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Cholera

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Summary

Cholera is an acute, secretory diarrhea caused by infection with *Vibrio cholerae* of the O1 and O139 serogroups. Cholera is endemic in over 50 countries and also causes large epidemics. Since 1817, seven cholera pandemics have spread from Asia to much of the world. The 7th pandemic began in 1961 and affects 3–5 million people each year, killing 120,000. Although mild cholera may be indistinguishable from other diarrheal illnesses, the presentation of severe cholera is distinct, with dramatic diarrheal purging. Management of patients with cholera involves aggressive fluid replacement; effective therapy can decrease mortality from over 50% to less than 0.2%. Antibiotics decrease volume and duration of diarrhea by 50% and are recommended for patients with moderate to severe dehydration. Prevention of cholera depends on access to safe water and sanitation. Two oral cholera vaccines are available and the most effective use of these in integrated prevention programs is being actively evaluated.

Cholera is an acute secretory diarrhea caused by the Gram-negative bacterium *Vibrio cholerae* (1–4). Cholera epidemics have been recently increasing in intensity, duration and frequency, highlighting the need for more effective approaches to prevention and control.

History

Descriptions of a disease thought to be cholera are found in Sanskrit back to the 5th century BC, and the disease has existed on the Indian subcontinent for centuries. In 1817, cholera spread beyond the Indian subcontinent and there were six world-wide cholera pandemics between 1817 and 1923. Between 1849 and 1854, London physician John Snow proposed that cholera was a communicable disease and that stool contained infectious material. He suggested that this infectious material could contaminate drinking water supplies, resulting in transmission of cholera. Filippo Pacini, working independently in Italy in 1854, first

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observed comma-shaped forms under a microscope in cholera stools. In 1884, Robert Koch first isolated *V. cholerae* in pure culture in work that began in Egypt and continued in Calcutta (Kolkata), India.

The ongoing seventh cholera pandemic began in Indonesia in 1961 and spread through Asia to Africa, Europe, and Latin America. This pandemic is caused by a new biotype of *V. cholerae* first isolated in 1905 in El Tor, Egypt (3). Although cholera is vastly under-reported, the WHO estimates that there are 3–5 million cases per year (5), predominantly in Asia and Africa, with periodic outbreaks such as recently in Haiti (6). Diarrheal diseases including cholera are the second leading cause of mortality worldwide among children under 5 years of age, and a principal cause of morbidity (7). Cholera is also a major cause of severe dehydrating diarrhea in adults.

Etiologic agent

V. cholerae is a member of the Vibrionaceae family of curved, Gram-negative rods that are found in coastal waters and estuaries (1;3). These organisms grow best in the presence of salt, although *V. cholerae* can grow in water of lower salinity when it is warmer and contains sufficient organic nutrients (8). *V. cholerae* is often associated with zooplankton and shellfish in water (8), and is capable of utilizing chitin as a carbon and nitrogen source (9). Chitin induces natural competence in *V. cholerae*, suggesting that lateral gene transfer may occur in water, particularly during zooplankton blooms (10). In water, *V. cholerae* enter a viable but non culturable form (11), also called active but non-culturable or conditionally viable environmental cells (4;12).

V. cholerae is classified into more than 200 serogroups based on the O antigen of the lipopolysaccharide (1); of these, only O1 and O139 serogroups cause epidemic cholera. *V. cholerae* O1 is further classified into two biotypes, classical and El Tor (3). There are two major serotypes, Ogawa and Inaba, which vary in prevalence over time (13). In 1992, *V. cholerae* O139 was first recognized in south Asia as a cause of epidemic cholera (14;15). This organism is derived from *V. cholerae* O1 El Tor by lateral transfer of a genomic island substituting the O139 for the O1 antigen, but is otherwise virtually identical to *V. cholerae* O1 El Tor (16;17). Although classical *V. cholerae* O1 caused the fifth and sixth pandemics (and presumably the earlier pandemics), the seventh pandemic is due to the El Tor biotype, which has now replaced the classical biotype.

Although earlier isolates of *V. cholerae* O1 were susceptible to most antibiotics, *V. cholerae* O139, as well as more recent isolates of *V. cholerae* O1 El Tor, have acquired an SXT element that mediates resistance to sulfamethoxazole-trimethoprim and streptomycin (18); this element is found in almost all strains isolated over the past decade (19). More recently, strains of *V. cholerae* O1 resistant to tetracycline, erythromycin, and/or ciprofloxacin have been recovered in Asia (19;20); some of these strains have acquired additional resistance genes in the SXT element. These multiresistant strains have not yet been recognized in other locations.

Pathogenesis and pathophysiology

After ingestion of *V. cholerae*, the majority are killed by gastric acid. Surviving organisms colonize the small intestine and elaborate cholera toxin, the major virulence factor for pathogenic strains of *V. cholerae* (3). Cholera toxin is a protein exotoxin that consists of a single A subunit associated with five B subunits (21). The B subunit pentamer binds to the ganglioside GM_1 on eukaryotic cells, and the A subunit is translocated intracellularly, where it acts enzymatically to activate adenylate cyclase and elevate intracellular cAMP; this leads to chloride secretion through the apical chloride channel and secretory diarrhea (22–24). The

second major virulence factor of pathogenic strains of *V. cholerae* is the toxin-co-regulated pilus, a colonization factor whose expression is regulated in parallel to cholera toxin (25;26).

The genes for cholera toxin are encoded within the genome of a filamentous bacteriophage, CTXφ (27). Classical and El Tor strains have different versions of this bacteriophage, which can insert at one or two attachment sites in the genome depending on the biotype. The bacterial cell surface receptor for CTXφ is the toxin-co-regulated pilus (27), which is itself encoded within a genomic island, vibrio pathogenicity island (VPI-1) (28;29). Evolution of virulence in *V. cholerae* involves sequential acquisition of VPI-1 followed by CTXφ.

All seventh pandemic strains of *V. cholerae* O1 El Tor contain VPI-1, as well as a second vibrio pathogenicity island VPI-2, and two genomic islands specific to the seventh pandemic strains, vibrio seventh pandemic islands 1 and 2 (30). Recent seventh pandemic strains have been described that have the classical form of CTXφ instead of El Tor CTXφ, or a variant of the El Tor CTXφ encoding the B subunit of cholera toxin (CtxB) found in classical *V. cholerae* O1 strains (31). The variant El Tor strains have largely replaced the earlier El Tor strains and may be associated with more severe diarrhea.

Epidemiology

Cholera occurs in both endemic and epidemic patterns. Cholera is endemic in many areas of Asia and Africa. In Asia, cholera occurs seasonally before and after the monsoon rains (3), and the incidence of disease peaks in children younger than five years, and may occur in neonates (32;33). Cholera epidemics occur in a longer cycle superimposed on existing endemic disease. This pattern relates to declining levels of population-level immunity from a previous outbreak, overlaid on cycles of climate variability (34). In recent years, devastating epidemics of cholera have occurred in Angola, Ethiopia, Zimbabwe, Pakistan, Somalia, Sudan, Vietnam, and Haiti (35). Among immunologically naïve populations, cholera affects all age-groups, and epidemics can be associated with high case fatality rates (35). This pattern was observed in Haiti, where cholera had been notably absent prior to 2010. Population density, lack of sanitation and health infrastructure, and logistical obstacles to appropriate case management also contribute to a high case fatality rate in epidemic settings.

Environmental factors are important in the epidemiology of cholera. Changes in surface water temperature and terrestrial nutrient discharge lead to a proliferation of phytoplankton and zooplankton and a consequent increase in *V. cholerae* (8;36;37). Cholera rates also increase dramatically during floods compared to non-flood periods (38). Natural disasters that disrupt public health facilities, such as cyclones and earthquakes, also contribute to cholera epidemics.

The infectious dose of *V. cholerae* O1 has been estimated to be $10^5 - 10^8$ in human volunteers, but may be as low as 10^3 in the presence of achlorhydria (39). The incubation period ranges between 12 hours and 5 days (1;40).

Molecular epidemiology

The genome of a *V. cholerae* O1 El Tor strain was sequenced in 2000 (41); as with all vibrios, this organism has a large and a small circular chromosome (42). All Vibrionaceae have a super-integron in the small chromosome that acts as a gene capture system (43;44). A comparison of genomic sequences of patient and environmental strains isolated over nearly 100 years demonstrated 12 distinct lineages of *V. cholerae* O1; the classical and El Tor O1 biotypes comprised one lineage in this phylogeny (31). All strains of *V. cholerae* O1 El Tor shared a highly conserved core genome, with variations due mainly to laterally transferred genetic elements and single nucleotide variation.

An analysis suggested that the 7th pandemic strains originated from a single source in the Bay of Bengal that has spread to distant locations in three independent but overlapping waves (45). The first wave, which spread from Asia into Africa and South America, lacked the SXT element. The second wave acquired the SXT element and replaced the isolate in the first wave; the third wave also contains the SXT element. Isolates in the Haiti outbreak are closely related to south Asian strains in the third pandemic wave (46).

Transmission of cholera

Patients infected with *V. cholerae* O1 or O139 who are asymptomatic generally shed the organism for only a few days; however, patients who are symptomatic shed the organism between two days and two weeks, and rarely longer (4;40). Transmission of cholera within households has been documented (40). *V. cholerae* are present in human stool both as individual planktonic cells as well as in biofilm-like aggregates (47;48). In environmental water, organisms convert to conditionally viable environmental cells (12) within 24 hours (49). These organisms are infectious upon reintroduction into humans, although the infectious dose in this form is not known. Filtration of water through sari cloth reduces cholera transmission by nearly 50%, consistent with removal of organisms attached to zooplankton (50).

The peak of a cholera epidemic is often preceded by increasing prevalence of the pathogenic strain in the environment (12). Bacteriophage that are lytic for *V. cholerae* O1 or O139 are also found in the stools of patients and in environmental water (12;51). Bacteriophage density increases as an outbreak proceeds, and these bacteriophages may modulate the severity and duration of an outbreak (12;51;52).

As *V. cholerae* leave the human, the organisms have a phenotype referred to as hyperinfectivity --that is, the infectious dose is 10 to 100 times lower compared to non-humanshed organisms (53). Hyperinfectivity of recently shed organisms persists in water for 5 to 24 hours, suggesting that organisms transmitted from person-to-person may be more infectious than those that have acclimated to the environment. When hyperinfectivity is incorporated into a mathematical model of a cholera outbreak, the characteristically explosive nature of a cholera outbreak is better reproduced than if hyperinfectivity is not included (54). Other key components of cholera transmission models (4;52;55;56) include the concentration of *V. cholerae* O1 or O139 in stool, the difference of infectivity between planktonic cells and stool aggregates, the rapidity of spread of the organism from human-to-human, the presence of lytic bacteriophage in stool and water, and the concentration in water of the conditionally viable environmental cells for environment-to-human transmission.

Host susceptibility

Concomitant infection with enteropathogenic bacteria or parasites exerts an immunomodulatory effect on *V. cholerae*-specific immunity (57;58), and a number of host factors contribute to susceptibility to cholera. In particular, retinol deficiency is associated with a higher risk of *V. cholerae* infection and with a higher risk of symptomatic disease (59;60). Blood group O has been associated with severe cholera in different populations (61–63). The prevalence of blood group O is lower in south Asia compared to other regions, perhaps related to evolutionary pressure from cholera (64). A family-based study from Bangladesh demonstrated that first-degree relatives of a cholera patient had greater odds of being infected compared to less closely related contacts in the same household independent of blood group (59), suggesting that additional genetic factors play a role in susceptibility. A variant in the promoter region of *LPLUNC1*, a component of the innate immune system, was associated with cholera in a candidate gene study (65;66). Additional studies of host

genetic factors related to cholera may provide further insights into the interaction between *V. cholerae* and the host.

Diagnosis

According to the WHO (67), a case of cholera should be suspected when (1) a patient aged 5 years or more develops severe dehydration or dies from acute watery diarrhea, even in an area where cholera is not known to be present, or (2) a patient aged 2 years or more develops acute watery diarrhea in an area known to have cholera. Where microbiology facilities are available, *V. cholerae* infection can be confirmed by isolation of the organism from stool on selective media, followed by biochemical tests, as well as serogrouping and serotyping with specific antibodies (68). Enrichment of stool in alkaline peptone water can increase the sensitivity of culture (69). Cholera can be rapidly diagnosed by examining fresh human stool under 400 × darkfield microscopy for vibrio-shaped cells with darting motility that is abrogated with specific antibody (70); approximately half of culture-positive stools are positive on darkfield microscopy (47).

Immunoassays that detect cholera toxin (71;72) or *V. cholerae* O1 and O139 lipopolysaccharide (73–75) directly in stool have also been developed. Such assays can be used in settings with limited laboratory capacity and facilitate early detection of cases during an outbreak. One such commercially available dipstick for both O1 and O139-associated cholera has a 97% sensitivity and 71–76% specificity compared with PCR under field conditions (76). Dipstick assays may be more sensitive for detecting *V. cholerae* in patients previously treated with antibiotics.

Clinical manifestations

Few diseases give a clinical presentation as arresting as that of cholera. Massive watery diarrhea, up to 1 liter per hour, can lead to hypotensive shock and death within hours of the first symptom (“cholera gravis”). Death rates in untreated patients with severe cholera can exceed 70% (77). Although the stools of cholera patients may contain fecal matter or bile in the early phases, the characteristic “rice-water” stool of cholera develops with ongoing purging (Figure 1); this term refers to the similarity of the stool to water in which rice has been washed. Vomiting is a common feature, particularly early in illness. The diarrhea of cholera is typically painless and not accompanied by tenesmus; some patients may experience abdominal discomfort or cramping due to fluid distention of the bowel. Fever is rare and should raise suspicion for secondary infection.

Dehydration and electrolyte abnormalities are the most important complications of cholera. Patients may be lethargic, and may have sunken eyes (Figure 1), dry mouth, cold clammy skin, decreased skin turgor, or wrinkled hands and feet. Kussmaul breathing may occur due to acidosis from stool bicarbonate losses and lactic acidosis associated with poor perfusion (78). The peripheral pulse is rapid and thready, and may become difficult to palpate as blood pressure drops; urine output decreases with time (79;80). Muscle cramping and weakness due to electrolyte losses and ion shifts (particularly potassium and calcium) are common. In children, depletion of glycogen stores and inadequate gluconeogenesis can lead to severe hypoglycemia, manifest by altered consciousness, seizures or even coma (81;82). “Cholera sicca” is an unusual form of the disease in which fluid accumulates in the intestinal lumen, and circulatory collapse and even death, can occur before the passage of the first loose stool (83).

The presentation of cholera differs between endemic and epidemic settings. In endemic settings, rates of asymptomatic *V. cholerae* infection range from 40 to 80% (4), and cholera may present as mild diarrhea indistinguishable from infection with other enteropathogens.

The most severe cases of cholera in endemic settings are concentrated among young children and previously un-exposed individuals. In epidemic cholera in a previously un-exposed population, severe disease occurs in adults as frequently as in children and is associated with high case fatality rates (84). Laboratory studies are not required to care for the vast majority of patients with cholera although they may be useful in patients with ileus, confusion, coma, or seizures, or in those with no urine output in response to fluid replacement. Laboratory abnormalities include alterations in serum electrolytes (hypokalemia, hyponatremia, hypocalcemia), renal dysfunction, the effects of hemoconcentration, and in a small percentage of children, hypoglycemia. The clinical features of cholera due to *V. cholerae* O1 and O139 are similar (85;86). Complications from severe hypotension can include stroke (especially in elderly patients), renal compromise, and vomiting can lead to aspiration pneumonia (87), but cholera itself is an acute infection with no chronic manifestations.

Management

Rehydration is the cornerstone of management of patients with cholera. Early attempts at oral rehydration met with limited success because the physiologic requirements for sodium-glucose co-transport were not recognized. The introduction of oral rehydration solution (ORS) in the late 1960s, utilizing equimolar concentrations of sodium and glucose to maximize sodium uptake in the small intestine, and carefully replacing preceding and ongoing fluid losses, ushered in current cholera treatment (83;88).

Employing the current standard of care, the mortality of severe cholera can be reduced to less than 0.2%, even in resource-limited settings (3). However, there are obstacles to administering optimal rehydration, and mortality rates may still exceed 10% early in cholera epidemics before appropriate resources are available (89;90). In the epidemic in Haiti, the median time between onset of symptoms and death within the community was 12 hours (91). Decentralized treatment centers (such as oral rehydration points) improve access to therapy, reduce time to initial rehydration, and may be critical in managing outbreaks.

The approach to rehydration during severe cholera differs markedly from the approach to patients with gastroenteritis in developed countries because:

- Patients with severe cholera present with a greater degree of initial dehydration.
- Patients with severe cholera suffer more rapid ongoing losses once they come to medical attention.
- Patients with severe cholera have proportionally greater electrolyte losses than seen in non-cholera gastroenteritis (Table 1).

For these reasons, the most common error in caring for cholera patients is to underestimate the speed and volume of fluids required. 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 (67;92). Estimating and replacing ongoing losses, even after correcting the initial fluid deficit, is critical. The rate of ongoing fluid loss may exceed 20 mL/kg/hour; cholera cots are inexpensive and useful for estimating ongoing volume losses (Figure 1). In the absence of cholera cots, ongoing losses can be estimated as 10 to 20 mL/kg of body weight for each diarrheal stool or episode of vomiting.

In severe cholera, the initial fluid deficit should be replaced within 3–4 hours of presentation. The route of administration of fluids depends on the severity of dehydration (Table 2). Patients with severe (≥10%) dehydration are in hypovolemic shock and require immediate intravenous rehydration administered as rapidly as possible until circulation is restored. Oral rehydration should begin as soon as patients are capable of drinking (typically

3–4 hours), because more potassium, bicarbonate, and glucose are available in ORS than in standard intravenous fluids. In patients with some dehydration, the initial deficit should also be replaced rapidly, with ORS whenever possible, and patients should be monitored until signs of dehydration have resolved. Patients with some dehydration but with profound vomiting or ongoing stool losses, may rapidly progress to severe dehydration if only ORS is provided, and should receive concomitant intravenous and oral rehydration. In patients without dehydration, management consists of oral fluids to replace ongoing losses. WHO ORS utilizes glucose as a carbohydrate source. Rice-based ORS formulations, if available, have been found in randomized trials to reduce the duration of diarrhea and stool losses in severe cholera (93). Home made ORS can be used in an emergency situation (Table 1). In patients with symptomatic hypoglycemia, 0.25–0.5 g/kg of intravenous glucose can be administered and correction of the hypoglycemia monitored until fluid repletion and the ability to take ORS has occurred (82).

Antibiotics are adjunctive therapy in patients with moderate to severe dehydration from cholera (39). As in other infections, use of antibiotics in cholera may contribute to increasing antimicrobial resistance. However, effective antibiotics shorten the duration of diarrhea and reduce the volume of stool losses by up to 50%; they also reduce the duration of shedding of viable organisms in stool from several days to 1–2 days (77;94). Antibiotics can be administered once the initial fluid deficit is corrected and vomiting has resolved, ideally within 4 hours of initiating therapy. Antibiotic therapy should be based on prevailing local resistance patterns (Table 3).

Nutritional interventions include the resumption of a high energy diet immediately after the initial fluid deficit is corrected to prevent malnutrition as well as immediate complications including hypokalemia and hypoglycemia. For infants, breastfeeding should be encouraged in concert with ORS. In a randomized trial, zinc supplementation reduced the duration of diarrhea and volume of stool in children with cholera (95). Zinc supplementation after childhood diarrhea also reduced the incidence of subsequent episodes of diarrhea for several months (96;97); the WHO recommends zinc for children under 5 years of age with diarrhea (10 mg/day for children under 6 months and 20 mg/day for 10 days for children 6 months to 5 years) (67). Children with diarrhea in developing countries also benefit from supplementation with vitamin A (98). Antimotility agents and anti-emetics have no established benefit for treatment of cholera, and may prolong infection or have sedating effects that interfere with effective oral rehydration (67;99).

In an outbreak, clinicians and public health officials often need to manage many patients at the same time. Critical response features include establishing cholera treatment centers; training staff in case recognition and management; and providing safe water and sanitation. Depending on the local situation, radio ads, cell phone messaging, messages on billboards, community volunteers and other means may be important ways to educate the public on seeking medical care, oral rehydration use, sanitation, and other ways to prevent or minimize transmission. Other important components of the public health response include disinfectants, proper disposal of waste and cadavers, and coordinating the response with community, regional, national and international health authorities. An excellent resource that can assist in managing such features is available online at www.cotsprogram.com. Some countries are reluctant to declare a cholera epidemic because of concern over creating panic and the implications for tourism and exports; however, rapid reporting and a coordinated public health response should be encouraged to minimize the extent of the outbreak and prevent further spread.

Prevention of cholera

The response to the cholera pandemics of the 19th century led to the development of systems to provide safe water and adequate sanitation, but 1 billion people still lack access to safe water and remain at risk of cholera (100). Continued progress in providing safe water and adequate sanitation is a Millenium Development Goal but may take decades to achieve (101). During a cholera outbreak, the major response should focus on case detection, rehydration-based treatment and provision of safe water, in conjunction with adequate sanitation, hand-washing, and safe food preparation (102). These goals have been used for decades in areas that remain at risk for cholera, without reducing the ongoing impact of this disease, suggesting that consideration of additional control strategies, such as vaccination, is warranted (101;103;104).

Although safe and effective cholera vaccines exist, cholera vaccination is not yet part of cholera control programs outside of Vietnam; discussions are in progress regarding potential use in Haiti. The reasons for this are logistical, financial, and historical. Current cholera vaccines are given orally, have an excellent safety profile, and target induction of mucosal immunity. There are two oral killed vaccines that are licensed and commercially available. Dukoral (WCrBS, Crucell, Sweden) contains multiple biotypes/serotypes of *V. cholerae* O1 supplemented with 1 mg/dose of recombinant cholera toxin B subunit. Shanchol (Shantha Biotechnics-Sanofi Pasteur, India) and mORCVAX (VaBiotech, Vietnam) contain multiple biotypes/serotypes of *V. cholerae* O1 as well as *V. cholerae* O139 without supplemental cholera toxin B subunit. Shanchol is the bivalent vaccine internationally available (5).

Oral killed cholera vaccines have been administered to millions of recipients and are safe and immunogenic. The vaccines are administered as two or three doses depending on age and vaccine (Table 4). Overall, the vaccines provide 60–85% protective efficacy for 2–3 years, although protection among younger children is of shorter duration (105–115). Dukoral has been safely administered to individuals with HIV (111).

Re-analysis of original studies of oral cholera vaccine in Bangladesh in the 1980s disclosed a measurable herd effect (116), and modeling suggests that vaccinating 50% of a population could result in a greater than 90% reduction in cholera incidence in that population overall (117). A cost effectiveness model suggested that oral cholera vaccine could be cost effective in areas endemic for cholera (118).

A number of live attenuated oral cholera vaccines have also been developed, including CVD 103-HgR, Peru-15, and others (119). These genetically modified vaccine strains have in common the inability to express cholera toxin. These vaccines have been shown to be safe and immunogenic in volunteer studies (119–124); however, CVD 103-HgR failed to show protective efficacy when evaluated in a field study (125). Peru-15 has been shown to be safe and immunogenic in different age groups in Bangladesh (126), but has not yet been evaluated in field studies. A number of other cholera vaccines are in various stages of development, including subunit vaccines, live attenuated vaccines, and conjugate vaccines (127;128).

The WHO has endorsed the inclusion of oral vaccine in cholera control programs in endemic areas in conjunction with other preventive and control strategies (5). The WHO also recommends that oral vaccine be considered as part of an integrated control program in areas at risk for outbreaks (5). The use of vaccine in reactive situations (i.e. after an outbreak has occurred) is currently less certain. A case-control study in Vietnam suggested that such use could be of benefit (129), and modeling further supports such potential use (55;56;130–132). At present, the WHO suggests that oral cholera vaccine be considered as part of an integrated program in reactive situations in both epidemic and endemic settings in

conjunction with provision of safe water, adequate sanitation, case detection and rehydration strategies, but that collection of additional data to support vaccination in such settings is warranted (5).

Areas of uncertainty in cholera

Cholera has had an immense impact on human history. Unfortunately, current control strategies have not proven highly effective in areas of the world bearing the global burden of cholera (101). Many areas of uncertainty remain. Will a new serogroup of *V. cholerae* arise, as O139 did? Why are altered variants of *V. cholerae* O1 El Tor developing? Will severe weather events such as regional flooding associated with global warming result in increased cholera? What role would surveillance, screening, vaccination or empiric treatment have in limiting the spread of cholera into immunological naïve populations? Would short course targeted chemotherapy with highly active antimicrobials among close community contacts of cholera patients limit transmission, or only lead to drug resistance? How can safe water and improved sanitation be attained in the many parts of the world lacking these? What are the obstacles to incorporation of current cholera vaccines into immunization programs in cholera endemic countries, and how can these be overcome? Who will support and pay for the manufacture, distribution and use of cholera vaccines? Will a vaccine stockpile be developed? And, if so, who will maintain, monitor and activate its use? Will the development of more effective or longer acting cholera vaccines simplify a number of these decisions?

We do not yet know the answers to these important questions, but the way forward will require scientific, medical, public health, environmental, financial, and political cooperation and action. As it has in the past, cholera remains largely a disease of impoverishment, social unrest and displacement, and continues to be a disease of major public health significance.

Search strategy

A search of Medline and Cochrane Library databases was performed using the terms “cholera”, “*Vibrio cholerae*”, and “randomized controlled trials” for the period January 1, 1966 through September 30, 2011 and in all languages.

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Figure 1.
(A). "Rice water" stool in a patient with cholera. (B). Cholera cot used in management of patients with cholera to monitor ongoing volume losses in stool. (C). Patient with cholera before rehydration. (D). Patient with cholera eight hours after starting rehydration therapy. (A, C and D) reproduced from *PLos Neglected Tropical Diseases* (133) with permission.

Table 1

Comparison of the composition of cholera stools and acceptable therapeutic fluids for cholera (67;134); (www.cotsprogram.com).

		Na+	K+	Cl-	HCO3-	Carbohydrate	Commentary
		millimoles/liter					
Electrolyte losses in stools *	Cholera stool, adult	130	20	100	45	--	The mean maximal rate of purging in severe cholera exceeds 10 ml/kg/ hour. Sodium losses in cholera stools exceed those seen in other causes of diarrheal illness.
	Cholera stool, child	100	30	90	30	--	
	Non-cholera stool child (ETEC)	50	35	25	20	--	
Intravenous Therapy	Lactated Ringer's Solution	130	4	109	28	-- (278 if D5LR# available)	Lactated Ringer's (LR) solution is usually readily available and preferred over normal saline because it contains potassium and bicarbonate. The optimal infusion, for cholera, such as 'Dhaka solution' contains more potassium and bicarbonate than LR and also contains dextrose; addressing complications of severe cholera including hypokaelemia hypoglycemia, and metabolic acidosis
	Normal Saline	154	0	154	0	--	
	Cholera Saline (Dhaka solution)	133	13	154	48	140	
Oral Rehydration Therapy	ORS (WHO 2002) **	75	20	65	10 (citrate)	75 (glucose)	WHO ORS utilizes glucose as a carbohydrate source Rice based ORS formulation have been found in randomized trials to reduce the duration of diarrhea and stool losses in severe cholera (93)
	Rice based ORS (eg. CeraORS 75®)	75	20	65	10 (citrate)	27 grams rice syrup solids	
	Home made ORS (135)	~75	0	~75	0	~75	
	- Half (1/2) teaspoon - Salt Six (6) teaspoons sugar. - 1 liter of safe water						A home made preparation of ORS could be used in an emergency situation.

* Compositions are estimates of the mean electrolyte composition of stools and are shown to demonstrate the significant difference in the pathophysiology of pediatric and adult cholera and non-cholera childhood gastroenteritis.

Dextrose 5%-Lactated Ringer's

** In 2002, the WHO replaced its previous formulation of ORS with the current lower osmolarity formulation. Subclinical hyponatremia is common among cholera patients using the current WHO formulation of ORS (136;137), but the rates of symptomatic hyponatremia in cholera patients do not appear to be significantly increased (138).

Table 2

Approach to rehydration in the patient with suspected cholera (67)

		Degree of Dehydration		
		None (< 5%)	**Some (5–10%)**	**Severe (>10%)**
Clinical assessment for dehydration	**General appearance**	Well, alert	Restless, irritable	Lethargic or unconscious
	Eyes	Normal	Sunken	Sunken
	Thirst	Drinks normally	Thirsty, drinks eagerly	Drinks poorly or unable to drink
Approach to rehydration[#]	**Skin turgor**	Instantaneous Recoil	Non-instantaneous recoil	Very slow recoil (>2 seconds)
	Pulse	Normal	Rapid, low volume	Weak or absent
	Requirement for fluid replacement	Ongoing losses only	75 mL/kg in addition to ongoing losses	>100 mL/kg in addition to ongoing losses
	Preferred route of administration	Oral [*]	Oral or Intravenous	Intravenous
	Timing	Usually guided by thirst	Replace fluids over 3–4 hours	As rapidly as possible until circulation is restored, complete the remainder of fluids within 3 hours
	Monitoring	Observe until it is determined that ongoing losses can be adequately replaced by ORS	Observe every 1–2 hours until all signs of dehydration resolve and patient urinates	Once circulation is established monitor every1–2 hours.

[#]Patients with co-morbid conditions including severe malnutrition, significant complications, infants and elderly patients may require adjustments from this standard which are detailed in the references.

[*]If losses are in excess of 10 ml/kg/hour per hour, it may not be possible to successfully employ oral therapy initially. An excellent resource is the Cholera Outbreak Training and Shigellosis (COTS) Program (www.cotsprogram.com) that provides free online information regarding the management of patients with cholera, based on WHO standards.

Table 3

Antibiotics for cholera.

Class	Antibiotic	Pediatric Dose*	Adult Dose	Comment(s)
Tetracyclines	Tetracycline	12.5 mg/kg/dose QID × 3 days	500 mg QID × 3 days	Antibiotic resistance to all tetracyclines is common (139) Empiric use is most appropriate in outbreaks caused by documented susceptible isolates. Tetracyclines are not recommended for pregnant women or children less than 8 years because of risk of irreversible discoloration of permanent teeth.
	Doxycycline	4–6 mg/kg × single dose	300 mg × single dose	
Fluoroquinolones	Ciprofloxacin	15 mg/kg/dose BID × 3 days	500 mg BID × 3 days	In highly susceptible strains, single dose ciprofloxacin compares favorably against erythromycin (140) and doxycycline (141) in randomized trials. However, reduced susceptibility to fluoroquinolones has become common in endemic areas, and is associated with treatment failure (142;143).
Macrolides	Erythromycin	12.5 mg/kg/dose QID × 3 days	250 mg QID × 3 days	Single dose azithromycin is the preferred therapy in children and has been shown to be more effective than ciprofloxacin in randomized trials in regions where reduced susceptibility to flouroquinolones are common (142;144). There are rare reports of macrolide resistance.
	Azithromycin	20 mg/kg × single dose	1 gram × single dose	

*Pediatric doses, based on weight, should not exceed maximum adult dose

QID: four times a day

BID, twice a day

Table 4

Internationally available oral killed cholera vaccines

Vaccine	Doses*	Dosing interval*	Dosing volume*	Boosters*	Protective efficacy	Comments	References
Dukoral ** **(Crucell)**						• Pre-qualified for use by WHO • Licensed in many countries • Has been safely administered to individuals infected with HIV • Provides short-term protection against diarrhea caused by heat labile toxin (LT) expressing strains of enterotoxigenic *E. coli* (ETEC)	(106– 111;145;146)
Children 2 – <6 years of age	3	14 days (7–42 permissible)	3 ml Vaccine and 75 ml buffer	Every 6 months	60–85% Protective Efficacy within 6 months of vaccination,		
>6 years of age	2	14 days (7–42 permissible)	3 ml Vaccine and 150 ml buffer	Every 2 years	decreasing to baseline over 24–36 months		
Shanchol (Shantha Biotechnics-Sanofi Pasteur)							(105;112– 115;147; 148).
>1 year of age	2	14 days (window probably same as Dukoral)	1.5ml	Every 2 years	60–70% Protective efficacy over 24–36 months	• Pre-qualified for use by WHO • Currently more affordable than Dukoral • Does not require buffer to administer vaccine • Currently undergoing field studies in Kolkata/ Orissa, India and Dhaka, Bangladesh, and pilot roll out in Haiti	

* Per manufacturer

** Listed field studies have involved both the current preparation of WC-rBS vaccine, supplemented with recombinant cholera toxin B subunit (rBS), and a previously available preparation of WC-BS containing non-recombinant B subunit (BS).