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REVIEW ARTICLE

Cholera — the new strike of an old foe

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ABSTRACT

Cholera is an acute bacterial gastrointestinal infection caused by ingestion of water or food containing the pathogen Vibrio cholerae. The incubation period can be very short and it takes between several hours and 5 days. During the 19th century, cholera was spreading from India across the world. Its original reservoir was located in the Ganges delta. So far, there have been six epidemics of cholera; the current outbreak is the seventh. It started in Asia, attacked Africa and then the Americas. Cholera causes thousands of illnesses and deaths annually, mostly in South Asia and Sub-Saharan Africa. The current outbreak began in Yemen in October 2016, it peaked in December with subsequent decline, then the epidemic has re-erupted in April 2017 and it still continues. It is currently the largest outbreak in the world, with 5000 new infections a day (as of August 19th, 2017 the number of cholera cases stands at 527,000 with 1997 deaths). The most common symptoms of the illness are diarrhoea, dehydration, vomiting, and abdominal cramps. Case-fatality rate is lower than 1%, if rehydration treatment is prescribed rapidly, but it can exceed 70% in patients not treated properly. Aggressive and rapid fluid repletion is the basis of treatment for cholera. In many cases, rehydration therapy, given orally or parenterally, is enough to rescue infected patients. Antibiotics, mainly fluoroquinolones, tetracyclines, and macrolides are an adjunctive therapy for patients with moderate to severe fluid loss.

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ETIOLOGICAL FACTOR

Cholera is a bacterial disease caused by an infection of small intestine by *Vibrio cholerae* after ingestion of products contaminated with toxigenic strains, serogroups O1 and O139 [1]. *Vibrio cholerae* is a distinctive, comma-shaped gram-negative rod. Besides O1 and O139 strains, there are many other serogroups of *V. cholerae*, but they do not cause outbreaks. Other serogroups are classified as *Vibrio cholerae* "non-O1, non-O139". Toxin-producing non-O1/ /O139 strains are linked to isolated cases of dehydrating diarrhoea. Non-toxin-producing non-O1/O139 strains have been associated with sepsis and gastroenteritis [2].

The O139 strain was discovered in 1992 in Bangladesh and has never been identified outside Asia. It caused outbreaks in the recent decades. Nowadays, it is only spo-

radically found. *V. cholerae* O1 is the cause of the current epidemic of cholera.

There is no difference in the course of the illness caused by the two serogroups; clinically they are indistinguishable [3]. *Vibrio cholerae* toxin is the virulence factor causing the cholera disease, which is characterised by an acute watery diarrhoea [4]. It is the cholera toxin which is the primary reason for the characteristic profuse watery diarrhoea. Only toxigenic strains (toxin-producing) of *Vibrio cholerae* are associated with cholera. After colonisation of the intestinal epithelium, the bacteria secretes cholera toxin [2].

SYMPTOMS

Cholera is an extremely virulent disease. The incubation period can be very short and it takes between several

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hours and 5 days [5]. It lasts typically 1 to 2 days. Although most people infected with *V. cholerae* do not develop any symptoms, the pathogen can be detected in their stool samples for 1–10 days after infection and it is shed back into the environment. It is an important issue, because of the potential for infecting other people [3].

Symptomatic patients may present with a mild infection or severe watery diarrhoea that can be fatal in several hours (cholera gravis). After ingestion, the bacteria experience the acidic gastric environment and if they survive, they will form colonies adhering to the small intestine epithelium. Once attached to the surface of the small intestine, *V. cholerae* begin to produce cholera toxin that is responsible for the secretory watery diarrhoea [2].

Abdominal discomfort, malaise, cramps and vomiting are common accompanying early symptoms of the infection. Fever, severe abdominal pain, tenesmus are uncommon. Patients presenting with elevated temperature probably have coinfection or complications.

The hallmark of cholera is the rapid passage of large amounts of "rice-water" stool, sometimes including mucus. The diarrhoea is usually painless, it can have fishy odour or is odourless. Complications are associated with massive fluid and electrolytes (sodium, potassium, bicarbonate and chloride) depletion [6]. Such significant fluid loss is unusual for other diarrhoeal infections. It can be as high as 1 litre per hour in adult patients [7]. Bacteraemia is rare.

Cholera sicca (dry cholera) is a rare form of the disease. Death can occur within hours as a result of circulatory collapse. Because of the accumulation of fluid in the intestines, diarrhoea — the typical symptom of cholera — is absent [8].

If properly treated, cholera does not cause any known long-term complications or sequels.

DIAGNOSIS

Most cases of cholera are found in resource-limited regions of the world and are diagnosed presumptively in patients with acute watery diarrhoea with rapid and severe volume depletion. The experience of medical staff is crucial, because only prompt and aggressive rehydration therapy can save the life of patients with cholera gravis. It is worth emphasizing that in many tropical settings, stool culture or even microscopy is not available.

The preliminary diagnosis can be confirmed by rapid dipsticks tests, dark field microscopy, identifying *V. cholerae* in stool samples and isolation of bacteria from stool cultures [9]. Rapid dipsticks tests have low specificity which limits significantly their use in endemic areas.

The most important abnormalities confirmed by laboratory examinations are electrolyte disturbances, e.g. hypokalaemia, hyponatraemia, hypocalcaemia. Acidosis is also

frequently seen. In cases with circulatory collapse and fluid loss, there is a risk of renal failure.

TREATMENT

Cholera is an easily treatable disease. Eighty per cent of cases can be effectively treated with rehydration therapy. In many endemic areas, ready-made oral rehydration solutions are available. They must be prepared with clean, treated water. For more severe cases, an antibiotic course may be necessary. Adults will need 6 or more litres of oral rehydration solutions in the first 24 h of infection. In more severe cases, patients require intravenous rehydrating therapy. The total volume loss may be even equal with a patient's body weight [10].

When patients are successfully treated, symptoms are most serious in the first 2 days, and then they are diminishing. Without prompt treatment, cholera can be fatal within hours. The degree of fluid loss should be categorised according to World Health Organisation (WHO) criteria of none (< 5% of body weight), some (5–10%), or severe (> 10%) based on physical examination.

Antibiotics are necessary in moderate or severe cholera and shorten the duration of diarrhoea, minimize *V. cholerae* shedding in stool and decrease the amount of rehydration fluids needed during the therapy [3]. The antibiotics used for cholera include fluoroquinolones, tetracyclines and macrolides [11]. Antibiotics reduce the duration of excretion of *V. cholerae* in stool, diminish the possibility of infection among family members and minimise the risk of a nosocomial infection [4]. Resistance to these medicines is reported worldwide and mass antibiotics administration during outbreaks is not recommended. It does not impede the spread of cholera and enhances antimicrobial resistance [3, 4].

The possible mistakes and errors in providing treatment to patients with cholera are using inadequate type of fluids to rehydrate them and underestimating the amount of fluids needed.

The fatality rate is high in untreated patients and it can reach from 50% to 70%. Initiation of proper rehydration therapy reduces the mortality among severe cases to less than 0.5%. During pregnancy the risk is approximately 8% [12].

CURRENT EPIDEMIOLOGICAL SITUATION WORLDWIDE

Vibrio cholerae has been known since the 19th century and it continues to infect and kill large numbers of people in a very short time. Favourable conditions for spreading the pathogen include crowded settlements without sanitation infrastructure and running water, such as peri-urban slums or refugees' camps.

The last WHO report containing complete data was issued in 2015. Forty-two countries reported a total of

172,454 cases with 1034 deaths due to cholera infection. During Haiti outbreak in 2011, the number of cholera infections was 340,311 cases. The majority of cases and deaths attributable to cholera were noted in Sub-Saharan Africa (41.3 and 74.6%, respectively), primarily in the Democratic Republic of Congo, Kenya, Tanzania, Mozambique, Somalia and Nigeria. Case fatality rate was 1.25% [13]. It is well known that the reported numbers of cholera cases are underestimated. Probably there are 3 million cases and approximately 100,000 deaths annually attributable to *V. cholera* infection [14].

Cholera continues to be a public health problem mostly for low and middle-income countries, particularly in Asia, Africa and the Caribbean [15]. Almost 1.8 billion people around the world live in conditions conducive to infection by water contaminated with faeces and 2.4 billion people exist without proper sanitation infrastructure [3]. Cholera health effects are exacerbated by poor health, pregnancy, comorbidities, malnutrition and infancy [16]. In endemic regions, the morbidity is highest in children below 5 years.

The current outbreak in Yemen began in October 2016, it peaked in December and continued then the epidemic erupted again in April 2017. It is currently the largest outbreak in the world, with 5000 new infections a day. It is called a man-made humanitarian disaster, as a result of an ongoing civil war and a collapsing health system. More than half of all health facilities in Yemen have been damaged, destroyed or do not possess enough funds to continue activity. As of August 19th, 2017 the number of cholera cases stands at 527,000 with 1997 deaths [17].

The toxic mix of conflicts, civil war, famine, deteriorating hygiene and sanitation conditions is far from solving the situation in Yemen. Blockades on Saudi-controlled air and seaports preclude humanitarian aid and import of medicines [16].

The International Coordinating Group on Vaccine Provision promised to send 1 million doses of cholera vaccine to Yemen, which is approximately half of the global supply. Currently, the vaccine provision is intermitted, instead of it the efforts are made to improve access to clean water across the country [16]. It seems, however, that only the end of the civil war could end this humanitarian catastrophe.

SUMMARY

It has been estimated that there are 1.3 to 4.0 million cases of illness and 21,000 to 143,000 deaths worldwide due to cholera annually [1]. It is expected that the global climate change, including rapid and often unplanned urbanisation, could also increase the rates of cholera infections [15].

Most of those infected will have no or mild symptoms, and can be successfully treated with oral rehydration solution [3], which reduces the mortality of severe cholera from over 10% to less than 0.5% [18]. A major determinant of host susceptibility to cholera is immunity acquired through a previous infection or cholera vaccination. A single episode of cholera protects against the subsequent infection [19]. Among nutritional factors, retinol deficiency is associated with an increased risk of cholera, and breastfeeding has been consistently shown to be protective against cholera [20]. Other determinants of human susceptibility to cholera include genetic factors, and interactions with other microbes.

The opportunities for cholera to strike arise in the settings where populations are displaced, where people are left vulnerable by malnutrition, drought and low educational status, and where sanitation and hygiene are poor [15, 21]. The areas of increased risk include, in particular, peri-urban slums, where the basic infrastructure is not available, as well as camps for internally displaced persons or refugees, where minimum requirements of clean water and sanitation have not been met [3], or where the existing infrastructure has been destroyed during an ongoing war. This has clearly been reaffirmed in the ongoing conflict in Yemen [16].

In spite of the fact that cholera is treated easily, it remains a global threat to public health and an indicator of inequity and lack of social development [3], especially in Sub-Saharan Africa, the region with the lowest coverage of improved water and sanitation facilities and a plethora of health system challenges. A cholera epidemic creates an additional burden on health facilities and personnel already stressed by HIV/AIDS, malaria, tuberculosis, and other infectious and non-infectious causes of morbidity and mortality (e.g. malnutrition) [22]. In many settings, access to basic health care is also hampered by war [23]. All these factors impair rapid access to treatment which is essential during a cholera outbreak. Oral rehydration should be available in communities, in addition to larger centres that can provide intravenous fluids and 24 h care. With early and proper treatment, the case fatality rate should remain below 1% [3].

Safe water, sanitation and hygiene are the primary measures for cholera prevention and control, as well as breastfeeding of young infants, which protects against cholera and other enteric infections in endemic settings. Since 2010, killed whole-cell oral cholera vaccines have been recommended by the WHO as an additional tool for endemic and epidemic cholera prevention and control and for reducing the severity of the disease [1]. However, they should only be used in conjunction with improvements in water and sanitation to control cholera outbreaks and for prevention in areas known to be high risk for cholera. Under no circumstances should they replace conventional control measures. According to the results of trials conducted in different settings, the conferred protection at 6 months is 80% and at 5 years it is 65% [24]. In order to facilitate the

fight against endemic and epidemic cholera, WHO created the world's first oral cholera vaccine stockpile in 2013, which continues to expand and more than 11 million doses of oral cholera vaccines have been shipped for use in mass vaccination campaigns with WHO support up to June 21st, 2017 [3].

Currently there are three WHO pre-qualified oral cholera vaccines: Dukoral®, Shanchol® and Euvichol®. All three vaccines require two doses for full protection [25]. While Dukoral® is mainly used for travellers, providing approximately 65% protection against cholera for 2 years, Shanchol® and Euvichol® do not require a buffer solution for administration, which makes them easier to administer to large numbers of people in emergency contexts [3].

Although cases in resource-rich settings are generally imported from travel to endemic or epidemic settings, most travellers from resource-rich to resource-limited settings are at low risk for cholera. Select travellers, such as aid, refugee, and healthcare workers planning to work among displaced populations (e.g., those in crowded camps and urban slums) in endemic or epidemic settings, are at a higher risk and may benefit from pre-travel cholera vaccination. Travellers should follow general precautions such as avoidance of tap water, food from street vendors, raw or uncooked seafood, and raw vegetables. Water can be treated with chlorine or iodine, by filtration, or by boiling. The epidemiologic clues that might increase the suspicion of *V. cholerae* infection in a patient with watery diarrhoea include travel to endemic areas where cholera outbreaks are occurring or ingestion of undercooked or raw shellfish.

CONCLUSIONS

Cholera, an easily treatable disease, still causes significant mortality and remains a global threat to public health as well as an indicator of inequity and lack of social equality. Moreover, politically, economically and religiously motivated armed conflicts which frequently are located in already underdeveloped areas, and which often cause internal displacement of persons or flight of refugees and the destruction of water and sanitation infrastructure, force people to live in conditions where the only water available for drinking is that contaminated with human faeces. In 21st century, it should be considered shameful for the global community.

REFERENCES

1. Scobie H, Phares C, Wannemuehler K, et al. Use of oral cholera vaccine and knowledge, attitudes, and practices regarding safe water, sanitation and hygiene in a long-standing refugee camp, Thailand, 2012-2014. PLOS Neglect Trop Dis. 2016; 11(7): e0005810, doi: 10.1371/journal.pntd.0005810.
2. Harris J, LaRocque R, Qadri F, et al. Cholera. Lancet. 2012; 379(9835): 2466–2476, doi: 10.1016/s0140-6736(12)60436-x.
3. World Health Organization. Cholera. Updated July 2017. Available at: http://www.who.int/mediacentre/factsheets/fs107/en/.
4. Dengo-Baloi LC, Semá-Baltazar CA, Manhique LV, et al. Antibiotics resistance in El Tor Vibrio cholerae 01 isolated during cholera outbreaks in Mozambique from 2012 to 2015. PLoS One. 2017; 12(8): e0181496, doi: 10.1371/journal.pone.0181496, indexed in Pubmed: 28792540.
5. Azman AS, Rudolph KE, Cummings DAT, et al. The incubation period of cholera: a systematic review. J Infect. 2013; 66(5): 432–438, doi: 10.1016/j.jinf.2012.11.013, indexed in Pubmed: 23201968.
6. Molla AM, Rahman M, Sarker SA, et al. Stool electrolyte content and purging rates in diarrhea caused by rotavirus, enterotoxigenic E. coli, and V. cholerae in children. J Pediatr. 1981; 98(5): 835–838, indexed in Pubmed: 6262471.
7. Harris JB, Ivers LC, Ferraro MJ. Case records of the Massachusetts General Hospital. Case 19-2011. A 4-year-old Haitian boy with vomiting and diarrhea. N Engl J Med. 2011; 364(25): 2452–2461, doi: 10.1056/NEJMcpc1100927, indexed in Pubmed: 21696312.
8. Ryan ET, Dhar U, Khan WA, et al. Mortality, morbidity, and microbiology of endemic cholera among hospitalized patients in Dhaka, Bangladesh. Am J Trop Med Hyg. 2000; 63(1-2): 12–20, indexed in Pubmed: 11357989.
9. Dick MH, Guillerm M, Moussy F, et al. Review of two decades of cholera diagnostics--how far have we really come? PLoS Negl Trop Dis. 2012; 6(10): e1845, doi: 10.1371/journal.pntd.0001845, indexed in Pubmed: 23071851.
10. Carpenter CC, Barua D, Wallace CK, et al. Clinical studies in Asiatic cholera. IV. Antibiotic therapy in cholera. Bull Johns Hopkins Hosp. 1966; 118: 216.
11. Nelson EJ, Nelson DS, Salam MA, et al. Antibiotics for both moderate and severe cholera. N Engl J Med. 2011; 364(1): 5–7, doi: 10.1056/NEJMp1013771, indexed in Pubmed: 21142691.
12. Tran NT, Taylor R, Antierens A, et al. Cholera in pregnancy: a systematic review and meta-analysis of fetal, neonatal, and maternal mortality. PLoS One. 2015; 10(7): e0132920, doi: 10.1371/journal.pone.0132920, indexed in Pubmed: 26177291.
13. World Health Organization. Cholera, 2015. Wkly Epidemiol Rec. 2016; 91(38): 433–440.
14. Ali M, Nelson AR, Lopez AL, et al. The global burden of cholera. Bull World Health Organ. 2012; 90(3): 209–218A, doi: 10.2471/BLT.11.093427, indexed in Pubmed: 22461716.
15. Saha A, Hayen A, Ali M, et al. Socioeconomic risk factors for cholera in different transmission settings: An analysis of the data of a cluster randomized trial in Bangladesh. Vaccine. 2017; 35(37): 5043–5049, doi: 10.1016/j.vaccine.2017.07.021, indexed in Pubmed: 28765003.
16. Yemen and cholera: a modern humanity test. Lancet. 2017; 390(10095): 626, doi: 10.1016/S0140-6736(17)32210-9, indexed in Pubmed: 28816124.
17. ProMED-mail. Cholera, diarrhea and dysentery update: Asia (Yemen). Available at: http://www.promedmail.org/direct.php?id=20170822.5265435 (Access: 01 Sept 2017).
18. Sack D, Sack R, Nair G, et al. Cholera. Lancet. 2004; 363(9404): 223–233, doi: 10.1016/s0140-6736(03)15328-7.
19. Levine MM, Black RE, Clements ML, et al. Duration of infection-derived immunity to cholera. J Infect Dis. 1981; 143(6): 818–820, indexed in Pubmed: 7252264.
20. Harris JB, LaRocque RC, Chowdhury F, et al. Susceptibility to Vibrio cholerae infection in a cohort of household contacts of patients with cholera in Bangladesh. PLoS Negl Trop Dis. 2008; 2(4): e221, doi: 10.1371/journal.pntd.0000221, indexed in Pubmed: 18398491.
21. The Lancet. Cholera in Yemen. Available at: www.thelancet.com/infection (Access: 17 August 2017).

22. Christian KA, Iuliano AD, Uyeki TM, et al. What We Are Watching-Top Global Infectious Disease Threats, 2013-2016: An Update from CDC's Global Disease Detection Operations Center. Health Secur. 2017 [Epub ahead of print], doi: 10.1089/hs.2017.0004, indexed in Pubmed: 28805465.

23. The Lancet. Cholera in Yemen: war, hunger, disease ... and heroics. Available at: www.thelancet.com/infection (Access: 17 August 2017).

24. Nishiura H, Tsuzuki S, Yuan B, et al. Transmission dynamics of cholera in Yemen, 2017: a real time forecasting. Theor Biol Med Model. 2017; 14(1): 14, doi: 10.1186/s12976-017-0061-x, indexed in Pubmed: 28747188.

25. Desai SN, Pezzoli L, Martin S, et al. A second affordable oral cholera vaccine: implications for the global vaccine stockpile. Lancet Glob Health. 2016; 4(4): e223–e224, doi: 10.1016/S2214-109X(16)00037-1, indexed in Pubmed: 27013303.