotavirus and cryptosporidium are frequent causative pathogens among infants and young children, whereas enterotoxigenic *Escherichia coli* predominates among older children and adults.

There are no signs or symptoms that can unequivocally distinguish cholera from other infectious causes of severe watery diarrhea. However, as above, suspicion for cholera should be raised if watery diarrhea is accompanied by severe and rapid volume depletion or occurs in an outbreak setting.

TREATMENT

Aggressive volume repletion is the mainstay of treatment for cholera. Replacement fluids can be given orally, except in the cases of severe volume depletion or shock, in which rapid fluid repletion is warranted and intravenous fluids should thus be given. Antibiotics are an adjunctive therapy for patients with some to severe volume depletion and may be of particular use in epidemic settings. Ensuring adequate nutrition is important for all patients, and children may additionally benefit from supplementation of certain micronutrients.

These issues are discussed in detail below. The discussion is consistent with recommendations from the World Health Organization (WHO), which are based upon the natural history and pathophysiology of cholera as well as practical considerations from a public health standpoint [45].

Fluid management — Fluid management of a patient with suspected or confirmed cholera is guided by the level of volume depletion and an assessment of ongoing fluid losses.

Assessment of fluid loss — Volume status can be readily assessed through simple examination of the mental status, eyes, mouth, skin, and pulse. The degree of volume depletion can be categorized by WHO criteria of none (<5 percent of body weight), some (5 to 10 percent), or severe (>10 percent) based on physical findings (table 2). Cholera cots (picture 2) are inexpensive and useful for estimating continued volume losses in stool. In the absence of cholera cots, continuing losses can be estimated as 10 to 20 mL/kg of body weight for each stool or episode of vomiting.

Fluid resuscitation — The type and quantity of fluids to administer is determined by the level of volume depletion and an assessment of ongoing fluid losses (table 2). The entire estimated fluid deficit should be replaced within three to four hours of presentation [45].

Detailed approaches to fluid repletion for adults (algorithm 1) and children with acute diarrhea are found elsewhere. (See "Approach to the adult with acute diarrhea in resource-limited countries", section on 'Rehydration' and "Approach to the child with acute diarrhea in resource-limited countries", section on 'Fluid and electrolytes'.)

Of note, while the general approach to volume repletion for severe cholera follows that for watery diarrhea from other causes, the specifics of fluid management for cholera are distinct in that patients with severe cholera present with more severe volume depletion (usually >5 percent), have more rapid fluid losses (typically 10 to 20 mL/kg/hour), and have proportionally greater electrolyte losses in the stool than patients with non-cholera gastroenteritis [53,54]. For these reasons, the most common errors in caring for patients with cholera include underestimating the amount of fluid needed to correct volume depletion and replace ongoing losses, or the use of incorrect, non-isotonic fluids to replace stool losses.

- Patients with some volume depletion — Oral rehydration solution (ORS) should be used for volume repletion (table 4), as it is as effective as and more practical than intravenous fluid repletion in this setting (see "Oral rehydration therapy", section on 'Efficacy'). In 2002, WHO recommended the use of a reduced osmolar ORS, which has been demonstrated to decrease stool output, vomiting, and the need for supplemental intravenous fluids [55]. Among patients with cholera, subclinical hyponatremia is common with this WHO recommended ORS formulation, but rates of symptomatic hyponatremia do not appear to be significantly increased [56]. A rice-based ORS that includes rice powder instead of glucose has also been demonstrated to reduce the duration of diarrhea and stool losses in severe cholera but is more tedious to prepare [57]. Types of ORS are discussed in detail elsewhere (table 1). (See

"Oral rehydration therapy", section on 'Commercial and standard ORS'.)

Of note, patients with profound vomiting or continuing stool losses in the setting of severe cholera can rapidly progress to severe dehydration if only ORS is provided, and intravenous therapy in conjunction with ORS may thus be warranted for these patients. Other indications for intravenous volume repletion in patients without severe volume depletion include an inability to drink because of vomiting or mental status changes.

- Patients with severe volume depletion or hypovolemic shock — Intravenous fluids should be urgently administered to rapidly restore circulation. An initial fluid volume of 100 mL/kg should be given over three hours (or five hours for infants), with 30 mL/kg given over the first half-hour (or first hour for infants). In patients with cholera, intravenous Ringer's lactate is the best commercially available intravenous solution for this purpose as it includes potassium and sodium bicarbonate, which are both lost in cholera stools (table 1). However, locally-prepared fluids, such as "Dhaka solution," containing glucose and more potassium than Ringer's lactate are available in some cholera-endemic regions and can address potential complications of severe cholera including hypokalemia, hypoglycemia, and metabolic acidosis.

Patients with severe cholera typically require an average of 200 mL/kg of isotonic oral or intravenous fluids in the first 24 hours of therapy and may require more than 350 mL/kg [45]. Adherence to current standards of fluid management reduces the mortality of severe cholera to less than 0.2 percent [58]. However, access to appropriate rehydration therapy is an important obstacle, particularly during cholera epidemics. For this reason, a community-based response and the strategic use of decentralized treatment centers (ie, oral rehydration points) to improve access to therapy are crucial to the successful management of cholera outbreaks [59].

Continued monitoring — Volume status should be assessed through physical exam on an ongoing basis (table 2), more frequently for more severe volume depletion. The rate of fluid repletion can be increased if volume depletion is not improving. Once the fluid volume to replace the estimated initial deficit has been administered, patients should then be managed based on the estimated degree of residual volume depletion from ongoing losses.

Antibiotic therapy — Antibiotics are an adjunctive therapy for patients with cholera and moderate to severe volume depletion. Several studies have demonstrated that in such patients, effective antibiotics for cholera (table 5) can shorten the duration of diarrhea, reduce the volume of stool losses by up to 50 percent, and lessen the duration of shedding of *V. cholerae* to one to two days [60]. As they can decrease shedding of an infectious organism, it is logical that antibiotics would play a particularly important role in interrupting cholera outbreaks, although this has not been directly demonstrated [61]. Antibiotics can be administered once the initial volume deficit is

corrected and vomiting has ceased.

The antibiotic options for cholera include macrolides, fluoroquinolones, and tetracyclines. The choice between them should be based on availability and local resistance patterns.

Tetracyclines are the antibiotic class for which there is greatest clinical experience, and several trials have demonstrated the efficacy of tetracyclines [60,62]. In a randomized trial from Bangladesh of 246 patients with severe volume depletion and culture confirmed tetracycline-susceptible *V. cholerae*, a single high dose of doxycycline (300 mg) had similar efficacy as a two-day course of tetracycline (500 mg every six hours) with respect to stool output, duration of diarrhea, vomiting, and requirement for oral rehydration solution [63]. However, resistance to tetracycline and doxycycline is common [39,64,65], so empiric use of these agents should be limited to outbreak settings in which the causative isolate has documented susceptibility.

In regions where tetracycline resistance is common, fluoroquinolones and macrolides are reasonable alternative agents, although resistance to fluoroquinolones is also growing in endemic areas.

Fluoroquinolones at varying doses, including a single dose, have had at least comparable efficacy as tetracyclines against both *V. cholerae* O1 and O139 in several trials [66-68]. In one randomized trial that included 260 adult men with moderate to severe volume depletion in the setting of *V. cholerae* O1 or O139 infection in Bangladesh, ciprofloxacin (1000 mg single dose) was effective against both strains, and superior to doxycycline (300 mg single dose) in eradicating organisms from stool [67]. In that study, 37 percent of the O1 isolates were resistant to tetracycline. However, in Asia and Africa, fluoroquinolone resistance among *Vibrio cholerae* O1 isolates has subsequently been described [69-71]. Between 2001 and 2004, the in vitro susceptibility of *V. cholerae* O1 to ciprofloxacin in Bangladesh decreased, as reflected by a 10-fold increase in the mean minimal inhibitory concentration [MIC] from 0.023 mcg/mL to 0.250 mcg/mL [69,71].

Macrolides are also effective in adults and children [69,71-74]. In a trial of 128 children with cholera, erythromycin (12.5 mg/kg every six hours for three days) and azithromycin (20 mg/kg single dose) had similar clinical and bacteriologic efficacy, although azithromycin was associated with less vomiting. Some trials have demonstrated greater efficacy with macrolides compared with fluoroquinolones, likely because of decreased susceptibility of *V. cholerae* strains to the latter [71,72,74]. As an example, in a randomized trial of 195 men with severe cholera in Bangladesh, single-dose azithromycin (1 gram) was superior to single-dose ciprofloxacin (1 gram) with regards to clinical efficacy (73 versus 27 percent ceased to have watery stool at 48 hours) and bacteriologic efficacy (78 versus 10 percent eradication of *V. cholerae* from stools at 48 hours) [71]. The median MIC to ciprofloxacin in this study was 11 to 83 times higher than observed in

previous studies at that site. Strains of *V. cholerae* O1 resistant to both erythromycin and azithromycin have rarely been reported [75].

Most *V. cholerae* O139 strains and many O1 El Tor strains are resistant to trimethoprim-sulfamethoxazole and furazolidone [65].

Nutrition and vitamins — As with other causes of acute diarrhea, adequate nutrition in patients with cholera is important to prevent malnutrition and facilitate recovery of normal gastrointestinal function [45]. Eating should resume as soon as possible after the initial fluid deficit of cholera is corrected, and breastfeeding of infants should be encouraged in conjunction with oral rehydration solution.

Among children who have acute diarrhea, zinc and vitamin A supplementation are also important interventions. Zinc supplementation reduces the duration and volume of stool in children with cholera [76]. This is discussed elsewhere. (See "Approach to the child with acute diarrhea in resource-limited countries", section on 'Vitamins and minerals'.)

PREVENTION

Preventing transmission — A clean water supply and appropriate sanitation are the cornerstones of cholera prevention. However, these can be difficult to achieve in resource-limited settings. Over 2 billion people lack access to clean water or sanitation and are thus at risk for waterborne diseases such as cholera [77]. Breastfeeding of young infants in endemic settings protects against cholera and other enteric infections (see "Infant benefits of breastfeeding", section on 'Prevention of illnesses while breastfeeding'). Additionally, filtering water through a sari cloth before drinking has been demonstrated to be effective in preventing *V. cholerae* infection acquired from surface water sources [7].

Travelers to regions where cholera is endemic should follow the general precautions for the prevention of travelers' diarrhea [78]. This includes avoidance of tap water, food from street vendors, raw or undercooked seafood, and raw vegetables [79]. Water can be treated with chlorine or iodine, by filtration, or by boiling [80]. (See "Travel advice", section on 'Food and water'.)

Vaccines

For residents in endemic areas — WHO recommends the inclusion of oral cholera vaccines in cholera control programs in endemic areas, in conjunction with other prevention and control strategies [81]. WHO also recommends that oral cholera vaccines be considered as part of an integrated control program in areas at risk for a cholera outbreak. The optimal use of cholera

vaccines after an outbreak remains an area of active investigation [82], although observational data suggest that vaccination following the onset of an epidemic is effective in reducing the risk of cholera [83], even if only a single dose can be given [84].

Internationally licensed, commercial, oral cholera vaccines include:

- Bivalent killed whole-cell vaccine (eg, Shanchol, Shantha Biotechnics-Sanofi Pasteur, India; or Euvichol, EuBiologics, Republic of Korea) – Contains killed whole cells of several biotypes and serotypes of *V. cholerae* O1 and *V. cholerae* O139 without supplemental cholera toxin B subunit. Its efficacy has been evaluated in several trials in India and Bangladesh [85-89]. Vaccine efficacy in these trials ranged from 53 to 67 percent and persisted five years following vaccination; herd protection has also been demonstrated. In children ≤5 years old, short-term efficacy was similar to that for older individuals, although was lower (42 percent) five years following vaccination. In situations in which the full vaccine series cannot be given, even a single vaccine dose appears to provide protection for older children and adults. In a randomized placebo-controlled trial, adjusted six-month vaccine efficacy of a single dose of Shanchol was 40 and 63 percent for all and severely dehydrating cholera, respectively, and protection was sustained over at least two years [87,90]. However, there was no evidence of protection in children under five years of age.

  Additionally, observational evidence suggests that when given shortly after the onset of a cholera epidemic, vaccination with Shanchol can provide protection within the first several months following administration. A case control study following a cholera outbreak in Guinea reported that two doses of Shanchol given as part of a nonselective mass vaccination campaign were associated with an adjusted vaccine efficacy of 87 percent [83].

- WC-rBS (eg, Dukoral, Crucell, Sweden) – Contains killed whole cells of several biotypes and serotypes of *V. cholerae* O1 in addition to recombinant cholera toxin B subunit. Its efficacy has been evaluated in several studies, including two that occurred in outbreak settings in Mozambique and Zanzibar [91,92]. In both studies, oral cholera vaccination was undertaken prior to the outbreak, and in both studies, receipt of one or more doses of vaccine was associated with 78 percent protection. Vaccination was equally effective in children ≤5 years and in older persons [91]. Protection declines rapidly in young children after six months but remains as high as 60 percent in older recipients for two to three years. The WC-rBS vaccine also appears to provide herd immunity when high levels of vaccine coverage are attained [93]. It is not effective against *V. cholerae* O139.

For travelers to high-risk areas — Most travelers to resource-limited settings are at low risk for cholera, even if they are traveling to endemic or epidemic locations. Select travelers, such as

aid, refugee, and healthcare workers planning to work among displaced populations (eg, those in crowded camps and urban slums) in endemic or epidemic settings, are at higher risk and may benefit from pre-travel cholera vaccination. (See "Immunizations for travel", section on 'Indications'.)

In the United States, a live oral vaccine CVD 103-HgR (Vaxchora) that prevents cholera caused by serotype O1 is available for adult travelers at high risk of exposure [94]. The efficacy of the vaccine was demonstrated in a placebo-controlled trial of 197 healthy volunteers who underwent oral challenge with a *V. cholerae* O1 strain [95]. Efficacy of a single vaccine dose against moderate to severe cholera (passage of over three liters of loose stool) was 90 and 80 percent among those who received the oral challenge 10 days and three months following vaccination, respectively. The vaccine was well tolerated without increased rates of diarrhea, other gastrointestinal complaints, or fever. Clinical use of this vaccine is discussed elsewhere. (See "Immunizations for travel", section on 'Cholera vaccine'.)

In other countries, such as Canada and Europe, the oral, inactivated whole cell recombinant cholera toxin B subunit vaccine (Dukoral) discussed above is available for prevention of cholera caused by serotype O1 in travelers. (See 'For residents in endemic areas' above.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Acute diarrhea in adults" and "Society guideline links: Travel medicine".)

SUMMARY AND RECOMMENDATIONS

- Cholera is an acute secretory diarrheal illness caused by toxin-producing strains of the gram-negative bacterium *Vibrio cholerae*. Strains of *V. cholerae* that do not produce toxin do not cause cholera. *V. cholerae* is classified serologically, based on differences in the structure of the O-antigen of lipopolysaccharide. Of over 200 serological groups identified, only two (*V. cholerae* O1 and O139) have caused cholera epidemics. (See 'Etiologic agent' above.)
- The precise burden of cholera is difficult to define, as the disease is vastly underreported. Cholera primarily affects resource-limited settings where there is inadequate access to clean water sources, as infection is most frequently acquired by the ingestion of food or water contaminated with *V. cholerae*. Cholera is endemic in approximately 50 countries, mostly in

Africa and Asia, and has caused extensive epidemics throughout Africa, Asia, the Middle East, South and Central America, and the Caribbean (figure 1). Patterns of cholera transmission and infection differ between historically endemic areas and areas experiencing cholera epidemics. (See 'Epidemiology' above.)

- Infection with *V. cholerae* results in a spectrum of disease, ranging from asymptomatic intestinal colonization to severe diarrhea. While mild cases of *V. cholerae* infection may be clinically indistinguishable from other causes of watery diarrheal illness, the profound and rapid loss of fluid and electrolytes mark severe cholera as a clinical entity distinct from other causes. Significant hypovolemia and electrolyte abnormalities, which can occur within a few hours of symptom onset, are the most important sequelae of severe cholera. Abdominal discomfort, borborygmi, and vomiting are other common symptoms, particularly in the early phases of disease. (See 'Clinical manifestations' above.)

- Most cases of cholera are presumptively diagnosed, based on consistent clinical manifestations. Cholera is a potential cause of any case of severe watery diarrhea with or without vomiting, especially in patients who develop rapid and severe volume depletion. Whereas many different microbial pathogens can lead to volume depleting diarrhea in young children, *V. cholerae* is the primary etiology in older individuals with such a presentation. The diagnosis can be confirmed by isolation from stool cultures performed on specific selective media. Rapid tests such as stool dipsticks or darkfield microscopy can support the diagnosis in settings where stool culture is not readily available. (See 'Diagnosis' above.)

- Aggressive volume repletion is the mainstay of treatment for cholera. The type and quantity of fluids to administer is determined by the level of volume depletion and an assessment of ongoing fluid losses (table 2). Replacement fluids can be given orally, except in the cases of severe volume depletion or shock, in which rapid fluid repletion is warranted and intravenous fluids should thus be given. Patients with severe cholera typically require an average of 200 mL/kg of isotonic oral or intravenous fluids in the first 24 hours of therapy and may require more than 350 mL/kg. (See 'Fluid management' above.)

- Antibiotics can shorten the duration of diarrhea, reduce the volume of stool losses, and lessen the duration of *V. cholera* shedding. We suggest antibiotics for patients who have moderate to severe volume depletion in the setting of suspected or documented cholera (**Grade 2B**). We also suggest antibiotics for patients who have suspected or documented cholera in the setting of an epidemic (**Grade 2C**). Antibiotics are usually given orally, after initial rehydration and when the patient is no longer vomiting. The antibiotic options for cholera include macrolides, fluoroquinolones, and tetracyclines (table 5). The choice between them should be based on

availability and local resistance patterns. (See 'Antibiotic therapy' above.)

- As with other causes of acute diarrhea, adequate nutrition in patients with cholera is important to prevent malnutrition and facilitate recovery of normal gastrointestinal function. In addition, children with acute diarrhea may benefit from zinc and vitamin A supplementation. (See 'Nutrition and vitamins' above.)

- A clean water supply and appropriate sanitation are the cornerstones of cholera prevention. In addition, two oral cholera vaccines that are available internationally have demonstrated protective efficacy of 60 to 80 percent in areas at high risk of outbreak. These vaccines may be particularly useful as part of cholera prevention programs in endemic areas or in areas at high risk for cholera epidemics. (See 'Prevention' above.)

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