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Treatment Strategies Of Cholera: A Review

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Abstract

Cholera is a contagious diarrheal disease which spreads through contaminated food and water. It is caused by Gram negative bacterium Vibrio cholerae of the O1 or O139 serogroup. Cholera can potentially spread as epidemic or endemic. If undiagnosed and untreated at the earlier stages, it can result in dehydration and death. Different endeavors are made for the treatment of cholera. Oral rehydration therapy (ORT), use of antimicrobials and antibiotics, probiotics and vaccinations are amongst the various alternative modes of treatment that can be used to treat cholera depending upon the severity of the disease. Also, antibiotics like tetracycline, azithromycin and doxycycline can be used synergistically for the treatment of acute infection and intense dehydration. Researchers have also advocated the use of different vaccines including oral cholera vaccine. In this review, we have provided a brief overview of the cholera disease and its pathogenesis along with different treatment strategies that can be used to treat it or reduce its symptoms.

Keywords: Cholera, antimicrobials, antibiotics, vaccination, pathogenesis.

1. INTRODUCTION

Cholera is an acute diarrheal infection is caused by Gram negative bacterium *Vibrio cholerae* of the O1 or O139 serogroup [2]. It being a contagious disease is caused by contaminated water and food. It can result in watery diarrhea like condition which quickly leads to dehydration. If not treated in early stage, dehydration can lead to demise within few hours [1]. The bacteria is transmitted either through direct infection from environment or through fecal-oral route [3]. *V. cholerae* is Gram negative, facultative anaerobe, comma shaped bacteria having flagellum and pilli at one cell pole and is ubiquitously present in saltwater and brackish water, aquatic plants [6]. *V. cholera* was first observed by Pacini, more than 160 years ago. On the basis of antigen O of lipopolysaccharides, there were around 200 serogroups of *V.cholerae*. Of these, only two seogroups, O139 and O1 can cause scourge cholera. *V. cholerae* O1 has two biotypes, El Tor and classical, serotype Ogawa or Inaba, which differ in ubiquity with time. *V. cholera*e O139 was initially reported in South Asia and which further caused outbreaks in Thailand or Bangladesh [7].

Cholera can potentially spread as epidemic or endemic. It occurs endemically in Southeast Asia and in sub-Saharan Africa, America and Haiti [2]. It was assessed that there are 1.3- 4.0 million cases and 21000-143000 mortalities worldwide due to cholera [4]. In 2015, 172,454 instances of cholera and 1304 deaths were reported from 42 nations [5]. In India, cholera is found in more than 10 states inculding Assam, West Bengal, Chandigarh, Chhattisgarh, Kerala, Haryana, Karnataka, Maharashtra, Gujarat, Odisha,

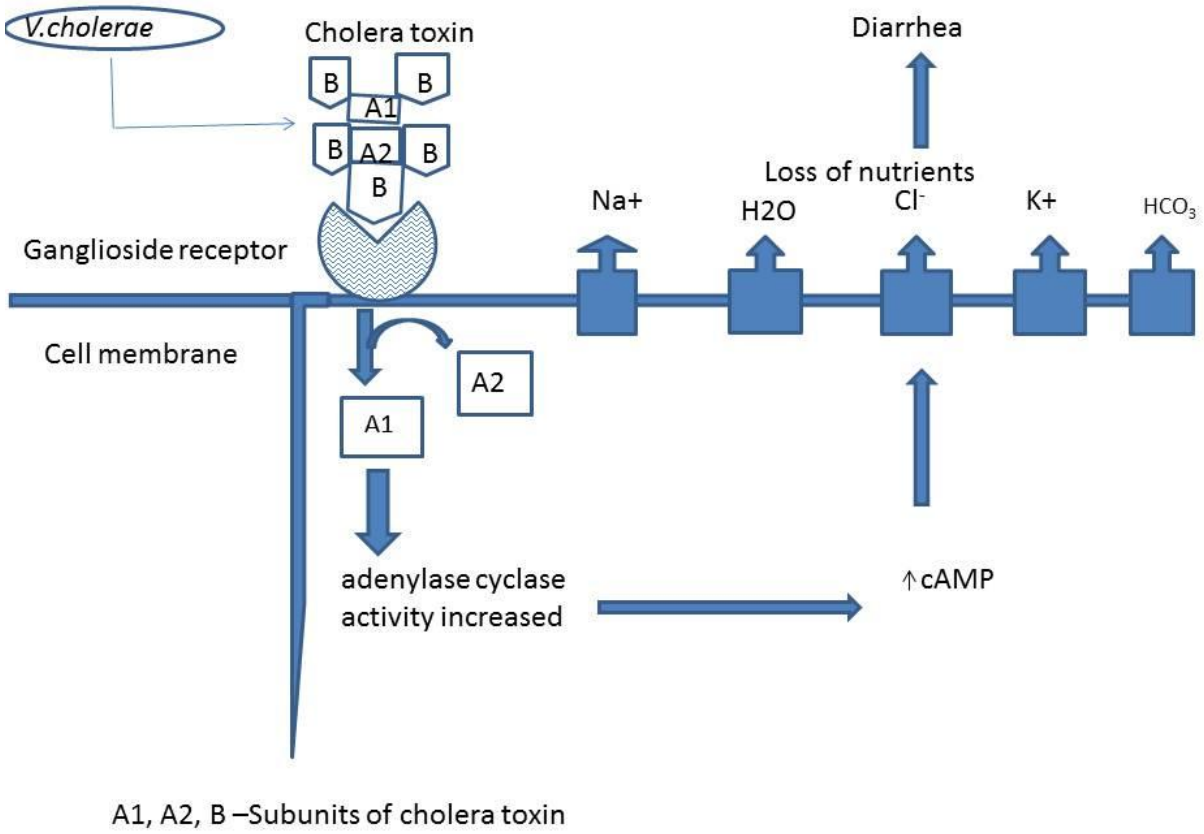
Rajasthan, Punjab, Tamil Nadu, Ganges-Brahmaputra delta. Due to its widespread existence across different states, India is sometimes been considered as the "country of cholera [1].

Cholera is generally spread in places with insufficient water treatment and poor sanitation and least wellbeing assets. Cholera requires immediate treatment otherwise it leads to death [8]. For long term management of cholera, sanitation conditions should be improved [9]. The absence of monetary assets like municipal water system, good sanitation infrastructure like flush toilet is related to cholera spread [10]. According to UN report published in 2015, 9% of world's population do not have accessibility to clean drinking water and 32% population of the world do not have access to modified sanitation facility, 58% are devoid of piped water on premises. All these infrastructure lacking makes it difficult to combat cholera. Quality of drinking water can be improved through simple and cheap approaches like water filtration and disinfection and these small initiatives help to fight against cholera [11-14].

PATHOGENESIS

V. cholerae enters the mouth through fecal contaminated water or food [15-17]. Most of bacteria entering the gastrointestinal canal are killed due to the low pH maintained by gastric acid [17]. However, if the bacterial load is too high, bacteria reach in small intestine and adhere to epithelial cell by special TCP (toxin-co regulated pilus) [18]. *V. cholerae* secrete protein exotoxin, which is made up of two subunit - A subunit and 5 B subunit [19]. These are enterotoxin which is antigenically identified as heat-labile enterotoxin of *E.coli* and can stimulate the creation of antibodies, and act on interior of the cell. Ganglioside GM1 fills in as the mucosal receptor for subunit B, which advances passage of subunit A into the eukaryotic cell. Subunit B never enter inside the eukaryotic cell because of its pentameric nature and is responsible for the binding with cholera toxin receptor.

GM1 is responsible for cell signaling. Subunit A enters inside the cell and get cleaves into A1 and A2. A1 increase adenylatecylase activity which further increases levels of intracellular cAMP inside the intestinal cell. This results in prolonged hypersecreation of electrolytes and water outside [2].



Lacking of treatment, the date rate of cholera case is 30% [23]. The first measure to control the illness is fluid replacement. For this, intravenous rehydration should be performed. Oral hydration should be encountered if emesis is not occurring frequently and after these antibiotics can be given to diminish the measure of stool volume and to diminish the term of ailment [24, 25]. The methods of treatment for the cholera are described below:

Oral rehydration therapy (ORT)

The endeavors to use ORT started in 1964. Based on literature studies, it was confirmed that the availability of glucose was necessary to encourage retention of water in the gut [26, 27], oral glucose saline was utilized by US Navy Capt. Robert Phillips to effectively treat cholera in two patients in Philippines (28). ORT replaces lost fluids and electrolytes during infection. The mortality rate of cholera has been diminished by over 97% by utilizing ORT and 99% patients survived *V. cholerae* infections after given ORT [29, 25].*V. cholerae* contamination causes epithelial cell lining in the intestine to lose large measures of electrolyte. World Health Organisation, has recommended the usage of sodium and potassium chloride and glucose ORT for treating cholera. However, these recommended constituents and their concentration has been modified several times. Glucose based formulations shortens the cholera symptoms by stimulating adsorption of electrolytes in the small intestine. Similarly, the rice based formulations decreases stool volume by 36% (30).

In Haiti, rice based oral rehydration formulations were successfully tested for the treatment of cholera (26). ORT composed of starch, shows resistance to metabolic degradation in gut, thus it persists for longer time than glucose (27, 30). It also stimulates synthesis of short chain fatty acid (SCFA) via fermentation of carbohydrates that are not degraded and absorbed in small intestine by the action of colonic normal flora (27). Also, starch and glucose could have a synergistic effect in suppressing cholera symptoms due to enhanced ion absorption (27). There are still cases where ORT was unable to curb the spread of cholera. Combined treatment with vaccines, antibiotic and antimicrobials is needed for reducing the cholera symptoms when ORT is ineffective (30,31, 32).

Antibiotics/Antimicrobials

ORT and antibiotics are used synergistically for the treatment of acute infection and intense dehydration [36-38, 39, 40]. Tetracycline, azithromycin and doxycycline are effective medicines for the treatment of cholera. Azithromycin is endorsed for pregnant women and children whereas tetracycline is appropriate for adults. Azithromycin and tetracycline have more advantages than erythromycin and ciprofloxacin [40, 37, and 38]. However, *V.cholerae* O1 and O139 strains show resistance to most of these antibiotics. Ciprofloxacin commonly used antibiotic, does not show any effect against *V.cholerae* in many countries like Bangladesh or Haiti [33, 41]. Some strains isolated from developing nation like India, Thailand, North Vietnam and Bangladesh have shown resistance to tetracycline [42, 29, 31].

Probiotics

The potential of host micro biome to inhibit the infection is a growing concept in microbiology. *V. cholerae* cause severe damage to the gastrointestinal microbiome during infections [43]. *V.cholerae* Type VI releases toxin against gut micro biome which is directly involved in colonization of bacteria (44, 45). Therefore, the colonization by probiotic bacteria is helpful to deal with cholera. Colonization of *Ruminococcusabeum* in human gut inhibits multiplication and colonization of *V.cholerae* in human gut (46). There is a positive correlation between *R. obeum* and prevention of cholera. According to study, the *Lactococcus. lactis* increase the production of lactic acid in response to *V.cholerae. V. cholerae* being is sensitive to acidic environment is killed in presence of lactic acid [47, 48].

Vaccination

In 1880s, the first injectable killed whole cell vaccine was devleoped producing (49, 50). In 20^{th} century, these vaccines were extensively used by travellers (51). Certain disadvantages like limited efficacy, high cost, and inefficiency of the vaccine to control expansion of disease were among few reasons that the vaccine was not much recommended (49, 50 and 51).

Various new vaccines against cholera were developed and tested in different countries. Oral cholera vaccines (OCV) which weaken or reduce the effect of cholera were advocated. According to WHO, these vaccines provide effective response in combination with other therapies (52, 53). OCV helps to produce antibodies (IGA) against the antigen produced by *V.cholerae*. These antibodies work well against O1 specific polysaccharides present on the surface of *V.cholerae* (54). Antibodies provide immunity for 6 months which further activates B cells and plasma cells to provide protection against the pathogen (54).

Most popular whole cell vaccine is 'Dukoral' which is the combination of inactivated *V.cholerae* O1 (E1) tor and classical biotype of recombinant B subtypes of CT (CTB) (55, 56, 57, and 58). It is widely used in endemic region due to cost effectiveness and efficiency rate of around 55-88% effect (59, 60). For adults, Dukoral is recommended after 2 years, for the children between 2 to 6 years dosage should be given 6 months [61].

Other vaccines, Shanchol and Euvichol are composed of deactivated O1 ogawa and O139 strains (56, 62). Shanchol has protection rate of approximately 65 %(52). These both vaccines are not recommended for pregnant women (56, 53). The oral live attenuated vaccine, vaxchora (CVD 103-HgR) is a single dose oral vaccine produced from classical O1 strain which is GMS of cholera (63). This vaccine has the ability to produce a desired or intended result against *V.cholerae* classical biotype with 65% effective response against *V.cholerae* E1 tor biotype (64). The vaxchora vaccine has high efficiency of 90% (65, 57, 66). Several other forms of vaccines developed from outer membrane vesicle (OMV), can also give rise to immunogenic responses (55) and provide protection against *V.cholerae*. Pandemic research indicated that as different region or area may be affected by different strains of cholera, new vaccines should be developed. The three vaccines are used for treatment of cholera are discussed below:

1. Killed whole cell monovalent (O1) vaccine with cholera toxin B subunit (WC-BS and WC-rBS)

This vaccine is manufactured and marketed with the brand name Dukoral. Dukoral was developed and certified in Sweden in the year 1991. This vaccine is made by combining subunit B of cholera toxin and heat killed whole cells. The whole cell consists of monovalent *V. cholerae* O1 representing serotype Ogawa and Inaba, biotype classical and EI Tor. Cholera toxin (B-subunit) was initially synthetically developed (WC-BS). However currently developed by recombinant innovation (WC-rBS), both BS and rBS produced indistinguishable immune response (67). The vaccine doesnot contain cholera toxin subunit A and is free from its toxic impacts. Since the heat labile toxin (LT) of *E. coli* cross respond with cholera toxin, this vaccine has appeared to provide short term cross protection against diarrhea caused by enterotoxigenic *E. coli* (68). Two doses for grown-ups and three doses for youngsters beneath five years old are required for the vaccine. The vaccine requires co-organization of a bicarbonate buffer in safe water to prevent debasement of the toxin B subunit. Sur et al., (2009) reported 85% efficacy for 6 months vaccination or 50% efficacy of 3 year for older children or adults in randomized controlled trial involving ninety thousand children (age 2 years) (57).

Mass vaccination was noted to be productive in averting cholera in population with 20-30% sero prevalence of HIV [69, 70]. In a case study, where 14000 individuals were injected with a minimum dose, 78% of population was protected from the disease whereas serious illness was prevented in 89% cases.

2. Modified and killed whole cell vaccines (WC) - mORCVAX

In 1980s, the government of Vietnam started production of local cheap oral O1 serogroup whole cell vaccines. Composition of mORCVAX is same to WC-rBS apart from B subunit toxin. During widespread occurrence of cholera, this vaccine showed 66% protection (71). In 1997, mORCVAX was licensed through Vabiotech in Hanoi, Vietnam with the properties of bivalent formulation (O1 and O139). In this vaccine there is no co-administration of oral

buffer because of lack of toxin. In Vietnam, 20 millions of doses were practiced. But due to quality aspects, vaccine did not prequalify the standard of WHO. Scientist of different nation together worked again on its production and improved quality, ingredients and which was then finally approved and the resulting vaccine is shanchol. In 2011, shanchol was prescreened by WHO by testing in Vietnam, Ethiopia and India (72-75). Trails conducted on more than 67000 youngsters and adult in Kolkata, India, have confirmed that shanchol has granted 67 % protection (76, 77). But the level of protection was not even for all age groups. In children between age between 1 to 5 years have shown efficacy of 42% (78). In Bangladesh, vaccine has shown efficiency upto 65%.

3. Attenuated and live oral cholera vaccines

Attenuated vaccines are conceivably more reactive and effective after just single-dose of vaccination. It has been postulated that attenuated immunizations can mirror normal infections, and therefore they ought to give dependable and explicit responses (81). They may have a few downsides, for example, presenting excessively high reactogenicity (82). The only authorized attenuated *V. cholerae* vaccine is CVD103-HgR, which is marketed as Orochol TM (Berna, Crucell, Switzerland). Orochol comes in sachets of two that contains attenuated vaccine and neutralizing buffer which protects it from gastric environment (83). Orochol TM comprises the hereditarily modified *V. cholerae* O1 Inaba strain 569B, likewise called CVD103-HgR. This derivative is created by deleting 550 bps in the ctxA gene. This expelled about 94% of the area encoding area of peptide A1 of the cholera toxin. A valuable quality gene *mer* is added. The antibodies produced in response to the vaccine are demonstrated to be immunogenic and safe (84).

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