CME

The Vibrio Cholera

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Introduction:

Vibrios are gram negative rods bacteria that are all widely distributed in nature the vibrose are found in marine and surface waters. They are curved aerobic rods and are motile, possessing a polar flagellum. V.vibrios sero group 01 and related Vibrios cause cholera cause sepsis or enteritis Vibrio cholerae The epidemiology of cholera closely parallels the recognition of V.cholerae transmission in water and the development of sanitary water system (1,2,6,9).

V. C is a comma-shaped, curved rod 2-4 long .It is actively motile by means of polar flagellu on prolonged cultivation. Vibros may become straight rod that resemble the gram-negative enteric bacteria (1,2,6,9).

V.C. grow well at 37^{O}C on many kinds of media .including defined media containing mineral salt sand asparagines as sources of carbon and nitrogen V. C. produce convex, smooth round colonies that are opaque and granular in transmitted light V.C. grows well on thiosulfate-citrate yellow colonies . V. are oxidase-positive, vibrio grow at Avery high Pi-Land are rapidly killed by acid (1,2,3,6).

V.C. and related produce a heat-lebile entero toxin with molecular weight of about 84,000 consisting of subunits A and B .The genes for V.C. enterotoxin are on the bacterial chromosome-cholera enterotoxin is antigenincally related to LT of E-coli and can stimulate the production of neutralizing antibodies .However, the precise role of antitoxic and antibodies in protection against cholera is not clear. (3,6)

Its structure was determined with one and two dimensional NMR spectra (COSY, HMBC, HMQC, HOHAHA on nuclei ^{1}H, ^{13}C and ^{31}P) and was further confirmed with HPLC (18).

Pathogenesis and Pathology:

Only for humans, a person may have to ingest 10-10 organisms to became Under natural condition V.C .is pathogenic infected and developed disease in contrast to salmonlosis or shigellosis, in which ingestion of 10-10 organism can induce infection (3,5,9).

Cholera is not an invasive infection/the organism do not reach the blood stream but remain with in the intestinal tract. Virulent V.C. organism attach to the microvilli of the brush border of epithelial cells, there they multiply and liberate cholera toxin and perhaps muenases and endotoxin (3,4,6).

Clinical finding:

After an incubation period of 1-4 day, there is a sudden onset of nausea and vomiting and profuse diarrhea with abdominal cramps. Stools which resemble rice water contain mucus, epithelial cells and large numbers of vibrios .There is rapid loss of fluid and electrolytes which leads to profound dehydration, circulatory collapse, and anuria (1,2,6).

Epidemiology:

Prevention:

Although cholera can be life-threatening it is nearly always easily prevented, in principle, if proper sanitation practices are followed. In the United States and Western Europe, because of advanced water treatment and sanitation systems, cholera is no longer a major threat. The last major outbreak of cholera in the United States was in 1911. However, everyone, especially travelers, should be aware of how the disease is transmitted and what can be done to prevent it. Good sanitation practices, if instituted in time, is usually sufficient to stop an epidemic (10). There are several points along the transmission path at which the spread may be halted:

Sickbed: Proper disposal and treatment of the germ infected fecal waste (and all clothing and bedding that come in contact with it)

produced by cholera victims is of primary importance.

Sewage: Treatment of general sewage before it enters the waterways or underground water supplies prevent possible undetected patients from spreading the disease. Sources: Warnings about cholera contamination posted around contaminated water sources with directions on how to decontaminate the water.

Sterilization: Boiling, filtering, and chlorination of water kill the bacteria produced by cholera patients and prevent infections, when they do occur, from spreading. All materials (clothing, bedding, etc.) that come in contact with cholera patients should be sterilized in hot water using (if possible) chlorine bleach. Hands, etc. that touch cholera patients or their clothing etc. should be thoroughly cleaned and sterilized. All water used for drinking, washing or cooking should be sterilized by boiling or chlorination in any area where cholera may be present Water filtration, chlorination and boiling are by far the most effective means of halting transmission. Cloth filters, though very basic, have greatly reduced the occurrence of cholera when used in poor villages in Bangladesh that rely on untreated surface water. In general, public health education and good sanitation practices are the limiting factors in preventing transmission. (5.6)

Recent epidemiologic research suggests that an individual's susceptibility to cholera (and other diarrheal infections) is affected by their blood type: Those with type 0 blood arc the most susceptible [10][11] while those with type AB are the most resistant. Between these two extremes are the A and B blood types, with type A being more resistant than type B [citation needed].

About one million V. cholcrae bacteria must typically be ingested to cause cholera in normally healthy adults, although increased susceptibility may be observed in those with a weakened immune system, individuals with decreased gastric acidity (as from the use of antacids), or those who are malnourished.

It has also been hypothesized that the cystic fibrosis genetic mutation has been maintained in humans due to a selective advantage: heterozygous carriers of the mutation (who are thus not affected by cystic fibrosis) are more resistant to V. cholerae infections [12]. In this model, the genetic deficiency in the cystic fibrosis transmembrane conductance regulator channel proteins interferes with bacteria binding to the gastrointestinal epithelium, thus reducing the effects of an infection.

Transmission:

Persons infected with cholera have massive diarrhea. This highly liquid diarrhea, which is often compared to “rice water,” is loaded with bacteria that can spread under unsanitary conditions to infect water used by other people. Cholera is transmitted from person to person through ingestion of feces contaminated water loaded with the cholera bacterium. The source of the contamination is typically other cholera patients when their untreated diarrhea discharge is allowed to get into waterways or into groundwater or drinking water supply. Any infected water and any foods washed in the water, and shellfish living in the affected waterway can cause an infection. Cholera is rarely spread directly from person to person. V. cholerae occurs naturally in the plankton of fresh, brackish, and salt water, attached primarily to copepods in the zooplankton. Both toxic and non-toxic strains exist. Non-toxic strains can acquire toxicity through a lysogenic bacteriophage [13]. Coastal cholera outbreaks typically follow zooplankton blooms. This makes cholera a zoonosis.

Diagnostic Laboratory Tests:

A. Specimens: specimens for culture consist of mucus-flecks from stools (3,6).

B. Smears: the microscopic appearance of smears made from stool samples is not distinctive, dark Field or phase contrast microscopy may show the rapidly motile Vibrios(3,6,9)

C. Culture: growth is rapid in peptone. agaer, bloodager with a PH near 9.0 or TCBS agar (3,6,9).

D. Specific Tests: V.V. organism are further identified by slide agglutination tests using anti-O group 1 antiserum and by bio chemical reaction patterns (3,9).

Gastric acid provides some protection against V.C. ingested in small numbers.

An attaches of cholera is followed by immunity to re-infection, but the Duration and degree of immunity are not known, in

experimental animals, specific IgA antibodies in serum develop after infection but last only a few months. The presence of antitoxin antibodies has not been associated with protection (3,16).

Biochemistry of the *V.cholerae* bacterium:

Most of the V. cholerae bacteria in the contaminated water that a potential host drinks do not survive the very acidic conditions of the human stomach [14], but the few bacteria that manage to survive the stomach's acidic conserve their energy and stored nutrients during the perilous passage through the stomach by shutting down much protein production. When the surviving bacteria manage to exit the stomach and reach the favorable conditions of the small intestine, they need to propel themselves through the thick mucus that lines the small intestine to get to the intestinal wall where they can thrive. So they start up production of the hollow cylindrical protein flagellin to make flagella, the curb whip-like tails that they rotate to propel themselves through the pasty mucus that tines the small intestine. Once the cholera bacteria reach the intestinal wall, they do not need the flagella propellers to move themselves any more, so they stop producing the protein flagellin, thus again conserving energy and nutrients by changing the mix of proteins that they manufacture, responding to the changed chemical surroundings. And on reaching the intestinal wall, they start producing the toxic proteins that give the infected person a watery diarrhea which carries the multiplying and thriving new generations of V. cholerae bacteria out into the drinking water of the next host if proper sanitation measures are not in place.

Cholera Toxin. The delivery region (blue) binds membrane carbohydrates to get into cells. The toxic part (red) is activated inside the cell (PDB code: 1xtc).

Microbiologists have studied the genetic mechanisms by which the V. cholerae bacteria turn off the production of some proteins and turn on the production of other proteins as they respond to the series of chemical environments they encounter, passing through the stomach, through the mucous layer of the small intestine, and on to the intestinal wall [15]. Of particular interest have been the genetic mechanisms by which cholera bacteria turn on the protein production of the toxins that interact with host cell mechanisms to pump chloride ions into the small intestine, creating an ionic pressure which prevents sodium ions from entering the cell. The chloride and sodium ions create a salt water environment in the small intestines which through osmosis can pull up to six liters of water per day through the intestinal cells creating the massive amounts of diarrhea [8]. The host can become rapidly dehydrated if an appropriate mixture of dilute salt water and sugar is not taken to replace the blood's water and salts lost in the diarrhea. By inserting separately, successive sections of V. cholerae DNA into the DNA of other bacteria such as E. coli that would not naturally produce the protein toxins, researchers have investigated the mechanisms by which V.cholerae responds to the changing chemical environments of the stomach, mucous layers, and intestinal wall. Researchers have discovered that there is a complex cascade of regulatory proteins that control expression of V. cholerae virulence determinants. In responding to the chemical environment at the intestinal wall, the V. cholerae bacteria produce the TcpP/TcpH proteins which, together with the ToxR/ToxS proteins, activate the expression of the ToxT regulatory protein. ToxT then directly activates expression of virulence genes that produce the toxins that cause diarrhea in the infected person and that permit the bacteria to colonize the intestine [15].Current research aims at discovering "the signal that makes the cholera bacteria stop swimming and start to colonize (that is, adhere to the cells of) the small intestine," [14].

Treatment:

The most important part of therapy consist of water and electrolyte replacement to correct the severe dehydration and salt depletion, many antimicrobial agent are effective against V.C., treatment is usually given for 3-4 day (3,7,16).

Oral tetracycline tends to reduce stool output in cholera and shortens the period of excretion of vibrio, in some endemic areas, tetracycline resistance of V.C. has emerged carried by transmissible plasmid (3,7,16).

The goals of pharmacotherapy are to eradicate the infection, to reduce morbidity, and to prevent complications.

Drug Category: Antibiotics — Although not necessarily curative, treatment with an antibiotic to which the organism is susceptible diminishes the duration and volume of the fluid loss and hastens clearance of the organism from stool. Pharmacotherapy plays a secondary role in the management of cholera.

Emerging drug resistance in certain parts of the world is a concern. In areas of known tetracycline resistance, therapeutic options include ciprofloxacin and erythromycin. Strains resistant to ciprofloxacin have been reported from Calcutta, India (16,17).

Chemoprophylaxis of household contacts is not necessary.

Drug Name: Tetracycjine (Sumycin) - Treats gram-positive and gram-negative organisms and mycoplasmal, chlamydial, and rickettsial infections. Inhibits bacterial protein synthesis by binding with 30S and possibly 50S ribosomal subunit(s)

Adult Dose: 2 g PO once

Pediatric Dose: <8 years: Not recommended

>8 years: Not established

Contraindications: Documented hypersensitivity; severe hepatic dysfunction.

Interactions: Bioavailability decreases with antacids containing aluminum, calcium, magnesium, iron, or bismuth subsalicylate; can decrease effects of oral contraceptives, causing breakthrough bleeding and increased risk of pregnancy; can increase hypoprothrombinemic effects of anticoagulants

Pregnancy: D - Unsafe in pregnancy

Precautions: Photosensitivity may occur with prolonged exposure to sunlight or tanning equipment; reduce dose in renal impairment; consider drug serum level determinations in prolonged therapy: tetracycline use during tooth development (last half of pregnancy through 8 y) can cause permanent discoloration of teeth; Fanconi-like syndrome may occur with outdated tetracycline

Drug Name: Doxycycline (Bio-Tab, Doryx, Vibramycin) - Inhibits protein synthesis and bacterial growth by binding to the 30S and possibly 50S ribosomal subunits of susceptible bacteria.

Adult Dose: 300 mg PO once

Pediatric Dose: <8 years: Not recommended

>8 years: Not established

Contraindications: Documented hypersensitivity; severe hepatic dysfunction

Interactions: Bioavailability decreases with antacids containing aluminum, calcium, magnesium, iron, or bismuth subsalicylate: can increase Interactions hypoprothrombinemic effects of anticoagulants, can decrease effects of oral contraceptives, causing breakthrough bleeding and increased risk of pregnancy

Pregnancy: D - Unsafe in pregnancy

Precautions: Photosensitivity may occur with prolonged exposure to sunlight or tanning equipment; reduce dose in renal impairment: consider drug serum level determinations in prolonged therapy: Precautions tetracycline use during tooth development (last half of pregnancy through 8 y) can cause permanent discoloration of teeth: Fanconi-like syndrome may occur with outdated tetracyclines

Drug Name: Ciprofloxacin (Cipro) – Fluoroquinolone with activity against pseudomonades, streptococci, MRSA, Staphylococcus epidermidis, and most gram-negative organisms. Does not have activity against anaerobes. Inhibits bacterial DNA synthesis and growth.

Adult Dose: 250 mg PO qd for 3 d or 1 g once, alternatively, 30 mg/kg PO once or 15 mg/kg PO bid for 3 d (not to exceed 1 g/dose)

Pediatric Dose: <18 years: Not recommended

>18 years: Administer as in adults

Contraindications: Documented hypersensitivity

Interactions: Antacids, iron salts, and zinc salts may reduce serum levels; administer antacids 2-4 h before or after taking fluoroquinolones; cimetidine may interfere with metabolism- reduces therapeutic effects of phenytoin; probenecid may increase serum concentrations; may increase toxicity of theophylline, caffeine, cyclosporine, and digoxin (monitor digoxin levels); may increase effects of anticoagulants (monitor PT)

Pregnancy: C - Safety for use during pregnancy has not been established.

Precautions: In prolonged therapy, perform periodic evaluations of organ system functions (e.g., renal, hepatic, hematopoietic); adjust dose in patients with renal function impairment; superinfections may occur with prolonged or repeated antibiotic therapy.

Drug Name: Erythromycin (Ery-Tab, E.E.S., E-Mycin. Eryc, Erythrocin) - Inhibits bacterial growth, possibly by blocking dissociation of peptidyl t-RNA from ribosomes, causing RNA-dependent protein synthesis to arrest. For treatment of staphylococcal and streptococcal infections. In children, age, weight, and severity of infection determine proper dose. When bid dosing is desired, half-total daily dose may be taken q12h. For more severe infections, double the dose.

Adult Dose: 40 mg/kg PO divided tid for 3 d

Pediatric Dose: Not established

Contraindications: Documented hypersensitivity: hepatic impairment.

Interactions: Coadministration may increase toxicity oftheophylline, digoxin, carbamazepine and cyclosporine; may potentiate anticoagulant effects of warfarin; coadministration with lovastatin and simvastatin increases risk of rhabdomyolysis

Pregnancy: B - Usually safe but benefits must outweigh the risks.

Precautions: Caution in liver disease; estolate formulation may cause cholestatic jaundice; adverse GI tract effects are common (give doses pc): discontinue use if nausea, vomiting, malaise, abdominal colic, or fever occur.

Drug Name: Trimethoprim and sulfamethoxazole (Bactrim DS, Septra DS) - Dihydrofolate reductase inhibitor that prevents tetrahydrofolic acid production in bacteria. Active in vitro against a broad range of gram-positive and gram-negative bacteria, including uropathogens (eg, Enterobacteriaceae and Staphylococcussaprophyticus). Resistance is usually mediated by decreased cell permeability or alterations in amount or structure of dihydrofolate reductase. Demonstrates synergy with sulfonamides, potentiating inhibition of bacterial Tetrahydrofolate production.

Adult Dose: 160 mg TMP/800 mg SMZ PO bid for 3d

Pediatric Dose: <2 months: Do not administer

>2 months: 8 mg TMP/40 mg SMZ PO divided bid for 3 d

Contraindications: Documented hypersensitivity; megaloblastic anemia due to folate deficiency

Interactions: May increase PT when used with warfarin (perform coagulation tests and adjust dose accordingly); coadministration with dapsone may increase blood levels of both drugs; coadministration of diuretics increases incidence of thrombocytopenia purpura in elderly; phenytoin levels may increase with coadministration; may potentiate effects of methotrexate In bone marrow depression: hypoglycemic response to sulfonylureas may increase with coadministration; may increase levels of zidovudine

Pregnancy: C - Safety for use during pregnancy has not been established.

Precautions: Discontinue at first appearance of skin rash or sign of adverse reaction; monitor CBC count (discontinue therapy if significant hematologic changes occur); prolonged high doses may cause bone marrow depression (if signs occur, give 5-15 mg/d leucovorin); caution in folate deficiency (eg, chronic alcoholism, elderly, anticonvulsant therapy, malabsorption syndrome); hemolysis may occur in G-6-PD deficiency; patients with AIDS may not tolerate or respond to TMP/SMZ; caution in renal or hepatic impairment (perform urinalyses and renal function tests during therapy); give fluids to prevent crystalluria and stone formation: may cause nausea, vomiting, and hypersensitivity reactions

Drug Name: Norfloxacin (Noroxin) – Fluoroquinolone with activity against pseudomonads, streptococci, MRSA, S epidermidis, and most gram-negative organisms. Does not have activity against anaerobes. Inhibits bacterial DNA synthesis and growth.

Adult Dose: 400 mg PO bid for 3d; not to exceed 800 mg/d

Pediatric Dose: <18 years: Not recommended

>18 years: Administer as in adults

Contraindications: Documented hypersensitivity

Interactions: Antacids, iron salts, and zinc salts may reduce serum levels; administer antacids 2-4 h before or after taking fluoroquinolones; cimetidine may interfere with metabolism: reduces therapeutic effects of phenytoin; probenecid may increase serum concentrations: may increase toxicity of theophylline, caffeine, cyclosporine, and digoxin (monitor digoxin levels); may increase effects of anticoaguiants (monitor PT).

Pregnancy: C - Safety for use during pregnancy has not been established.

Precautions: In prolonged therapy, perform periodic evaluations of organ system function (eg, renal, hepatic, hematopoietic); adjust dose in renal function impairment; superinfections may occur with prolonged or repeated antibiotic therapy.

Drug Name: Furazolidone (Furoxone) – Nitrofuran with antiprotozoal activity. Alternative drug for children because of availability in liquid susp. Most common adverse effects are Gl tract upset and brown discoloration of urine.

Adult Dose: 100 mg PO qid for 3 d

Pediatric Dose: 5 mg/kg/d PO divided qid for 3 d or 7 mg/kg PO once

Contraindications: Documented hypersensitivity

Interactions: Increases levodopa blood concentrations, with potential for toxicity: causes disulfiram reactions when taken with alcohol: toxicity of meperidine, paroxetine, fluoxetine, sertraline, trazodone, MAO Is, sympathomimetic amines, and TCAs increase when taken concurrently

Pregnancy: C - Safety for use during pregnancy has not been established. Caution in G-6-PD deficiency when administering prolonged treatments; inhibits enzyme monoamine oxidase

Control:

Control rests on education and improvement of sanitation, particularly of food and water.

Patients should be isolated, their excreta disinfected, and contact followed up/ (3)

CHMOPROPHLAXIS with antimicrobial drug may have a place. Repeated injection of vaccine containing either lipopoly saccharides exd from rios or dense vibrio suspension can confer limited protection to heavily exposed persons(family contacts) but is not effective as an epidemic control measure. (3)

Very few countries require that travelers arriving from endemic areas have proof of immunization with these vaccines. (3)

The WHO vaccination certificate for cholera is only valid for 6months. As well as human serum immunoglobulin, antibodies from other species(e.g immunized bovin colostrums) have been used. (3)

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