79 Cholera

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Case

A 6-year-old refugee child is brought to the camp hospital in the early morning hours by his parents. A review of the history is significant for abundant watery diarrhea and non-bilious emesis that began the night before. An older sibling had mild gastroenteritis earlier in the week but quickly recovered. Physical exam reveals a thin boy with sunken eyes, dry mucus membranes, and 3 second skin pinch of the abdomen. He is unable to take anything by mouth and is too tired to answer questions. How should you proceed?

The patient is assessed as severely dehydrated. Rehydration is immediately started with Lactated Ringers after IV access is established and continued with oral rehydration solution when the patient is able to drink. A sample of stool is collected and sent to the nearby field laboratory for diagnosis. Due to volume of watery stool, you suspect cholera and immediately notify the health directors to begin investigation of a new outbreak.

Definition/Classification

Cholera is one of the oldest and most notorious of epidemic diseases with the hallmark of profuse, severe watery diarrhea that can result in death over a matter of hours. Despite advances in the genetics of *Vibrio cholerae*, the pathophysiology of the disease, and advent of oral rehydration therapy, cholera can still cause significant morbidity and mortality throughout the developing world, particularly in vulnerable populations.

Vibrio cholerae belong to the family Vibrionaceae which shares characteristics with the Enterobacteriaceae. The organism is classified into serogroups according to the carbohydrate determinants of its somatic O antigen of the cell surface lipopolysaccharide. Over 200 serogroups have been discovered, classified broadly as those that agglutinate in anti-sera to the O1 group antigen or those that do not. Only the O1 and O139 serogroups are currently responsible for the epidemiologic characteristics and clinical picture of cholera. Non - O1 strains may be associated with a mild gastroenteritis.

There are two biotypes of O1 cholera: Classical and El Tor. Each differs in clinical presentation and biochemical properties. The El Tor biotype causes more asymptomatic infections with 20–100 asymptomatic infections to 1 symptomatic case. This is compared to 2–5 asymptomatic cases to 1 symptomatic case of the Classical biotype. O1 El Tor and Classical biotypes can each further be serotyped as Inaba, Ogawa, or (rare) Hikojima, distinguished by different expression of the O1 subspecific antigens A, B, and C.

Epidemiology

Allusions to a cholera - like illness have been made through ancient times. In the modern era, seven cholera pandemics have been recognized since the early 1800s. The first six pandemics, from 1817 to 1923, were thought to be of the O1 Classical biotype, largely originating from the Indian subcontinent with extension to Europe and the Americas. Transmission of the disease was recognized in the sentinel work in London in 1854 by John Snow, who recognized that transmission could be blocked by stopping access to a contaminated water source. The seventh and most recent pandemic started in 1961 in Indonesia, spread to Asia, Africa, and finally to Latin America, causing explosive epidemics in Peru in 1991. This pandemic has been the longest lasting and is caused by the O1 El Tor biotype.

In 1992, a non-O1 serogroup that caused an epidemic of a cholera-like illness was identified in Madras, India. It was named the O139 Bengal serogroup. O139 is a genetic derivative of El Tor biotype, is largely confined to Asia.

In 2009, 45 countries from all over the world reported a total of 221,226 cases of cholera to the World Health Organization. Most of the 4,946 deaths were recorded in Africa, with a worldwide overall case-fatality rate of 2.24%. The actual number of cholera cases worldwide can only be estimated due to limitations in surveillance systems, underreporting, and inconsistencies in the application of case definitions. As a result, the true burden of disease due to cholera is estimated at 3–5 million cases and 100,000–120,000 deaths each year. Reminders of this deadly disease are evident in recent times, such as the

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Goma experience in 1994 where over a 6 week period, an estimated 12,000 deaths and 70,000 cases occurred in eastern Zaire (currently the Democratic Republic of the Congo) among Rwandan refugees. Epidemics in Zimbabwe in 2008 and Haiti in 2010 highlight the continued need for surveillance and early response.

Among industrialized nations, imported cases of cholera have been reported in international travelers. Sporadic cases in the USA have occurred in the Gulf Coast region, with identification of an environmental reservoir of *V. cholerae* O1 El Tor Inaba. Seasonal variation in areas of endemic infection indicates the possible role of environmental factors in triggering the epidemic process. Humans are the only known host, but *Vibrio* organisms may exist in the dormant state in aquatic environments in association with copepods or other zooplankton. Transmission occurs by the fecal-oral route with ingestion of contaminated water and food.

Microbiology and Pathogenesis

Vibrio cholerae are gram-negative, comma-shaped, motile rods that are facultatively anaerobic. Genetic material consists of two circular chromosomes. Virulence factors are located on the larger chromosome and clustered on two main areas: a "pathogenicity island" and a prophage called CTXϕ which encodes the cholera toxin. The infectious dose causing disease varies from as few as 10^2 up to 10^6 organisms, depending on the vehicle of transmission and host characteristics. Once ingested, the acid content of the stomach may serve as a natural defense mechanism against *V. cholerae* which are killed at low pH.

Organisms multiply rapidly in the alkaline environment of the proximal portion of the small intestine and colonize, but do not invade, the mucosa of the small intestine with the aid of a pilus and other adherence factors. Inflammation is minimal and the epithelium remains intact. The cholera toxin is a multimeric protein and consists of two units: A (active) and B (binding). The B portion binds to the ganglioside receptor on local enterocytes. The A unit consists of A1 and A2 subunits. A2 connects A1 to the B unit. Internalization of the A1 subunit leads to transfer of an ADP-ribose molecule to a G-protein. This results in persistent activation of the G binding protein, upregulating cyclic adenosine monophosphate production. Elevated cAMP leads to the blocked absorption of sodium and chloride by microvilli and promotes the secretion of chloride and bicarbonate by intestinal crypt cells, resulting in massive of loss of water across the osmotic gradient.

It has been observed that individuals with *Heliobacter pylori* gastritis and those taking antacids or histamine blockers are at increased risk of cholera infection. Interestingly, persons with blood group O are at a higher risk of developing severe cholera, although the exact mechanism is unknown. Younger children are particularly vulnerable in endemic areas, as older children and adults benefit from some acquired immunity. Breast-fed children are normally protected against severe disease due to less exposure to contaminated water and foods and because of protective antibodies obtained in breast milk. Lack of breast feeding in parts of the world where mothers are unable to or opt not to breast-feed may demonstrate increased rates of cholera in infants.

Clinical Manifestations

The incubation period is dependent on the infectious dose and can vary from several hours up to 5 days. Most patients with cholera are asymptomatic, and some have mild or moderate diarrhea lasting up to 1 week. Vomiting, if it occurs, is usually early on in the disease course. Fever may be seen in children but because the bacteria are noninvasive, it is usually not present. Less than 5% of infected children develop *cholera gravis*, characterized by the sudden onset of profuse, painless watery diarrhea accompanied by emesis and severe dehydration that can occur over hours.

Stools are described as "rice water" due to the color and consistency resembling the water used to wash or cook rice. Cholera stools do not contain red blood cells or leukocytes. Diarrhea is uncontrollable and voluminous and may be accompanied by abdominal cramping, presumably due to fluid distension in the bowels. Urine output may decrease or cease. Within hours, metabolic acidosis, hypovolemic shock, renal failure, altered mental status, seizures, coma, or death may occur.

Electrolyte abnormalities are common. Hypokalemia may result in paralytic ileus, leading to severe distension of the abdomen. "Cholera sicca" ("*dry cholera*") can occur as intestinal secretions remain contained in the distended small intestine and colon, with little or no diarrhea. Hypoglycemia is more common in children and may result in altered mental status or seizures. After dehydration, hypoglycemia is the second most common cause of death in pediatric patients with cholera. Metabolic acidosis can result from bicarbonate loss in the stool and is exacerbated by hypoperfusion of tissues, leading to lactic acidosis. During the rehydration phase, patients are at risk for hypocalcemia, manifest by muscle cramping and tetany.

Diagnosis

Vibrio organisms can be identified by dark-field examination or wet preparation of stool. The use of specific cholera anti-sera to block the movement of the *V. cholerae* allows confirmation of the diagnosis. Rapid tests with direct antigen detection dipstick are now available, although results should be culture confirmed. Growth of *V. cholerae* on selective media, such as thiosulfate-citrate-bile salts-sucrose agar or tellurite taurocholate gelatin agar, remains the gold standard for diagnosis and analysis of microbial drug sensitivities. If laboratory facilities are not immediately available, Cary Blair transport medium can be used to transport or store a fecal or rectal swab. Stools can also be placed on blotting paper and kept in sealed plastic bags. Molecular assays, such as PCR, are available in certain reference laboratories. Acute and convalescent titer measurements are useful in epidemiological studies.

Cholera is a World Health Organization–reportable disease, recognized by its epidemic potential. The clinical case definition for suspected cholera by the WHO is as follows:

- Acute watery diarrhea (three or more loose stools in a 24 hour period) with or without vomiting in a patient age 5 or older in an *endemic* area.
- Severe dehydration or death from acute watery diarrhea in a patient age 5 or older in a *non-endemic* area.

By WHO standards, once laboratory confirmation of a single case of cholera has occurred, it becomes unnecessary to confirm all subsequent cases. In a cholera *outbreak*, any patient who has acute, profuse watery diarrhea should be treated as a cholera case. Intermittent laboratory confirmation of cholera cases in these settings is encouraged to monitor for drug sensitivities and to confirm the end of an outbreak.

Differential Diagnosis

Mild disease is often difficult to distinguish from gastroenteritis caused by other enteric pathogens such as *rotavirus, Enterotoxigenic Escherichia coli* (ETEC), or bacterial food poisoning with *Staphylococcus aureus* or *Bacillus cereus*.

Treatment

Treatment for dehydration should not be delayed for laboratory confirmation of disease. The World Health Organization outlines steps to the treatment of a patient with suspected cholera, which include the following:

1. Assess and classify the level the patient's of dehydration.
2. Rehydrate according to algorithm (*Fig. 79.1*) with frequent monitoring.
3. Maintain hydration and replacement of fluids until diarrhea stops.
4. Administer an oral antibiotic to patients with severe dehydration.
5. Resume food intake/breast feeding as soon as possible. Give zinc supplements.

Low osmolality oral rehydration solution (ORS) is the preferred first line treatment for children who have no or mild dehydration. Newer rice-based or amylase-resistant starch versions of ORS may be available. ORS can also be used to manage patients suffering from some dehydration who are able to drink. ORS can be administered via syringes or nasogastric infusions for infants and children unable to sip from a cup. Food should be offered as soon as children are able to eat. Mothers are encouraged to continue breast feeding.

Children unable to take ORS should have fluids administered intravenously. Access is critical, and larger veins may be utilized to enable boluses. The solutions of preference include Lactated Ringers or regional variants, such as Dhaka Solution or Peru Polyelectrolyte. ORS, which contains a higher amount of potassium compared to these IV solutions, should be started as soon as the patient is able to take fluids by mouth. The use of cholera cots, constructed with a hole in the center for stool and a collecting pot underneath, to accurately measure output is recommended. Fluid administration rates must be closely monitored, particularly in infants and severely malnourished children who are at risk for pulmonary edema and cardiac overload. Signs of over-hydration include periorbital edema, tachypnea, and crackles in the lungs.

Oral antibiotics may be used to decrease the volume and duration of diarrhea and shorten the period of communicability but are reserved for children who are severely ill. Mass chemoprophylaxis in the community is generally not warranted, but selective prophylaxis may be utilized in certain scenarios. Single dose or 3-day regimens exist, and antibiotic sensitivities should guide specific management in each outbreak (*Table 79.1*). IV or IM antibiotics are not necessary. The addition of 10–30 mg of elemental zinc for 2 weeks has been shown to decrease stool output and duration of diarrhea in children.

Cholera Treatment Algorithm

The *World Health Organization* has established guidelines* for rehydration and cholera treatment which have been adapted with permission and summarized below:

1. Assess and classify level of dehydration (severe, some, no/mild)
2. Rehydrate according to algorithm below with frequent monitoring
3. Maintain hydration and replacement of fluids until diarrhea stops
4. Administer an oral antibiotic to patients with severe dehydration (table 1)
5. Resume food intake / breastfeeding as soon as possible. Give zinc supplements

Severe Dehydration >10% loss of body weight	Treatment
At least 1 of the following: **Lethargy** **Unable to drink** **Skin pinch >2sec** Plus 1 or more: No tears Very sunken eyes Very dry mucus membrane Feeble pulse	Start IVF: Reassess every 15–30 min. 30 ml/kg / 70ml/kg <1 yr old: In 1st hr / Over 5 hrs >1 yr old: In 30 min / Over 2.5 hrs Then, **reclassify dehydration** [severe, some, none] and continue treatment as noted below **Be aware of hypoglycemia **Give ORS 5 ml/kg/hr as soon as able to take po **If no IV access: ORS by NG 20 ml/kg/hr x 6 hrs.

Some Dehydration 5–10% loss of body weight	Treatment
At least 1 of the following: **Irritability / fussy** **Thirsty, wants to drink** **Skin pinch 1–2 sec** Plus 1 or more: No tears Sunken eyes Dry mucus membrane Increased pulse rate	Start ORS: If weight is known calculate volume over 4 hrs by 75 ml x weight in kg If weight not known, use chart below. Reassess every 30 min. 0–4 mo: 200–400 ml over 4 hrs 4–12 mo: 400–700 ml over 4 hrs 12–24 mo: 700–900 ml over 4 hrs 2–5 yr: 900–1400 ml over 4 hrs 5–14 yrs: 1400–2200 ml overt 4 hrs 14 and above: 2200–4000 ml over 4 hrs Then, **reclassify dehydration** and continue treatment

No dehydration	Treatment
2 of the following: **Alert, well appearing** **Tears** **Mouth Moist** **Wants to drink** **Normal skin pinch**	After rehydration achieved, maintain hydration. Resume breast feeding and regular diet as soon as tolerated. Supplement with 10-30 mg of zinc daily. In an outpatient setting most patients can drink ORS to replace stool losses. Replacement of stool output: age <2: 50–100 ml/stool episode up to 500 mL per day. age 2–10: 100–200 ml/stool episode up to 1L per day. age 10+: po ad lib up to 2L per day **Reassess the patient** for signs of dehydration at least every four hours

*Department of Child and Adolescent Health and Development. (2005) Treatment of Diarrhoea. A Manual for physicians and senior health workers. World Health Organization. http://whqlibdoc.who.int/publications/2005/9241593180.pdf Accessed on Nov 15, 2010
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*World Health Organization. 2004. First steps for managing an outbreak of acute diarrhoea. http://www.who.int/topics/cholera/publications/en/first_steps.pdf Accessed Dec 2, 2010.

Figure 79.1
Cholera Treatment Algorithm

Table 79.1
Pediatric dosages for antibiotics in cholera

Antibiotic	Single dose regimen	Multiple dose regimen	Source
Erythromycin		12.5 mg QID × 3 days. Max 1 g/day	WHO First steps (2004)
Azithromycin	20 mg/kg Max 1 g	–	Khan et al. (2002)
Ciprofloxacin[a]	20 mg/kg max 1 g	–	Saha et al. (2005)
Doxycycline[b]	4–6 mg/kg . Max 300 mg	–	Alam et al. (1990), Sack et al. (1978)
Tetracycline[b]	–	12.5 QID × 3 days, Max 2 g/day	Roy et al. (1998)

Increasing resistance to TMP-SMX and furazolidone has limited their use in practice
[a]Fluoroquinolones are generally avoided in patients younger than 18 years because of concerns about arthropathy in animal studies. The AAP states use of fluoroquinolones may be justified in children <18 years of age in special circumstances after careful assessment of the risks and benefits for the individual patient and after these benefits and risks have been explained to the parents or caregivers
[b]Doxycycline and tetracycline doses are extrapolated from adult studies. Both are generally contraindicated for children under age 8 due to staining of permanent teeth. Short courses are not thought to contribute highly to this

Prognosis

Attack rates in endemic areas are highest in children under age five who have less acquired immunity. Immunologically naïve persons of all ages are at risk in a non-endemic setting. Mortality can approach 50% if treatment is unavailable or delayed. Pregnant women and infants are at particular risk for complications. For those that survive, cholera itself is self-limiting, with resolution in approximately 1 week. Stools may remain positive for *V. cholerae* up to 1–2 weeks after diarrhea ends, although occasionally the carrier state may persist for longer. With appropriate therapy, case-fatality rates should be less than 1%

Prevention and Control

Situations with overcrowding and poor sanitation can promote and perpetuate cholera epidemics. Epidemics often occur after man-made and natural disasters, particularly in complex emergencies and refugee camps, when water and food supplies become contaminated with *V. cholerae*. Social disruption, poor infrastructure, and poor access to health care can contribute to increased mortality. Systematic reporting to local, national, and international health bodies will help to coordinate the appropriate response and limit spread to other areas.

Once an outbreak has been identified, a multitiered approach is necessary, addressing public health education, treatment facilities, and ensuring safe water supply and maintenance of latrines. Hospitalization with enteric/contact precautions is desirable for severe cases. Less severe cases can be managed in an outpatient setting with ORS. Disinfection of articles used by patients, particularly linens and diapers is important.

The use of oral cholera vaccines is considered an additional public health tool that may be used in conjunction with the recommended cholera control measures such as ensuring safe water and adequate sanitation. Three oral cholera vaccines are available: WC/rBS (Dukoral) and the two versions of the variant WC (mOrcVax and Shanchol). Only one, WC/rBS, is currently prequalified by the WHO and available to purchase by UN agencies.

WC/rBS was developed in Sweden in 1991 and consists of killed whole-cell *Vibrio cholerae* O1 with a purified recombinant B-subunit of cholera toxin. It is not licensed for children less than 2 years of age and may be used in pregnant and HIV-positive individuals. Two doses a minimum of 7 days apart, if age greater than 6, or three doses, if between ages 2–5, is needed to induce immunity within 1 week after the last dose. Clinical trials in Bangladesh, Mozambique, and Peru conferred a range of protection from 78–90% for 4–6 months among all age groups. For children aged 2–5 years, 1 booster dose is recommended every 6 months and for those older than 6 years, one booster every 2 years. Reanalysis of data from clinical trials in Bangladesh revealed considerable herd protection from WC-rBS, including protection for children too young to be vaccinated.

Variants of the WC/rBS vaccine without the recombinant B-subunit resulted from transfer of technology to Vietnam and India. Both vaccines, mOrcvax (Vietnam) and Shanchol (India) are based on serogroups O1 and O139 and are identical in terms of strains but formulated by different manufacturers.

A recent reevaluation of parenteral cholera vaccines in a Cochrane review demonstrated an overall efficacy of 48% (95% CI: 35–58%, with protection for two years). Other cholera vaccines remain under development, with the goal to offer lifelong immunity in a single dose.

Useful Web Resources

World Health Organization: http://www.who.int/cholera/en/index.html

Centers for Disease Control: http://www.cdc.gov/cholera/

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