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REVIEW ARTICLE

An overview of cholera

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ABSTRACT

Cholera is caused by Vibrio Cholera. It is also referred to as blue death. It has caused a huge number of epidemics all around the globe. It is a Gram-negative bacterium which can colonize in the gastrointestinal tract of the host organism. Due to significant number of mutations in the bacteria new serotypes are emerging which is a potential cause of concern. These new serotypes cause a high rate of morbidity. If the patient is left untreated, due to severe dehydration the patient dies. O1 strain of vibrio has caused epidemics in Asian as well as in African nations. The review article focuses on the host pathogen interaction, the clinical manifestations, as well as the recommended treatments which are most commonly administered. However, a deep research is needed to understand the complexity of the disease which can help in the progress of development of vaccines.

Keywords: Immunity, Pathogenesis, Cholera, Diarrhea, Cytokines

INTRODUCTION

Vibrio cholera is a Gram-negative bacterium that is known to cause the disease cholera.[1] It is facultative anaerobe. The bacteria reside in the marine environment. The bacteria cause diarrhea that is the leading cause of morbidity all around the globe. Most of the cases go unreported due to its negative impact on the economy of a country. The bacteria are differentiated serologically on the basis of presence or absence of the O antigen in its lipopolysaccharide.[2] The serotype which causes severe diarrhea is O1 and O139. The O1 group can be classified further on the basis of its phenotype. The pathogens possess toxins called the enterotoxins.[3] These are responsible for the virulence of the pathogen. The toxin coated pilus often called the toxin coregulated pilus holds the bacterial cell together in the intestine. It provides resistance against the churning force in the gut, the cholera toxin binds to the epithelial cells of the gut. This triggers endocytosis.[4] However, virulence of cholera toxins depends on a lot of factors. The review will focus on the host pathogen interaction, molecular pathogenesis of the pathogen followed by the mechanism of antibiotic resistance and the environmental factors that provoke the spread of the disease.[5-7]

METHODOLOGY

The review paper has been prepared by collecting research papers from several journals published on bib, PubMed, dip. The articles covered a broad range of topics starting from pathogenesis to transmission, host pathogen interaction as well as recent development in vaccinations, articles published on the website of the WHO, ICMR, and Centers for Disease Control (CDC) were also used for reference. Data published on unreliable websites have been excluded, a total of 30 research papers have been referred in total.

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SYMPTOMS

The symptoms usually develop usually 2–3 days after ingestion of contaminated food and water.[2] Usually, the symptoms are mild to moderate; however, in certain cases it can become severe. The incubation period is usually serotype dependent; however, the average is usually 5 days.[8] The onset of symptoms can be characterized by discomfort in the abdomen followed by loss of appetite, The color and texture of stool changes from brown to rice water in appearance.[9-11] Usually cholera is characterized by severe vomiting, dehydration as well as low blood pressure. Usually, the skin becomes scaly and wrinkles start appearing on the hands. Body temperature is usually normal.[12] In certain cases, it can cause necrosis of the heart. The blood pH becomes low and convulsions can occur in children.

CLINICAL MANIFESTATION

Infection with vibrio cholera can cause a lot of some of which are dehydration, diarrhea, etc. Vibrio cholera usually spreads from contaminated food and water. The bacteria colonize in the small intestine of the host.[3,4,13] The symptoms start appearing usually 12–72 h after the infection. It usually starts with severe cramps in the stomach followed by vomiting. It is followed by diarrhea and leads to an excessive loss of fluid from the body.[14] Due to excess dehydration it hampers the major metabolic process of the body leading to the death of the person. In few cases, the pathogen might persist in the stool even before the symptoms start to appear.[15] Asymptomatic persons can spread the bacteria but a much lower level.[16] It becomes very difficult to identify the asymptomatic persons. In a demographical analysis, it was concluded that children usually below 5 years are more susceptible to become asymptomatic. To understand the dynamics of the disease further a proper research should be carried out. Recent researches show that nutrition as well as genetic factors influences the susceptibility of the population.[17] The blood of a person is also a key determinant. The antigens in blood are a set of glycoproteins which influence the interaction of the host pathogen binding. The O blood group has an unmodified antigen hence its at a lesser risk to infection. But once the patients with O blood group are infected, the condition of the patients usually becomes severe.[10,18] Zinc is an important micronutrient that is an integral component of immune system.[12,19] Its depleted during severe diarrhea. Cholera does not cause any inflammation. The architecture of the gut is retained in case of cholera infection. However, the levels of cytokines increase during infection such as tumor necrosis factor as well as interleukins.[2,20,21] The infiltration of the neutrophils and the macrophage cause severe cholera. The Immunoglobulin A (IgA) prevents the colonization of the pathogen in the gut. Eight days after infection the level of chemokines are upregulated in case of infection.[22] Once the pathogen starts colonizing the intestinal mucosa they cannot be detected in blood. After 3 days antibodies start developing. These antibodies last only for a year. Memory B cells are often detected a year after the infection. The antibody titer value is the marker of inflammation.[23,24] The titer value remains high even after 6–9 months of infection. However, vibrio is a non-invasive pathogen, the degree to which these pathogens can provide protection is questionable.[9] Herd immunity plays a very critical role in providing protection. Vaxchora vaccine is the most commonly administered vaccine in case of cholera infection. However, a large-scale vaccination is needed to provide protection. To understand the transmission of the bacteria several animal models were studied. More such studies need to be done for studying the complex dynamics of the disease.

INFECTION MODEL IN ANIMALS

Infection of the host by the pathogen is a very complex process and a multistage one. To colonize the intestine, the pathogen must escape the innate immune system of the body. Bacterial shedding occurs in the rice water stool, the virulence genes are not expressed in the rice water stool, the exact mechanism is not clear. The virulence of vibrio can be attributed to to the presence of chemotaxis genes.[25] When vibrio cholera enters the body, it uses mucinoses to penetrate the mucosa of the gut.

Some of the other factors are N acetyl glucosamine binding protein. The expression of certain genes is changed. Certain enzymes such as the cycle di GMP are hydrolyzed. The enzyme responsible for the hydrolysis is phosphodiesterase, the activity of RoPs as well as Mine Health and Safety Act is downregulated.[2] The cdi GMP genes are activated that allow the bacteria to prepare for transmission to other host. The chemotaxis is responsible for the hyperinfectivity of the bacteria.[3] The bacteria have a tendency to form biofilm on the surface and it is characterized by the formation of polysaccharide on the surface.[26] The escape mechanism in the bacteria allows the bacteria to de attach from the intestinal epithelium. The expression of certain genes is needed to mediate the survival of the bacterium in the host body. Vibrio remains hyper infectious 5 h after it is passed out from the host body.

MECHANISM OF PATHOGENESIS

Vibrio cholera spreads from contaminated food, water from an infected person. Planktons and zooplanktons can also spread the disease. The bacteria attaches itself to the mucosal layer of the gut.[18,27] It uses mucolytic enzymes to destroy the mucosal epithelial cells of the gut. The bacteria attaches to the surface of the intestinal microvilli using pili. Cholera toxin is a type of endotoxin produced by the bacterium and it is responsible for the pathogenicity of the bacterium.[20,28] The cholera toxin consist of six subunits in total: One A subunit and B subunits. The GM ganglioside of the intestinal epithelium binds to the B subunit of the enterotoxin. The increased adenylate cyclase activity activates the A subunit of the enterotoxin.[11,15] The increased level pf cAMP increases the permeability of the intestine of the chloride ion pumps in the intestine.[16] Water, sodium ions are secreted. The absorption of water is also increased. Vibrio cholera has the tendency to form biofilm on the surface. Biofilms consist of cells that are attached on the substratum.[10] This includes the attachment of the bacteria to the abiotic surfaces or biotic surfaces. The motility genes are usually downregulated during formation of biofilms.[29] A major change in transcriptome is usually observed during biofilm formation, the signaling pathway is unknown. The cells packed in biofilm have small volume and diffusion is limited. It is synthesized from GTP by the enzyme diguanylate cyclase. The *Vibrio cholerae* genome encodes HD-GYP, and 10 combined GGDEF-EAL domain proteins. VSPR and VSPT are the major genes for biofilm formation. The vibrio genes also encode PilZ proteins responsible for the formation of biofilm as well as motility and virulence.[12] The biofilm is made of proteins, nucleic acid as well as polysaccharides. The extracellular DNA is responsible for the stability of the biofilms The level of extracellular DNA is upregulated by dns as well as xds.[19] It acts as a source of phosphate for the degradation of the biofilm.

Therapy

Oral rehydration therapy can be used for treating along with the administration of antibiotics. Intravenous rehydration should be administered within ½ h of the infection. The recommended dose for children is 30 ml per kg of body weight in every 4 h.[15] The stool output should be monitored, and if patient should be administered with rehydration therapy. ORS contains optimum amount of glucose, electrolytes for sodium absorption.[20] Antibiotics should be administered immediately after the infection. Some of the strains show drug resistance. The most common drug administered is tetracycline. Norfloxacin as well as ciprofloxacin can be administered as well.

IMMUNE RESPONSE AND VACCINATION

The immunity developed is dependent on the serotype. Patients infected with O1 serotype gains absolute immunity against the pathogen whereas the one with E1 develops 90% immunity against the infection.[25] Infection with vibrio can cause mild to severe dirrhea. The degree of symptoms depends on the availability of toxins as well as the availability of receptors. The flagellar antigen (H), toxin as well as the somatic antigen can detect the antibodies.

The antibodies can lyse the specific components of the bacteria, certain antibodies such as IgA, IgA, IgM, and IgG are found in mucosa.[30] Even in the absence of complement system the antibodies can confer protection against the bacteria. The main antibody that provides protection is the IgA. Since it's a motile pathogen the antibodies directed against the flagellar antigen can arrest their motility. Cholera vaccines have been developed recently to elicit a protective function. The first attempt was made in 1960, it was not efficient as well as the antibodies were not long lasting. Parenteral vaccines have a low level of secretory antibodies. Hence, there has been as shift from parenteral route to the oral route. Oral vaccines can be stored for a longer duration. Vaxchora is the vaccine which has been recommended by the FDA. However, no vaccines are fully effective.

EPIDEMOLOGY

Cholera is an endemic mostly in Asian and African countries. Cholera mostly occurs in the monsoon season in the Asian countries. Usually, the number of cases is common in children below 5 years. Pakistan, China, and Bangladesh have reported the endemic in all age groups The fatality rate was extremely high.[4] The key factors are high population density lack of health infrastructure and proper sanitation. A lot of environmental factors are also responsible for the outbreak. Due to change in the temperature of water the population of phytoplankton's as well as zooplanktons increase.[13] The infection also increases in case of floods, etc. All the strains of vibrio have a gene capture system and over these years several distinct lineages have been identified such as the most virulent strains O1 as well as EO1.[2] The outbreaks in Asia, Africa, etc., reported that the SXT gene segment was missing.

PREVENTION OF CHOLERA

Since the 19th century several countries across the globe have reports a huge number of outbreaks hence proper sanitation and clean water.[2] The prime goal is to maintain proper hygienic condition. If an outbreak occurs the focus should be given on rehydration therapy, washing hands.[2.24] On top of everything people should be vaccinated. Some of the vaccines available are Dukoral recombinant DNA vaccine hanchol (Shantha Biotechnics-Sanofi Pasteur, India) and mORCVAX (VaBiotech, Vietnam) are internationally available. A number of killed and attenuated vaccines are available as well. These vaccines are safe however CVD 103-HgR failed to show desired immune response.[28] The WHO focuses on the development of oral vaccines along with parenteral routes of administration. Hence, an effective vaccination strategy along with rehydration therapy can curb outbreak.

CONCLUSION

Vibrio cholera is a virulent bacterium that had caused a large of pandemics as well as pandemics all around the globe. The O139 serotype is the most virulent strain. Conventional methods of screening are not effective. Molecular screening methods are effective. Infections can be due to the lack of proper hygiene. This infection is usually observed in developing countries and it usually spreads by contaminated food and water. Hence, proper sanitation is mandatory followed by immunization to curb the spread of the disease. The antigenic variants hinder the development of proper vaccines which are 100 percent effective. If majority of the population is vaccinated herd immunity might develop. The WHO is working in collaboration with CDC to determine the antigenic variants. The people all across the globe should be properly educated and the importance of maintaining cleanliness should be highlighted. Proper prophylactic measures as well as proper surveillance can save the developing countries from such epidemics.

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