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Diagnosis, Clinical Management, Prevention, and Control of Cholera; A Review Study

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Context: Cholera is an intestinal infection caused by Vibrio cholera and transmitted by the fecal-oral route. The source of V. cholerae in nature is human and the most common vehicle of this infection is water and infected food. Here, we reviewed diagnosis, treatment, and prevention routes of cholera.

Evidence Acquisition: Electronic databases (PubMed and EMBASE) were searched from 1980 to 2013 regarding epidemiology, treatment, and prevention routes of cholera. Keywords including cholera, epidemiology, clinical manifestation, and treatment of cholera, and control and prevention routes were searched. In this review article, we focused mainly on the treatment and control of cholera.

Results: Cholera is a rare disease in industrialized countries; but, is still common in other parts of the world, including the Indian subcontinent, Sub-Saharan Africa, and Latin and Central American countries (like Haiti). Symptoms begin with a sudden onset of painless watery diarrhea which can quickly become voluminous. Antibiotics regimen is also recommended in addition to adequate hydration. Health education and education in environmental control are critical for the prevention of cholera.

Conclusions: Safe water supply and adequate sanitation and hygiene are the important routes for the control and prevention of cholera infection.

*Keywords:*Cholera; Diagnosis; Prevention and Control; Therapeutics

1. Context

Cholera, an acute intestinal infection is rare in industrialized countries; however, the disease is still prevalent in other parts of the world, including the Indian subcontinent and sub-Saharan Africa. It is an important health problem in many developing countries including India, Pakistan, Bangladesh, Latin and Central American countries (like Haiti) and African countries (Zimbabwe, South Africa, Mozambique, Botswana and Zambia (1-4). Epidemic infection sometimes occurs in southeastern of Iran in the border of Pakistan and Afghanistan. Cholera is an ancient disease like tuberculosis. Although the disease may be asymptomatic or mild, severe cholera can cause dehydration, renal failure and death within hours of onset (3).Cholera is caused by the bacterium *Vibrio cholera*e. Discovery of *V. cholerae* is credited to Robert Koch a German bacteriologist, who identified the micro-organism in 1883 during an outbreak in Egypt (5). The genus name refers to the fact that the organism appears to vibrate when moving. Since 1816, 7 cholera pandemics have occurred. The seventh pandemic of cholera began in 1961 and continued to 1991. This seventh pandemic caused by the El Tor biotype of *V. cholerae* O1and originated from the Celebes Islands and Indonesia. A new strain of infection, *V. cholera* serogroup O139 (Bengal) observed in the fall of 1992 and caused outbreaks in Bangladesh and India in 1993. Now, this strain is endemic in at least eleven countries. In some endemic countries, cholera outbreaks were occurred in a significant seasonal pattern (6-8). Huq et al. defined a significant correlation of water temperature, water depth, and rainfall with the occurrence of cholera from the data on four rural regions of Bangladesh (7). Hashizume et al. also found that the number of patients with cholera increased with both high and low rainfall in the weeks preceding hospital visits in Dhaka, Bangladesh (8). Lower temperature predicted a lower incidence of cholera in the first 15 weeks of the year, and low rainfall predicted a peak in spring, and high rainfall predicted a peak at the end of the monsoon (9). Due to the sensitivity of *V. cholera* to climate changing, the world health organization (WHO) has suggested an early warning system for cholera epidemics, using climatic parameters (10).

2. Evidence Acquisition

Electronic databases (PubMed and EMBASE) were searched from 1980 to 2013 regarding epidemiology,

Implication for health policy/practice/research/medical education:
Health education and education in environmental control are very important for the prevention of cholera. It is important for health care personnel to promote knowledge and educate people through the media or by scientific conferences.

treatment, and prevention routes of cholera. Keywords including cholera, epidemiology, clinical manifestation, treatment of cholera, control and prevention routes were searched. We found many papers about the cholera, but we selected mainly those which discussed diagnosis, new treatment, and control of cholera.

3. Results

3.1. Microbiology

V. cholera is a comma-shaped, gram-negative aerobic and sometimes, facultatively anaerobic bacillus variable in size from 1-3 μm in length and 0.5-0.8 μm in its diameter (11). It has two different antigenic structures; a flagellar antigen (H) and a somatic O antigen. The differentiation of the somatic antigen leads to pathogenic and nonpathogenic strains. Among more than 200 serogroups of *V. cholerae*, *V. cholerae* O1 and *V. cholerae* O139 are the most common serogroups associated with epidemic cholera (12, 13).Organisms in both the classical and the El Tor biotypes of serogroup *V. cholerae* O1 are subdivided into serotypes according to the structure of the O antigen, as follows:

1. Serotype Inaba
2. Serotype Ogawa
3. Serotype Hikojima

The clinical manifestations and epidemiologic features of disease caused by *V. cholerae* o139 are indistinguishable from those of disease caused by o1 serogroup. Clinical disease in both serogroups occurs by producing an enterotoxin that promotes the secretion of fluid and electrolytes into the lumen of the small intestine (11-14). This organism is not acid-resistant. The infectious dose is 10^3-10^6 organisms, when *V. cholerae* is ingested with water. When ingested with food, fewer organisms (10^2-10^4) are required to produce the clinical infection (12-14).

3.2. Host Factors

V. cholerae is not acid-resistant therefore, use of antacids, proton pump inhibitors and histamine receptor blockers can increase the risk of infection and predispose to severe disease (15). Moreover, gastrectomy and chronic gastritis secondary to *Helicobacter pylori* infection are two the important risk factors for severe clinical disease. Malnutrition increases the chance of infection and then clinical diseases. The incidence of cholera is twice in people with type O blood compared with other blood groups. The reason for increased susceptibility in type O blood is unknown (16). Infection with *V. cholerae* 01 dose not lead to immunity against *V. cholerae* 0139. People who had a history of El Tor cholera are not protected against further infection episodes. Nonetheless, those infected with classic biotype of *V. cholerae* usually produce antibodies that protect them against recurrent infection by either biotype (17). Infection rates of household contacts of cholera infection vary from 20-50%. This rate is lower in areas where infection is endemic and people, especially adults, may have antibodies from previous infection with the organism. For this reason, adults patients are less symptomatic than children, and second infections rarely occur or are mild (17, 18).

3.3. Clinical Manifestation

After one or two days of incubation, symptoms begin with sudden onset of a painless watery diarrhea which can quickly become voluminous and usually without vomiting. Symptoms can begin as soon as a few hours or as long as five days after the infection (15). Often symptoms are mild, but sometimes they are very serious. One of 20 patients infected with *V. cholera* has severe watery diarrhea accompanied by vomiting, which can quickly lead to dehydration. If not treated, dehydration can lead to a severe shock and death in a few hours (13, 14, 19, 20). Although many infected people may have minimal or no symptoms, but they can still spread out the infection. The characteristic cholera stool is opaque white and usually has a “rice water” appearance which is not malodorous. Profuse watery diarrhea is a hallmark of disease (15, 19). Sometimes, patients with severe cholera have a stool volume of more than 250 mL/kg of body weight during 24 hours. Due to this large volume of diarrhea, patients may have frequent and uncontrolled bowel movements (13-15). Physician should take into account cholera when a patient older than five years develops severe dehydration from acute, severe and watery diarrhea often without vomiting or in any patient older than two years who has acute watery diarrhea and lives in an endemic area or where an outbreak of cholera has occurred, currently. The amount of fluid loss and the corresponding clinical signs of cholera are as follows:

- 3-5% loss of normal body weight: excessive thirst;
- 5-8% loss of normal body weight: postural hypotension, tachycardia, weakness, fatigue, dry mucous membranes or dry mouth;
- > 10% loss of normal body weight: oliguria, sunken eyes, sunken fontanelles in infants, weak, absent pulse, wrinkled skin, somnolence, and coma.

3.4. Metabolic Manifestations

After dehydration is occurred, hypoglycemia is the most common lethal complication of cholera especially in children (17, 18). Hypoglycemia is a result of diminished food intake during the acute illness and defective neoglucogenesis secondary to insufficient storage. Hypokalemia results from potassium loss in stool. Hypokalemia develops only after correction of acidosis and intracellular hydrogen ions are exchanged for extracellular potassium. Hypokalemia is most severe in children with preexisting malnutrition status who have diminished body stores

of potassium, which may be presented as paralytic ileus (17-20). Bicarbonate loss in the stool is another complication. Rehydration therapy with bicarbonate-containing fluids can also produce hypocalcemia by decreasing the proportion of ionized serum calcium. Accumulation of lactate due to decreased perfusion of peripheral tissues occurs and hyperphosphatemia is common (19). Patients are faced with accidemia, when respiratory system is not able to sustain a normal blood pH. Cholera sicca is an old term describing a rare, severe form of cholera, which manifests as ileus and abdominal distention from massive outpouring of fluid and electrolytes into dilated intestinal loops. Mortality rate is high, and failure of diagnosis is common which is because of the unusual clinical presentation (15-17).

3.5. Diagnosis

Laboratory diagnosis is necessary not only for identification of microorganism, but also for epidemiological purposes. For definitive diagnosis, direct microscopic examination of stool including dark-field examination, gram staining, culture, serotype and biotype identification are performed. Isolation of *Vibrio cholera* serogroup O1 or O139 by stool culture is the gold standard method for the laboratory diagnosis (15, 19, 21). Although, other causes of diarrhea may be considered, but the clinical picture of cholera is unlikely to be confused with any other enteric diseases. This is especially true in adults, in whom no other infectious disease causes such profound dehydration, quickly. According to the World Health Organization (WHO) standard case definition, a case of cholera is suspected when the following conditions are met:

- In an area where the disease is not known to be present, a patient aged five years or older with severe dehydration or dies from acute watery diarrhea;
- In an area with a noted cholera epidemic, a patient aged 5 years or older who develops acute watery diarrhea, with or without vomiting.

Polymerase chain reaction (PCR) has been developed to identify *V. cholerae*. This test has a high sensitivity and specificity. However, this test is used only for screening of food samples (22). *Vibrio cholera*e is a gram-negative curved bacillus motile by a single flagellum. *V. cholerae* is not fastidious in nutritional requirements for growth. However, organism needs an adequate buffering system. Many of the selective media used for enteric pathogens do not support the growth of *V. cholerae*. Colonies of *V. cholera* are lactose-negative, like all other intestinal pathogens, but sucrose-positive. Unlike other Enterobacteriaceae, *V. cholerae* is oxidase-positive. As vibrio grows at a high pH or in bile salts, it inhibits many other Enterobacteriaceae (15, 19, 21). On thiosulfate-citrate-bile-sucrose-agar (TCBS), the sucrose-fermenting *V. cholera* grows as large, smooth, round yellow colonies. A positive immobilization test can be observed if the antiserum is specific for the *V. cholera*. In endemic area, this test is a very quick method of diagnosis. This method is important for epidemiologic studies, because El Tor and classic biotypes also can be identified (15, 19, 21). Hematologic tests are altered in patients with cholera. Hematocrit, serum-specific gravity, and serum protein are increased in dehydrated patients due to hemoconcentration (15, 21). At onset, patients can have a mild leukocytosis (15).

3.6. Treatment

Oral or intravenous hydration is the most important aspect in the treatment of cholera. In conjunction with suitable hydration, treatment with antibiotics is also recommended (15, 23-25). Antibiotics should be prescribed for patients severely or moderately dehydrated and those who lost a large volume of stool during the rehydration therapy. Antibiotic therapy is also recommended for all hospitalized patients. Antibiotics should be selected using local antibiotic susceptibility patterns. In most countries, doxycycline is recommended as the first-line treatment for adults (23, 25), and azithromycin as the first-line treatment for pregnant women and children (15, 24). Other antibiotics effective against *V. cholera* are trimethoprim-sulfamethoxazole (TMP-SMX), erythromycin, and ciprofloxacin. Azithromycin is more effective than erythromycin and ciprofloxacin (23-25). There are no guidelines to recommend antibiotics as prophylaxis for cholera prevention. All guidelines recommended that antibiotics should be administered along with aggressive hydration. Treatment with a single 300 mg dose of doxycycline has shown to be equivalent to tetracycline treatment for 3 days. Resistance to tetracycline and other antimicrobial agents among *V. cholerae* has been reported in endemic and epidemic cholera settings. Resistance can be acquired through selected mutations over the time, or due to widespread use of antibiotics for prophylaxis in asymptomatic individuals (15, 23-28). Antibiotic resistance has been observed in previous epidemics in the context of prophylaxis for household contacts of patients with cholera. It is suggested that antibiotic using can reduce secondary transmission of cholera (26).

3.7. WHO Guidelines for Cholera Management

Steps of treatment for a patient with cholera include:

1. Evaluate the degree of dehydration upon arrival to the hospital
2. Rehydrate the patient in 2 phases; these include rehydration (for 2-4 hours) and maintenance (until diarrhea abates). Use the intravenous route only:
    A. During the rehydration phase, an infusion rate of 50-100 mL/kg/h is advised for severely dehydrated patients
    B. For moderately dehydrated patients who do not tolerate the oral route, and;
    C. During the maintenance phase in patients

considered as high stool purgers (> 10 mL/kg/h).

3. Maintain hydration; replace fluid losses until diarrhea stops. During the maintenance phase, use oral rehydration solution at a rate of 800-1000 mL/h, unless the patient has a high stool purgers (> 10 mL/kg/h). In this situation, intravenous (IV) route is recommended.
4. Administer an oral antibiotic to the patient with moderate or severe dehydration. An effective antibiotic can reduce the volume of diarrhea in patients with severe cholera and shorten the period during which Vibrio cholerae O1 is excreted. In addition, it usually stops the diarrhea within 48 hours, thus shortening the period of hospitalization.
5. Feed the patient and discharge patients if oral tolerance is equal to or greater than 1000 mL/h, urine volume is equal to or greater than 40 mL/h, and stool volume is equal to or less than 400 mL/h (23, 25).

3.8. Prevention

For prevention of cholera, more attention to strategies to integrate all services in the general health system is very important. Health education is recommended for high-risk groups. Considering children and pregnant women and immune-compromised patients as high-risk groups is very important (29-33). WHO recommends safe water supply and adequate sanitation and hygiene (WASH) as the main steps to prevent cholera (28). Official recommendations also include the use of oral cholera vaccines (OCVs) for control of cholera outbreaks (26, 29, 30, 33). Two cholera vaccines are available and recommended by WHO (30).

Oral cholera vaccines are safe, effective and currently licensed by WHO as follows: 1-Dukoral (Crucell, Leiden, Netherlands), and 2-Shanchol (Shantha Biotechnics Ltd., Basheerbagh, Hyderabad, India). Both vaccines are given as a two-dose regimen. Vaccines are safe and provide sustained protection for several years. In 2010, they were added to WHO recommendations to control cholera outbreak (29, 30). However, doubts about feasibility, timeliness, and acceptability by the people at risk, and the fear of discouraging to use other preventative routes have discouraged their use during epidemics. Although, the Shanchol vaccine showed 66% efficacy over a three year period (29). In conclusion; Education in environmental control, safe water, adequate sanitation, and hygiene are important and critical for the prevention of cholera.

4. Conclusions

Cholera can be acquired by ingestion of water and food contaminated with pathogenic microorganism. Infection can also occur through person-to-person transmission, especially among members of the same household or in the crowded places, such as nursing homes and day care centers. Successful prevention of infection in the community depends mainly on adequate control measures such as rapid and accurate microbiological diagnosis, prompt treatment, patient isolation and preventative education, and adequate follow-up strategies to monitor fecal shedding after treatment in at risk groups.

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Authors' Contribution

Dr. Sharifi-Mood and Dr. Metanat wrote the manuscript.

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