CHOLERA

Introduction

Cholera is an acute diarrhoeal disease caused by the gram negative bacillus *Vibrio cholerae*. Although more than 100 serogroups exist, only two cause human disease: V. cholerae O1, of which there are two biotypes (Classical and El Tor) and *V. cholerae* O139 which emerged in 1992. Cholera is known to cause worldwide pandemics. *V. cholerae* O1, biotype El Tor accounts for most cases in the current, seventh pandemic, although serogroups O139 and O1 (Classical biotype) are present in India and Bangladesh. The O139 epidemic has been occurring in populations assumed to be largely immune to V. cholerae O1 and has rapidly spread to many countries including the United States

V. cholerae is endemic in many resource-poor countries, particularly in areas of inadequate sanitation and food hygiene practices. Man is the only known host of cholera.

ETIOLOGY

V. cholerae are short (0.2 to 0.4 μm by 1.5 to 4.0 μm), slightly curved gram-negative rods that are readily seen in Gram-stained smears of the watery excreta of patients with cholera. V. cholerae grows rapidly on a number of selective media, including bile-salt agar, glycerin-tellurite-taurocholate agar, and thiosulfate- citrate-bile-salt-sucrose (TCBS) agar. Distinction between the two major serotypes -Inaba and Ogawa- is made by slide agglutination with type-specific antiserums. Identification of the El Tor biotype is important for epidemiologic purposes; it is distinguished from the classic biotype by its resistance to polymyxin B and by its ability to cause hemolysis of sheep erythrocytes.

EPIDEMIOLOGY

John Snow lived in the 19th century and was well known as the anesthesiologist who administrated chloroform to Queen Victoria in childbirth. However, Snow's true love was the epidemiology of cholera, a disease that was a major problem in England in the middle of the 19th century. John Snow believed that cholera was transmitted through contaminated water. Remember that in Snow's day the enterotoxic *Vibrio cholerae* was unknown. Nothing was known about the biology of the disease. Snow's conclusion that contaminated water was associated with cholera was based entirely on observational data.

John Snow find that the risk of cholera in London was related, among other things, to the drinking of water supplied by a particular company. Snow's epidemiological studies were one aspect of a wide-ranging series of investigations that involved an examination of physical, chemical, biological, sociological and political processes.

Snow located the home of each person who died from cholera in London during 1848-49 and 1853-54, and noted an apparent association between the source of drinking water and the deaths. He prepared a statistical comparison of cholera death in districts with different water supplies, and thereby showed that both the number of

death and, more importantly, the mortality rate were high among people supplied by the Southwark Company. On the basis of this research, Snow constructed a theory about the communication of infectious diseases in general and suggested that cholera was spread by contaminated water. He was thus able to encourage improvements in the water supply long before the discovery of the organism responsible for cholera; his research had a direct impact on public policy.

Snow could make such calculations because drinking water was provided by a number of separate companies in different part of London. If everybody in the population had received water from the same source, this type of analysis would not have been possible.

Snow's work remind us that public health measures, such as the improvement of water supplies and sanitation, have made enormous contributions to the health of populations, and that in many cases since 1850 epidemiological studies have indicated the appropriate measures to take.

History and spread of epidemic cholera

Cholera has smoldered in an endemic fashion on the Indian subcontinent for centuries. There are references to deaths due to dehydrating diarrhea dating back to Hippocrates and Sanskrit writings. In 1883, Robert Koch successfully isolated the cholera vibrio from the intestinal discharges of cholera patients and proved conclusively that it was the agent of the disease.

Cholera has always been endemic in India and Bangladesh, in the huge delta formed by the confluence of the Ganges, Brahmaputra, Jamuna and Meghna rivers. Probably there was no cholera in Europe or America before the 19th century.

The first pandemic which started in 1817 did not reach Western Europe. In 1829 the bacterium was introduced into the countries around the Persian Gulf via a British army unit stationed in India. From Iran the infection spread to Iraq, Syria, Georgia and Astrakhan (north of the Black Sea. The third pandemic merged with the second and was amplified by the miserable conditions during the Crimean war. The pathogen was discovered in 1884 by Robert Koch during the fifth pandemic (first work in 1883 in Alexandria, Egypt, confirmation followed by research in India in 1884, with isolation of the bacterium in culture

Cholera pandemics since 1817

Number	**Years**	**Origin**	**Pathogen**
1	1817-1823	India	?
2	1829-1851	India	?
3	1852-1859	India	?
4	1863-1879	India	?
5	1881-1896	India	*V. cholerae* O1, classic
6	1899 -1923	India	*V. cholerae* O1, classic
7	1961 to present	Sulawesi	*V. cholerae* O1, El Tor
8	1992 to present	Madras, India	*V. cholerae* O139

After the sixth pandemic there was a strange silence for about 40 years, for which no good explanation exists. The seventh pandemic was caused by El Tor. It started in 1961 in Celebes (Sulawesi), Indonesia, reached India in 1964 and Africa in 1970. There are several characteristics of the El Tor strain that confer upon it a high degree of "epidemic virulence" allowing it to spread across the world as previous strains have done. First, the ratio of cases to carriers is much less than in cholera due to classic biotypes (1: 30-100 for El Tor vs. 1: 2 - 4 for "classic" biotypes). Second, the duration of carriage after infection is longer for the El Tor strain than the classic strains. Third, the El Tor strain survives for longer periods in the extraintestinal environment.

In 2 years the infection passed through 29 African countries. In 1973 it arrived in the Gulf of Mexico. Early in 1991 the infection spread rapidly in Peru. In 3 weeks there were 30,000 cases. The bacterium then spread further into South America, causing 360,000 cases within the year. In the summer of 1992 a second, less severe outbreak occurred. The case-fatality ratio varied depending on the region. After 1993 the disease assumed an endemic character in several countries, sometimes with local outbreaks. At the end of 1993 the cumulative total amounted to 900,000 cases in three years (1991-1993), with a cumulative mortality of 8,000.

About 80% of the cholera in 1997 occurred in Africa, chiefly in the horn of Africa (118,000 cases were reported officially). The increase in cholera in this region followed heavy rains and flooding (possibly associated with the El Niño weather phenomenon).

Since 1992 *V. cholerae* O139 is recognised as a cause of a disease which is clinically identical to classic cholera, but which also occurs frequently in adults. Classic cholera in India, on the other hand, is common in children. There is no cross immunity with *V. cholerae* O1. Bacteria of the 0139 serogroup have a polysaccharide capsule (unlike *V. cholerae* O1), which may explain the increased risk of septicaemia. In the following years this new serogroup spread across Bangladesh, India, Pakistan and Southeast Asia. By the end of March 1993 more than 100,000 cases had been reported in Bangladesh. If further spread continues, as with the earlier epidemics, it will be possible to refer to this as the beginning of the eighth pandemic. It was observed in India that, after the first spread of *V. cholerae* O139, new variants (clones) of *V. cholerae* O1 El Tor once more gained the upper hand. Cholera also surfaces regularly in Madagascar. From the beginning of December 1999 until the end of February 2000 more than 12,400 cases were reported. The disease can thus certainly not be regarded as an entity which only existed "in the past".

Humans are the only documented natural host and victim of V. cholerae. Cholera is transmitted through the faecal-oral route, most commonly by consumption of contaminated water and to a lesser degree food; direct person-to-person transmission is rare. A high infecting dose (as many as 1011 organisms) is required to cause illness in healthy individuals.

Water clearly plays a major role in the transmission of V. cholerae in endemic rural areas. During major epidemics, however, the direct contamination of food with infected excreta is also important. Persons with mild or asymptomatic infections (contact carriers) probably play an important role in the dissemination of epidemic

disease. The ratio of persons with asymptomatic infection to those with clinical disease varies from 4:1 to more than 20:1 in different outbreaks. A prolonged gallbladder carrier state may develop in up to 3% of patients convalescing from cholera caused by the El Tor biotype. The gallbladder carrier state has never been observed in the pediatric age-group. The role of such convalescent carriers in the transmission of the disease is not known. In the endemic areas of Bangladesh and West Bengal, cholera is predominantly a disease of children; attack rates are 10 times greater in the 1- to 5-year age-group than in the those over the age of 14 years. However, when the disease spreads to previously uninvolved regions, the attack rates are initially at least as high in adults as in children.

Pathogeny

An infective dose varies from 10^6 to 10^{11} bacteria, with the higher number applying when the stomach's acidity is high (i.e., low pH), but it can go as low as 10^4 when ingested together with an antacid or food. The standard pH of an empty stomach is between 0.9 and 3.0, generally around 1.0, and *Vibrios* are killed when the pH is below 2.4, so some people will not succumb to the disease.

Cholera is transmitted through contaminated water and manifests itself as an acute infection of the gastrointestinal tract. Although *Vibrios* are free living in water (in fact, they can survive on algae for quite some time), they cause infection only in humans. The bacteria bind to the walls of the small intestine where they secrete a potent toxin. This toxin alters the membrane transport mechanism; instead of causing the water to leave the lumen of the gut and enter the tissues, large quantities of water, chloride, and sodium are drawn into the gut.

The disease proceeds in possibly three stages (a) ***Invasion****:* at the end of the incubation period the symptoms are malaise, headache, severe diarrhea resulting in the so-called "**rice water stool**," (which derives its characteristic whitish color from intestinal tissue which is exfoliated (shed) and excreted along with innumerable Vibrios), anorexia, and a slight fever. This severe diarrhea can be as high as one liter per hour. The resulting loss of fluid and the accompanying electrolyte imbalance can lead to hypovolemic shock, renal failure, and cardiac failure. (b) ***Collapse****:* circulation is almost completely arrested, accelerated respiration, weak pulse, decreased systolic blood pressure, diminished or no urine output. This stage lasts from a few hours to one or two days. The mind remains clear until just before death, when coma occurs. Death follows shortly thereafter. Death can follow the onset of symptoms in little as six hours. (c) ***Reaction****:* sometimes, even when the grim reaper is about to claim victory, vomiting ceases, diarrhea becomes less frequent and less watery, and convalescence follows. Talk about your near-death experiences!

MANIFESTATIONS

The clinical onset of cholera (following a usual incubation period of 6-72 hours) is generally that of abrupt, painless, watery diarrhea. In severe cases, several liters of liquid may be lost within a few hours, rapidly leading to profound shock. At varying intervals after the onset of diarrhea, vomiting may ensue. This is characteristically effortless and is not preceded by nausea. In the more severe cases, muscle cramps are almost invariably present and commonly involve the calves.

When first seen by the physician, the patient who is severely ill with cholera is cyanotic and has sunken eyes and cheeks, a scaphoid abdomen, poor skin turgor, and thready or absent peripheral pulses. The voice is high pitched or inaudible; the vital signs include tachycardia, tachypnea, and low or unobtainable blood pressure. The heart sounds are distant and often inaudible, and bowel sounds are usually hypoactive. Major alterations in mental status are not common in adults; the patient usually remains well oriented, though apathetic, even in the face of severe hypovolemic shock. As many as 10% of small children may have central nervous system abnormalities that range from stupor to convulsions. In all epidemics, there are large numbers of mild cases in which the loss of liquid from the gut is not severe enough to require hospitalisation.

The loss of liquid and electrolytes continues for 1 to 7 days, and subsequent manifestations depend on the adequacy of replacement therapy. With prompt replacement, physiologic recovery is remarkably rapid and uniform despite continuing voluminous diarrhea If therapy is inadequate, the mortality rate in hospitalized patients may exceed 50%. The important causes of death are hypovolemic shock, uncompensated metabolic acidosis, and uremia. When renal failure occurs, the characteristic pathologic findings are those of acute tubular necrosis secondary to prolonged hypotension.

In endemic or epidemic areas, the working diagnosis of cholera should be made on the basis of the clinical picture. Liquid and electrolyte replacement therapy should be instituted immediately. Although a cholera-like illness may be caused by microorganisms other than V. cholerae-most frequently by enterotoxigenic Escherichia coli - the resulting physiologic and metabolic abnormalities are the same, so that identical intravenous and peroral electrolyte therapy should be used in all such cases.

Diagnostic culture techniques are relatively simple. A reliable and practical method consists of direct plating of feces on TCBS agar. Typical opaque yellow colonies appear in 18 hours. Final identification requires agglutination with group- and type-specific antiserums and the demonstration of characteristic biochemical reactions. Rapid, tentative diagnosis may be made by the direct darkfield microscopic observation of the characteristically rapid motility of the comma-shaped bacilli in fresh feces. Group- and type-specific antiserums immobilize homologous strains and clearly distinguish them from other vibrios.

With adequate therapy, the mortality rate approaches zero. Largely because of the mechanical problems inherent in the administration of large amounts of liquid to small children, their mortality rate still remains at 1% to 2% despite the best current therapy. A single attack of cholera confers protection against subsequent infection by the same serotype of V. cholerae for several years.

THERAPY

Successful therapy demands only prompt replacement of gastrointestinal losses of liquid and electrolytes. Of the several appropriate commercial preparations, lactated Ringer’s solution is the most widely available. This isotonic liquid should be given rapidly by IV injection-50 ml to 100 ml per minute-until a strong radial pulse is restored. Subsequently, the same solution should be infused in quantities equal to gastrointestinal losses or, if these losses cannot be measured accurately, at a rate sufficient to maintain a normal radial pulse volume and normal skin turgor. Overhydration can be avoided by careful observation of the veins in the neck and by

auscultation of the lungs. Close observation of the patient is mandatory during the acute phase of the illness. An adult patient can lose as much as 1 liter per hour of isotonic liquid during the first 24 hours of the disease. Inadequate or delayed restoration of electrolyte losses results in a very high incidence of acute renal insufficiency. Serious hypokalemia is rare in adults, and potassium replacement may usually be carried out by giving approximately 15 mEq of potassium chloride PO for each liter of feces that is produced.

In children, complications are both more frequent and more severe. The most serious include stupor, coma, and convulsions (unique to pediatric patients); pulmonary edema and cardiac arrhythmias may occasionally lead to cardiac arrest. The central nervous system complications may be due to hypoglycemia (observed only in pediatric patients), hypenatremia resulting from the administration of isotonic solutions to the pediatric patient (who, unlike the adult patient, produces feces with a sodium concentration significantly less than is present in plasma), or cerebral edema-presumably secondary to rapid shifts of liquid during intravenous administration. Pulmonary edema may result if liquid is given intravenously at too rapid a rate, especially in the presence of severe metabolic acidosis. Cardiac arrhythmias may result from potassium depletion in children but occur rarely in adults with cholera. Each of these complications can be avoided by the careful intravenous administration of solutions especially designed to replace the fecal electrolyte losses of children with cholera.

Lactated Ringer's solution is also satisfactory in children but should be supplemented by peroral administration of water and glucose; one glass (240 ml) of 5% glucose should be given PO, every 6 hours, to children who are receiving lactated Ringer's solution by intravenous injection. The intravenous administration of this solution must be carefully monitored, with frequent auscultation of the lungs and inspection of venous filling in the neck in order to avoid over-hydration.

Peroral replacement of water and electrolytes is effective in almost all patients who are alert. Glucose-electrolyte solutions may be given perorally in mild cholera throughout the course of illness. Early peroral therapy prevents serious depletion of electrolytes in all except the most severe (2% to 4%) cases of cholera. In the most severe cases, the initial hypo-volemic shock must be corrected by initial, rapid intravenous treatment. Losses from the gut may be replaced by peroral administration of an isotonic solution prepared by adding 20 g glucose, 3.5 g sodium chloride, 2.5 g sodium bicarbonate, and 1.5 g potassium chloride to a liter of water

If glucose is not available, sucrose (table sugar) may be substituted in a concentration of 40 g/liter; in the small bowel, sucrase splits sucrose into glucose and fructose; that is, half of the sucrose becomes available to facilitate the absorption of sodium. Liquids are initially given perorally in large quantities (e.g., 250 ml every 15 minutes in adults) until balance has been restored, as gauged by clinical observations. Thereafter, sufficient quantities are administered to balance the output of feces: 1.5 liters of glucose-electrolyte solution should be given PO for each liter of feces. The peroral administration of liquids does not decrease the volume of liquid lost through the gut, but provides replacement to counterbalance the enterotoxin-induced secretion of liquid.

Provision of adequate liquid with correction of the attendant biochemical derangements results in rapid recovery in virtually all patients with cholera. However, adjunctive treatment with antimicrobics dramatically reduces the duration and volume of diarrhea and results in the early eradication of vibrios from the feces. Tetracycline in a dose of 30 mg to 40 mg/kg body wt/day, PO, as four equal portions, every 6

hours, for 2 days was once uniformly successful. However, since 1979, a number of isolates of V. *cholerae* from patients in Bangladesh and Tanzania have exhibited resistance to tetracycline. That phenomenon is now emerging. Tetracycline resistant strains are now treated with Co-trimoxazole, erythromycin, doxycyclin, furazolidone and chloramphenicol

A cholera vaccine is available, but is normally not recommended by the CDC or the World Health Organization because only 50 to 70 percent of those who take the vaccine develop immunity to cholera, and the immunity lasts only a few months. Currently, no country requires the cholera vaccine for entry if arriving from cholera-infected countries.

EPIDEMIC CONTROL AND PREVENTIVE MEASURES

When cholera appears in a community it is essential to ensure three things: hygienic disposal of human faeces, an adequate supply of safe drinking water, and good food hygiene. Effective food hygiene measures include cooking food thoroughly and eating it while still hot; preventing cooked foods from being contaminated by contact with raw foods, including water and ice, contaminated surfaces or flies; and avoiding raw fruits or vegetables unless they are first peeled. Washing hands after defecation, and particularly before contact with food or drinking water, is equally important.

Routine treatment of a community with antibiotics, or "mass chemoprophylaxis", has no effect on the spread of cholera, nor does restricting travel and trade between countries or between different regions of a country. Setting up a *cordon sanitaire* at frontiers uses personnel and resources that should be devoted to effective control measures, and hampers collaboration between institutions and countries that should unite their efforts to combat cholera.

Limited stocks of two oral cholera vaccines that provide high-level protection for several months against cholera caused by *V. cholerae* O1 have recently become available in a few countries. Both are suitable for use by travellers but they have not yet been used on a large scale for public health purposes. Use of this vaccine to prevent or control cholera outbreaks is not recommended because it may give a false sense of security to vaccinated subjects and to health authorities, who may then neglect more effective measures.

In 1973 the WHO World Health Assembly deleted from the International Health Regulations the requirement for presentation of a cholera vaccination certificate. Today, no country requires proof of cholera vaccination as a condition for entry, and the International Certificate of Vaccination no longer provides a specific space for recording cholera vaccinations.