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Review Paper

The Causes, Diagnosis, and Current Course of Medical Care for Cholera

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ABSTRACT:
Vibrio cholerae-containing contaminated water is the main way that cholera is spread around the world and has done so for generations. The seventh pandemic of cholera, which began in the 1960s and is still continuing strong today, is thought to be the one that has been going on the longest and is responsible for millions of deaths annually. With two of its strains, V. cholerae O1 and V. cholerae O139, known to cause cholera, a deadly diarrheal disease that has repeatedly plagued the world in pandemics since 1817 and continues to be a public health problem globally today, Vibrio cholerae (V. cholerae) are a Gram-negative, curved, rod-shaped bacteria. According to projections, India has 1.6 cases of cholera per 1000 people each year, or 40 cases of acute diarrhea for every 1000 people. There are more than 200 serogroups of Vibrio cholerae based on somatic antigens, and the epidemic strains O1 and O139 are among them. This review article discusses the pathogenesis, aetiology, medical treatment, diagnosis, risk factors, and signs and symptoms of V. cholerae.

Keywords: Vibrio cholerae, Epidemiology, Etiology, Risk factors, Diagnosis and Treatments.

INTRODUCTION:

A facultative anaerobe with a flagellum for motility, Vibrio cholerae (V. cholerae) is a member of the Vibrionaceae family. It is oxidase-positive, bean-rod shaped, and Gram-negative but does not produce spores (1). The bacteria bring on a contagious illness called cholera Vibrio cholerae O1 and O139. When consumed, its clinical aftereffects include the sudden onset of severe diarrhea with a rice-like secretion. A previously healthy person may get severe dehydration within three to four hours of the onset of symptoms, and if untreated, may pass away within twenty-four hours. This makes cholera one of the infectious diseases with a known high mortality rate for which the only effective treatment is simple rehydration, which is also affordable, secure, and life-saving (2). The bacterium is divided into cholera vibrio (pathogenic) and noncholera vibrio (non-pathogenic) forms based on the O antigen of its lipopolysaccharide. While the non-toxigenic O1/O139 group causes non-epidemic periodic diarrhoea, wound infection, gastroenteritis, septicemia, and skin infections, cholera toxin-producing O1 and O139 serogroups cause acute enteric human diarrhea (3). A gram-negative, aerobic, facultatively anaerobic bacillus with a comma form, V. cholera can range in size from 0.3 to 1.3 µm in length and 0.5 to 0.8 µm in diameter. It possesses a flagellar antigen (H) and a somatic O antigen, two distinct antigenic structures. Pathogenic and nonpathogenic strains result from the somatic antigen's differentiation. The two most prevalent V. cholerae serogroups associated with epidemic cholera, O1 and O139, are found among the more than 200 serogroups of this bacteria. Cholera infection rates among friends and family range from 20 to 50%. This rate is lower in locations where the virus is endemic and where people, particularly adults, may already be immune to the organism thanks to prior infections. Because of this, adult patients experience fewer symptoms than children do, and second infections are either extremely rare or light (4). A small intestinal infection brought on by the "Vibrio cholera" bacterium causes severe diarrhea. The bacteria that causes the deadly disease cholera is known to be the bacterium Vibrio cholerae. The first effective isolation of the V. cholerae bacterium marks a significant turning point in medical history as a whole. It is quite difficult to pinpoint who first found cholera. The causes are not difficult to find. The majority of people credit the renowned German scientist Robert Koch with discovering cholera. Although cholera is simply one of many different types of diarrheal diseases, its inclusion

in the WHO Communicable Disease Surveillance and Response (CSR) Framework highlights its worldwide significance (5,6). Due to its quick spread and capacity to trigger significant epidemics, cholera places a significant economic burden on areas where it is endemic. Cholera has spread to all inhabited continents since the first recorded pandemic in the 19th century on the Indian subcontinent, and it is now endemic in Africa, South and East Asia. In the near future, it's possible that cholera outbreaks will become more frequent due to the unpredictable appearance and transmission of antibiotic-resistant strains, the escalating severity of meteorological events, and variations in water temperature and nutrition levels (7,8). Since 1817, the worldwide spread of cholera, an acute enteric diarrheal infection, has been sporadic (9). Based on the past, the Indian subcontinent has suffered from severe dehydrating diarrhea for generations with no knowledge of the creatures responsible for the deaths that resulted from it. A London doctor by the name of Snow established in 1849 that cholera spreads naturally through water. Aberth was the first scientist to isolate the cholera-causing agent from a cholera patient's stool (10,11). Highly contagious diarrheal disease outbreaks travel quickly inside and between nations, and even continents, in varying degrees of severity. Cholera outbreaks are thought to cause 3-5 million illnesses and over 200 000 fatalities year, according to the World Health Organization (WHO). The disease is fatal because it is very contagious and 75% of the population can be infected without showing any symptoms. This causes the disease to spread more quickly when people move between different geographic areas and nations (12).

EPIDEMIOLOGY:

Around four million cases of cholera are reported annually, and the illness is responsible for approximately 140,000 fatalities. Nearly 1.8 million people globally get their drinking water from places that may harbor cholera bacteria because they are tainted with human feces. In the impoverished world, where requirements for water filtration and sanitation may not exist, outbreaks are known to happen. Cholera is currently thought to be endemic in about 50 countries, predominantly in Asia and Africa. Depending on when the region's rainy season begins, the incidence is linked to a seasonal distribution. However, epidemics in other parts of the world, such as South and Central America, can be more widespread. Epidemics have been known to spread when a species is introduced to a new area during which cleanliness and health services have collapsed (13,14). According to estimates, there are 40 instances of acute diarrhea for every 1000 people in India each year, or 1.6 cases of cholera per 1000 people. Vibrio cholerae possesses more than 200 serogroups based on somatic antigens, of which O1 and O139 are epidemic strains (15).

ETIOLOGY:

Comma-shaped, facultative, gram-negative, oxidase-positive rod known as Vibrio cholerae is common in underdeveloped nations. There are two serotypes known to be responsible for outbreaks. All recent epidemics have been caused by O1, whereas O139 only occasionally produces outbreaks, mostly in Asia. Between the two, there is no etiologic distinction. V. cholerae can be discovered in food typically shellfish and water that hasn't been properly sterilized. Since the bacteria is known to spread by the fecal-oral route, it is endemic to regions with poor food and water hygiene (16,17).

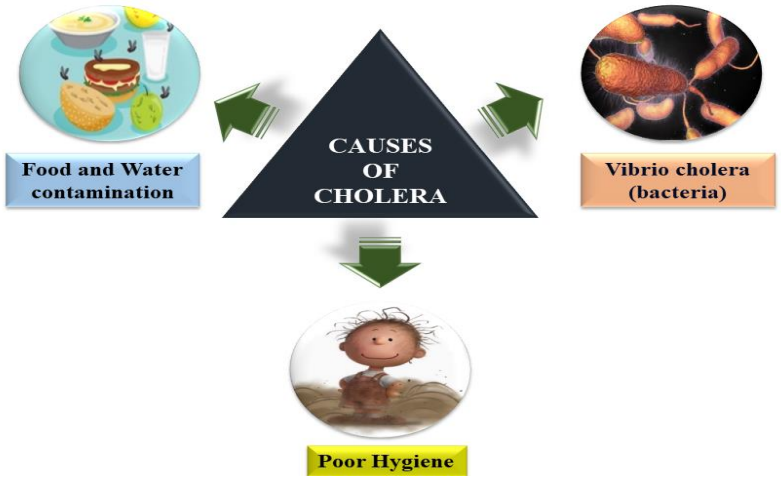

Fig.1: Several major causes of cholera.

SIGN AND SYMPTOMS:

The symptoms of cholera can range from mild to severe diarrhea. Vomiting, diarrhea, and abdominal pain are typical symptoms. Due to the severe and quick loss of fluid and electrolytes, severe cholera can be clinically recognized from other diarrheal diseases. Stools are frequently described as having a "rice water" consistency and can contain mucus and bile. Children can produce up to 20 cc/kg/hr, compared to adults who can produce up to one liter per hour. Hypovolemia as a result causes the typical signs of fluid loss, such as chilly skin, decreased skin turgor, and dry oral mucosa. Lack of blood flow to bodily tissue can cause lactic acidosis, which in turn can lead to hyperventilation and Kussmaul breathing. Additionally, generalized muscular weakness and cramping may be brought on by electrolyte imbalances such hypokalemia and hypocalcemia (18). After ingesting the bacteria, these symptoms often appear anywhere from five days to a day and a half later. The diarrhea may smell fishy and is usually described as "rice water" in nature. A cholera patient who is left untreated may have 10 to 20 liters (3 to 5 US gal) of diarrhea every day. Most victims of severe cholera die, roughly half of them. The ratio of asymptomatic to symptomatic infections has been estimated to be anywhere from 3 and 100. The reason why cholera is known as the "blue death" is because it can cause significant fluid loss, causing a person's skin to turn bluish-gray (19).

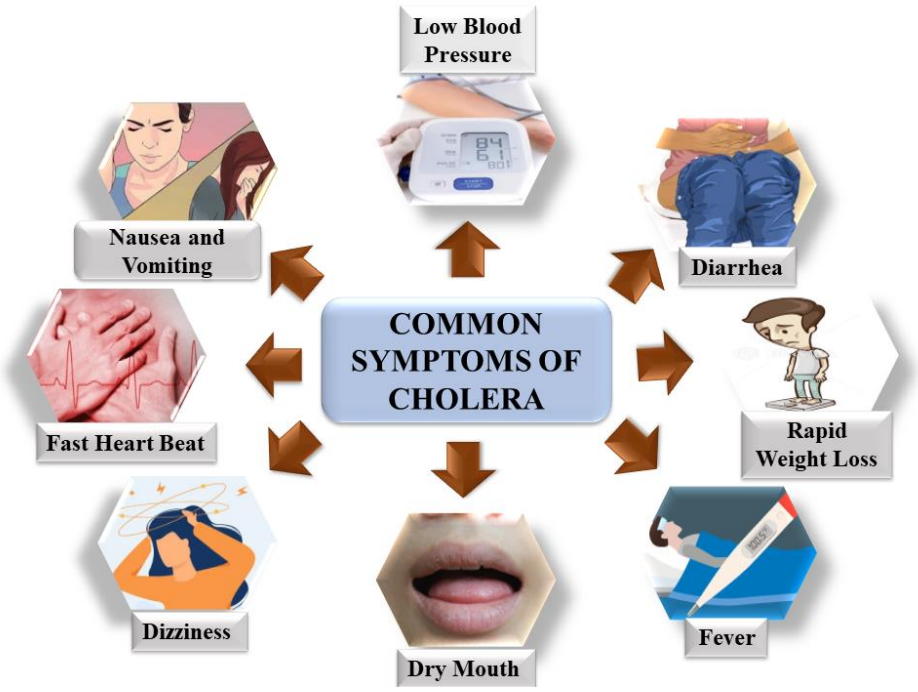

Fig.2: A few common symptoms and sign of cholera.

RISK FACTORS RELATED TO CHOLERA TRANSMISSION:

Infants who are breastfed seem to be more resistant to cholera, whether it's endemic or epidemic. Gunn discovered that cholera was more prevalent in bottle-fed infants than it was in breast-fed infants during a cholera outbreak in Bahrain. He was unable to determine whether this danger resulted from infant formula contamination or from the preventive qualities of breast milk itself. Breastfeeding appears to protect against cholera in infancy in endemic regions like Bangladesh. Children with cholera in Dhaka were less likely to be breastfed than children with diarrhea from any other agent, with the exception of shigella, as cholera typically spares children in their first two years of life (20,21). There is minimal evidence to support the notion that those who are undernourished or malnourished have an increased risk of disease or severity with cholera. Despite the fact that undernutrition or malnutrition has frequently been regarded a risk factor for diarrheal infections. Between cholera patients and a healthy control population, Rosenberg was unable to find any difference in the levels of thiamine, ascorbic acid, folate, or B12 in 1962–1963. In a group of Thai patients with acute cholera, Gangerosa showed histological signs of malabsorption on biopsy; alterations were later

discovered to be nonspecific, persistent, and typical among Thais and other people in South and Southeast Asia. Children in the lowest weight quartile who took tetracycline had longer diarrheal episodes, according to Lindenbaum and Karchmer, who were looking for the best effective antibiotic treatment for cholera in children (22). This chapter's earlier discussion of the connection between the infectious dosage and gastric acidity level. An individual exposed to V. cholerae 01 is more susceptible to illness because of hypochlorhydria. Malnutrition, gastritis, gastric surgery, or drugs that lessen or neutralize stomach acid can all contribute to low acid output. Investigations into cholera epidemics as well as volunteer studies have both shown the significance of stomach hypoacidity. For instance, in Italy, index patients with cholera were 5.8 times more likely than controls to have undergone stomach surgery in the past (P = 0.0005) (22). Family members of cholera sufferers are at high risk of getting the disease themselves in many cholera-infected locations with poor hygiene standards. This could be caused by secondary spread of V. cholerae 01 from the index patient to other contacts or by sharing a common exposure (such contaminated water). In other cases, suggestions for preventative treatment of family contacts have resulted from recognition of the high incidence of infection among family contacts (23).

PATHOPHYSIOLOGY:

The small intestine may get colonized as a result of ingesting V. cholerae. The creature can reach the intestinal wall by swimming through mucus thanks to its flagella. Toxic V. cholerae makes toxin-coregulated pilus there, which adheres to ganglioside receptors in the mucosal wall. ADP-ribosylation of the Gs subunit of the G protein complex in the gut epithelium occurs as a result of the production of cholera toxin. Adenylate cyclase begins to function normally as a result, which raises intracellular levels of cAMP. Consequently, there is an increase in the secretion of chloride, bicarbonate, salt, and potassium. The osmotically drawn water from the intestinal cells by the production of these electrolytes results in diarrhea. Previous exposure to the organism has an impact on host vulnerability and can lead to immunity, albeit this depends on the biotype and serotype of the earlier organism encountered. Since it is a labile acid bacterium, an adult who is healthy needs to get a significant dose of the vaccine to become infected. This explains why decreased gastric acidity (as shown in achlorhydria instances) can lower the infection threshold required by the bacteria. It's interesting to note that blood type O has also been linked to a higher risk of infection. It is yet unclear what is causing this heightened susceptibility to illness. Antihistamines and proton pump inhibitors can make a patient more susceptible to infection and make their symptoms more severe. The colon is insensitive to the toxin, whereas the fluid losses often come from the duodenum. Most of the time, there are no neutrophils seen in fecal collections because the enterotoxin only has a local effect and is not invasive (24–26).

DIAGNOSIS:

Clinical suspicion can be used to make the diagnosis of cholera. A diagnosis may be made based only on the characteristic high amount of diarrhea and travel to an endemic area. As a result, laboratory tests are frequently not needed before starting medication. However, the isolation and culture of V. cholerae from stool isolates can help to confirm the diagnosis. Selective media with a high pH that inhibit the growth of intestinal microflora while allowing V. cholerae to proliferate can be used to improve culture. Rapid assays can also be used to determine whether stool samples contain the O1 or O130 antigen. There are techniques that can be used to quickly identify or see the organism, including dipsticks and darkfield microscopy of the feces (27). In addition to helping identify microorganisms, laboratory diagnosis is essential for epidemiological research. Direct microscopic examination of the stool, including dark-field examination, gram staining, culture, serotype and biotype identification, is carried out for a conclusive diagnosis. The most accurate way to diagnose Vibrio cholera is through stool culture, which is the gold standard approach. A single flagellum propels the gram-negative, curved bacillus known as Vibrio cholerae. When it comes to nutritional requirements for growth, V. cholerae is not particular. However, the organism requires a strong filtration system. V. cholerae cannot grow in many of the selective medium used for enteric infections. Like all other intestinal infections, V. cholera colonies are sucrose-positive but lactose-negative. V. cholerae differs from other Enterobacteriaceae in that it is oxidase positive. Numerous other Enterobacteriaceae are inhibited while vibrio thrives in bile salts or at high pH levels. (28–30). Although there are other potential causes of diarrhea, it is doubtful that cholera's clinical features will be mistaken for those of any other enteric disorders. This is especially true for adults because no other infectious disease rapidly dehydrates people to such a significant degree. In accordance with the World Health Organization's (WHO) standard case definition, cholera is presumed to be present when the following circumstances exist: Patients aged five years or older who suffer from severe dehydration or pass away from acute watery diarrhea in a region where the disease is not known to be prevalent; patients aged five years or older who get acute watery diarrhea, with or without vomiting,

in a region where there is a recognized cholera outbreak. To identify V. cholerae, polymerase chain reaction (PCR) has been created. The sensitivity and specificity of this test are very good. However, only food samples are screened using this technique (31). Large, smooth, spherical, yellow colonies of the sucrose-fermenting V. cholera develop on thiosulfate-citrate-bile-sucrose-agar (TCBS). If the antiserum is specific for the V. cholera, a positive immobilization test will be seen. This test is a relatively quick way to diagnose an endemic area. Due to the ability to distinguish between El Tor and traditional biotypes, this approach is crucial for epidemiologic investigations. In cholera patients, hematologic tests are changed. Patients who are dehydrated have hemoconcentration, which leads to a rise in hemocrit, serum-specific gravity, and serum protein. Patients may initially experience a moderate leukocytosis (4).

VARIOUS CHOLERA TREATMENTS THAT ARE CURRENTLY AVAILABLE:

On the basis of the degree of volume depletion, rapid fluid resuscitation is the cornerstone of cholera treatment. Oral rehydration solution ought to be taken if an estimated 5% to 10% of body weight has been lost. The length of diarrhea and volume of stool loss can both be reduced, according to clinical investigations, by using an oral rehydration solution based on rice. One liter of water, six tablespoons of sugar, and a half teaspoon of salt can be combined to create an emergency remedy. Fluids should be supplied intravenously to patients who are in hypovolemic shock or have lost more than 10% of their body weight. The first three hours should include the administration of about 100 mL/kg of lactated ringers. Rapid fluid treatment for severe cholera can lower mortality from over 10% to less than 0.5%. Antibiotic therapy can begin once the proper volume status has been reached. The most often utilized class of drugs is tetracyclines. The length of the illness can be shortened by taking a single dose of 300 mg of doxycycline or 500 mg of tetracycline every 6 hours for two days. Alternative treatments include fluoroquinolones like ciprofloxacin as well as macrolides like erythromycin and azithromycin because resistance is frequent in some regions (14,15,32). Patients who are moderately or severely dehydrated or who lost a lot of stool during the rehydration therapy should be given antibiotics. The use of antibiotics is also advised for all hospitalized patients. Utilizing regional antibiotic susceptibility trends, antibiotics should be chosen. The first-line treatment for adults in the majority of nations is doxycycline, while the first-line treatment for children and pregnant women is azithromycin. Erythromycin, ciprofloxacin, and trimethoprim-sulfamethoxazole (TMP-SMX) are additional antibiotics that are effective against V. cholera. Compared to erythromycin and ciprofloxacin, azithromycin is more efficient. There are no recommendations for using antibiotics as prophylactic to prevent cholera. Antibiotics should be given along with rigorous hydration, per all recommendations. It has been demonstrated that treatment with a single 300 mg dose of doxycycline is equivalent to three days of tetracycline treatment. In both endemic and epidemic cholera environments, V. cholerae has been found to be resistant to tetracycline and other antimicrobial drugs. Resistance may develop over time as a result of specific mutations or from the widespread use of antibiotics as prophylactic in asymptomatic people. In the context of cholera prophylaxis for home contacts of patients, antibiotic resistance has been seen in prior epidemics. It is hypothesized that utilizing antibiotics can lessen cholera's secondary transmission (30,33–38). Guidelines from WHO for Cholera Management. Treatment for cholera patients involves the following steps: When the patient gets to the hospital, gauge how dehydrated they are. Rehydrate the patient in two stages, including maintenance (until diarrhea stops) and rehydration (for 2-4 hours). Use just the intravenous route: Patients who are very dehydrated should receive an infusion at a rate of 50 to 100 mL/kg/h during the rehydration phase. When patients are in the maintenance phase and are high stool purgers (> 10 mL/kg/h), for moderately dehydrated individuals who cannot tolerate the oral route. Until diarrhea ends, keep hydrated and replace any lost fluids. Unless the patient has large stool purges (> 10 mL/kg/h), utilize oral rehydration solution at a rate of 800-1000 mL/h throughout the maintenance phase. It is advised to use the intravenous (IV) method in this case. Give the patient who is moderately or severely dehydrated an oral antibiotic. In patients with severe cholera, an efficient antibiotic can lessen the amount of diarrhea and speed up Vibrio cholerae O1 excretion. Additionally, it typically ends the diarrhea within 48 hours, cutting the length of the hospital stay. If the patient's oral tolerance is 1000 mL/h or higher, their urine volume is 40 mL/h or higher, and their stool volume is 400 mL/h or less, they should be fed and discharged (35,37).

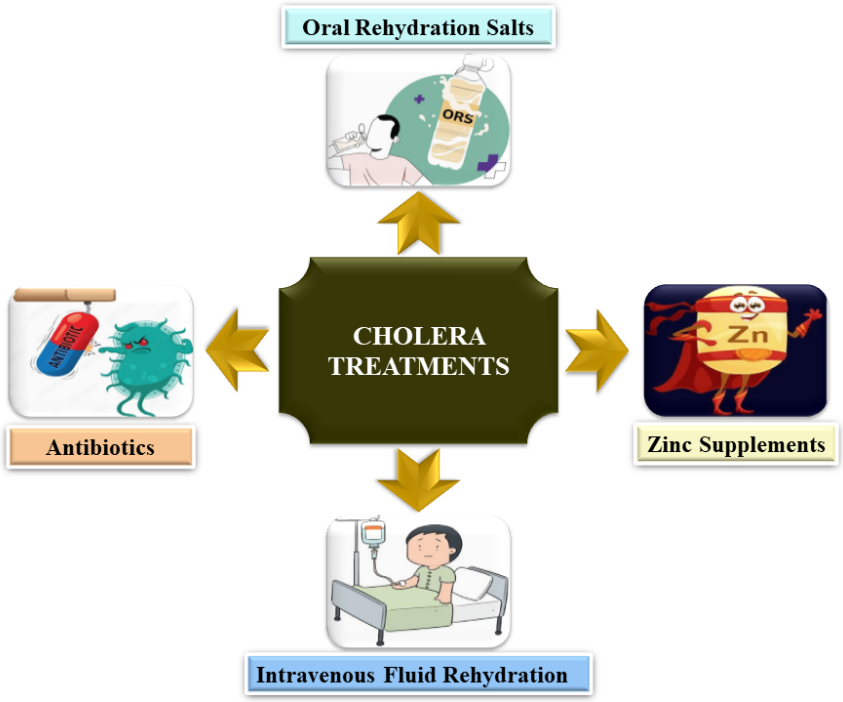

Fig.3: Cholera treatments alternatives that are currently available.

STOCKPILE OF ORAL CHOLERA VACCINES:

Hispaniola presently has an endemic case of cholera, and the disease is still prevalent across Africa, Asia, and the Middle East as a result of multiple previous severe cholera epidemics that caused thousands of deaths as well as significant economic and social losses. In 2013, the WHO collaborated with private international partners to invest in a stockpile of bivalent inactivated whole cell vaccines that could be quickly deployed in reaction to these events and in recognition of enhanced vaccination efficacy. Before the stock pile was established, suggestions for controlling outbreaks sometimes consisted only of improvements to water and sanitation. Recent outbreaks have been so enormous and spread so quickly that it is now widely acknowledged that it is frequently difficult to meet the fundamental demand for safe drinking water in situations of tragedy, war, and massive refugee populations. Because of this, the purchase of a vaccine stockpile signifies a paradigm shift in how cholera epidemics are handled. The stockpile was used for the first time in South Sudan in 2014, arriving 30 days after the Ministry of Health made the request. For outbreaks in both endemic and non-endemic areas, 15 nations received cholera vaccines from the global stockpile during the first four years of use. Cholera vaccination has become a crucial instrument in the fight against sickness because to successful vaccine production, purchases, and deployment (39–41).

PREVENTION:

More focus on methods to integrate all services in the general health system is crucial for cholera prevention. High-risk populations are advised to receive health education. It is crucial to recognize immune-compromised patients, children, pregnant women, and pregnant women as high-risk populations. The essential measures to prevent cholera are, according to the WHO, a reliable supply of potable water and appropriate sanitation and hygiene (WASH). For the purpose of containing cholera outbreaks, official recommendations also call for the use of oral cholera vaccines (OCVs). There are two cholera vaccines on the market that the WHO recommends. The following oral cholera vaccines are now authorized by the WHO and are safe and effective: 2 Shanchol (Shantha Biotechnics Ltd., Basheerbagh, Hyderabad, India), and 1 Dukoral (Crucell, Leiden, Netherlands). The recommended dosage for both vaccinations is two doses. Vaccines are secure and offer long-lasting defense for several years. They were incorporated into the WHO's cholera epidemic control recommendations in 2010. However, their usage during epidemics has been limited by concerns regarding their viability, timeliness, and acceptability by the individuals who are at risk as well as the worry of inhibiting the adoption of other preventative measures. The Shanchol vaccine, however, demonstrated 66% effectiveness over a three-year period. For the prevention of cholera, education in environmental

management, access to safe water, proper sanitation, and hygiene is crucial (42–46).

CONCLUSION AND FUTURE DIRECTION:

The aetiology, pathophysiology, epidemiology, risk factors, and available treatments for cholerae, as well as its signs and symptoms, are all thoroughly discussed in the first portion of our review articles. Although pharmaceutical drugs have no adverse effects, immunizations produce greater results. To learn more about the best cholera treatment, additional randomized controlled research must be conducted. On cholera research, we want to keep working. With the assistance of our colleagues, a second study that includes counseling will be carried out in our country or state in order to assess the physical and mental well-being of patients and to present a more comprehensive understanding of cholerae and its enhanced treatment.

ETHICAL STATEMENT:

An excellent pharmacist offers patients compassion and understanding in addition to the appropriate drugs.

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CONFLICT OF INTEREST:

The authors attest that they are free of any known financial or personal conflicts of interest that would taint the findings of this study.

INFORMED CONSENT:

Using websites, review articles, and other sources to produce research content.

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