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## **CHOLERA & OTHER VIBRIOS**

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Vibrios are gram-negative, curved, rod-shaped bacteria that are natural inhabitants of the marine environment. In the USA transmission of *Vibrio* infections is primarily through the consumption of raw or undercooked shellfish or exposure of wounds to warm seawater. The most common clinical presentation of *Vibrio* infection is self-limited gastroenteritis, but wound infections and primary septicemia may also occur. Patients with liver disease are at particularly high risk for significant morbidity and mortality associated with these infections. Many cases of *Vibrio*-associated gastroenteritis are under-recognized because most clinical laboratories do not routinely use the selective medium, thiosulfate-citrate-bile salts-sucrose (TCBS) agar, for processing of stool specimens unless they are specifically requested to do so.

Early detection and initiation of treatment of these infections are very important, particularly for cholera and invasive *Vibrio* infections, because these may rapidly progress to death. Prevention of *Vibrio* infections requires a heightened awareness of these infections by clinicians, laboratory technicians and epidemiologists. There are at least 12 pathogenic *Vibrio* species recognized to cause human illness. The *Vibrio* species of most medical significance include *Vibrio cholerae*, *Vibrio vulnificus* and *Vibrio parahaemolyticus*. In this review, we discuss the epidemiology, clinical presentation, diagnosis and treatment of these medically important vibrios.

### **Bacteriology**

#### *Vibrio cholerae*

O1 antigen: Cholera is classified in groups according to its somatic antigen O. Until 1992, all cases associated with typical Asiatic cholera belonged to the O1 group. There are 6 major O groups and numerous serovarieties within these groups.

Serotypes Igawa Inaba and Hikojima are part of the O1 group.

There are two biotypes: Classical cholera and the El Tor biotypes. El Tor, a variant of the classical cholera has become nowadays the agent responsible for the 7<sup>th</sup> pandemic of cholera. El Tor differs from classical *V.cholerae* in its ability to agglutinate chicken erythrocytes, sensitivity to polymyxin B, and resistance to cholera phage group 4.

Cholera O1 is also classified by toxin production: toxigenic or nontoxigenic

In 1992, toxigenic *V. cholerae* O139 (the Bengal strain) was recognized as another cause of cholera. *V. cholerae* O139, first discovered on the Indian subcontinent, has been reported in the United States as an imported infection. Although the primary organism that causes cholera globally is *V cholerae* O1,

continued laboratory surveillance of *V. cholerae* O139 is recommended because it has similar epidemic potential.

## **Epidemiology**

### *Vibrio cholerae* and Pandemic cholera

The world is now experiencing a 7<sup>th</sup> cholera pandemic. It started in Indonesia in 1961, spread through the Middle East in the late 1960's and into Africa in the 1970's where it remained endemic. In 1991 the pandemic reached South America through Peru and spread rapidly. This pandemic is due to the El Tor variant. An epidemic is constituted by a group of common source outbreaks from contaminated food or water. The main source is the stool of an infected individual: a severe cholera case may produce up to 20 liters of stools /day with a content of 10<sup>7</sup> Vibrios /ml (200 billion Vibrios /day).

Common sources of infection in areas of pandemic cholera are:

- Drinking water contaminated at its source or during storage, ice made from contaminated water.
- Food contaminated during or after preparation
- Seafood, particularly shellfish taken from contaminated waters
- Vegetables and fruits eaten raw, cultivated on contaminated grounds or irrigated with contaminated water or "freshened" with contaminated water.

### *Vibrio cholerae* in Louisiana

Currently, most cases of cholera in the Louisiana are acquired through eating seafood from the Gulf Coast or through foreign travel. A particular strain of *V cholerae* O1 strain (biotype El Tor, serotype Inaba) has become endemic in the Gulf waters. It can be found in surface water or sewage. Domestically acquired cholera has been associated with consumption of shellfish. There is no endemic of *V. cholerae* O139 in the USA.

Person to person transmission is uncommon in the USA because the infectious dose of *V cholerae* is high (more than 1,000,000 micro-organisms). Chronic carriers on the other hand excrete low numbers of bacilli and do not play a major role in the transmission. Cholera Dolores, a Texas cholera chronic carrier of *V.cholerae* for 11 years did not infect anyone.

Vibrios are very common organisms in surface waters. Among these, just a handful are pathogenic for humans, mostly *Vibrio cholerae*, *Vibrio parahaemolyticus* and *Vibrio vulnificus*.

### *Vibrio cholerae* non-O1

Non O1 are found in surface waters (freshwater rivers, ocean) throughout the world. The infection is acquired by ingesting heavily contaminated water or food (raw or poorly cooked seafood, especially oysters, clams, shrimp or crabs). Small outbreaks are sometimes reported. These infections usually occur in individuals with increased susceptibility to infections: immunocompromised, individuals with gastric disease (low gastric acidity) and liver disease.

### *Vibrio parahaemolyticus*

*V. parahaemolyticus* is a natural inhabitant of US and Canadian coastal waters and is found in higher concentrations during the summer. Outbreaks are rare, sporadic cases are more common. Most infections are associated with ingestion of raw or undercooked shellfish harvested from both the Gulf of Mexico and the Pacific Ocean. Raw oysters are the primary source of ingestion-associated *V. parahaemolyticus* infection (close to 90% of patients with *V. parahaemolyticus* gastroenteritis or primary septicemia and

known food history reported eating raw oysters). Consumption of crustacean and molluscan shellfish has commonly been implicated in the transmission of *V. parahaemolyticus*.

### *Vibrio vulnificus*

*V. vulnificus* is the most important pathogenic vibrio in the United States because of its invasiveness and the high fatality rates associated with infection. It is the leading cause of seafood-associated deaths in the United States.

*V. vulnificus* is a natural inhabitant of the Gulf Coast waters and is present in seafood. Mean counts of *V. vulnificus* in oysters vary from 300 to 5,000 colonies expressed as Most Probable Number (MPN)/g.

The incubation period for symptomatic cholera ranges from a few hours to five days (mean 2-3 days). The mean incubation period for *V. parahaemolyticus* is 15 hours (range: 4-96 hours).

Infectious Dose is important in the pathogenicity of disease:

- For *V. cholerae* 1,000 microorganisms produce asymptomatic infections, 10,000 to 1 million produce simple diarrhea in 60% of volunteers, doses of more than 1 million Vibrios produce severe diarrhea with dehydration in 25 to 50% of volunteers.
- For *V. vulnificus* the infectious dose is in the range of 2,000 CFU.
- For *V. parahaemolyticus* the infectious dose is about 100,000 viable cells ingested.

### **Clinical Description**

Infection by *V. cholerae* may result from asymptomatic infection to violent dehydrating diarrhea with acute onset and death within a few hours. The spectrum of illness in cholera includes asymptomatic infection (75%), mild illness (18%), moderate illness (5%), and severe illness (2%).

The most common clinical manifestation of *V. parahemolyticus* is gastroenteritis. Acute watery diarrhea, abdominal cramps, and nausea usually characterize the illness. The illness is usually mild to moderate and self-limited, although some cases may be severe and require hospitalization. The clinical forms are gastroenteritis (59%), wound infections (34%), primary septicemia (5%), and other sites of infections (2%).

Infection by *V. vulnificus* is more common among people with the risk factors: Liver disease, hemochromatosis, diabetes, cancers, particularly on chemo or radio-therapy, leukemia, lymphoma, Hodgkin's, immune suppression (HIV), long term steroid use, alcoholism, chronic kidney disease and old age. The clinical forms are wound infections (45%), primary septicemia (43%), gastroenteritis (5%) and other sites of infection (7%).

Primary septicemia acquired through ingestion of the organism through the GI tract, may be fulminant and result in death within hours. Distinctive bullous skin lesions filled with hemorrhagic fluid (typically present on the extremities or the trunk), thrombocytopenia, leukopenia, and DIC are often seen in patients with fulminant primary septicemia.

*V. vulnificus* can also cause an infection of the skin when open wounds are exposed to warm seawater. These skin infections may lead to cellulitis, ulceration, necrotizing fasciitis, and sepsis. In addition to wound infections, septicemia, and gastroenteritis, *V. vulnificus* has been associated with other clinical syndromes, including pneumonia, osteomyelitis, spontaneous bacterial peritonitis, eye infections, and meningitis.

## Summary of clinical picture of miscellaneous Vibrios

Organism	Gastroenteritis	Wound infection	Primary septicemia
<i>Vibrio alginolyticus</i>	+	++	
<i>Vibrio cholerae non-O1</i>	++	+	+
<i>Vibrio cholerae O1</i>	++		
<i>Vibrio cincinnatiensis</i>			
<i>Vibrio damsela</i>		++	
<i>Vibrio fluvialis</i>	++	+	+
<i>Vibrio furnissii</i>	++		
<i>Vibrio hollisae</i>	++	+	+
<i>Vibrio metschnikovii</i>	+		
<i>Vibrio mimicus</i>	++	+	+
<i>Vibrio parahaemolyticus</i>	++	+	+
<i>Vibrio vulnificus</i>	+	++	++

Infection by *V. cholerae non-O1* can produce a wide range of symptoms: asymptomatic infections, simple diarrhea or severe diarrheal disease. Some isolates are capable of producing a toxin indistinguishable from O1 *V. cholerae*. Approximately a quarter of infected patients have bloody stools. Septicemia with non-O1 *V. cholerae* is seen in immunocompromised hosts, particularly patients with cirrhosis.

### Laboratory Tests

Laboratory confirmation is indispensable to confirm the diagnosis.

A case of cholera is confirmed by culturing the bacteria from stool, or rarely, a wound. Stool specimens should be collected on cotton tipped swabs and placed in a tube of Cary-Blair culture medium. These can be obtained from the regional laboratories. Specimens in Cary-Blair should be refrigerated and transported to the lab under refrigerated conditions as soon as possible. If necessary to hold 48 hours or longer, freeze samples at -7 °C and transport to the lab in a frozen state. When processing stool specimens, Vibrios may grow on blood and MacConkey agars, but isolation is enhanced by using TCBS agar. After inoculation on TCBS agar, *V. cholerae* appears as yellow colonies.

A cholera diagnosis may also be made serologically with evidence of serologic conversion (vibriocidal antibody titer of greater than 1:640 suggests recent infection) or a four-fold rise in vibriocidal antibody titer. Serologic diagnosis may also be made by an increase in titers two weeks after exposure and a decrease in titers two months after exposure. Collect one red-topped tube of blood. This blood should either be spun down and the sera sent or the whole blood sent refrigerated to the central laboratory for processing. This test is only done at the Centers for Disease Control and is not done routinely. Check with the Infectious Disease Epidemiology Section before offering this test.

History of ingestion of raw or insufficiently cooked seafood with clinical symptoms associated with a diarrheal illness and isolation of vibrio from the implicated food constitutes a suspected case but is not considered a confirmed case.

### Surveillance

Vibrio infections are reportable conditions: *Vibrio cholerae* within 24 hours, other vibrio infections within five business days.

## Case Definition

### Cholera

Clinical description: An illness characterized by diarrhea and/or vomiting; severity is variable. Laboratory criteria for diagnosis: Isolation of toxigenic (i.e., cholera toxin-producing) *Vibrio cholerae* O1 or O139 from stool or vomitus, or serologic evidence of recent infection.

Illnesses caused by strains of *V. cholerae* other than toxigenic *V. cholerae* O1 or O139 should not be reported as cases of cholera. The etiologic agent of a case of cholera should be reported as either *V. cholerae* O1 or *V. cholerae* O139.

Case classification: **Confirmed**: a clinically compatible illness that is laboratory confirmed. Only confirmed cases should be reported.

### Other Vibrios:

A case of a vibrio infection is defined as an illness characterized by the manifestation of symptoms such as diarrheal illness, septicemia, or localized wound infections and is laboratory confirmed. Laboratory criteria for diagnosis: Isolation of a *Vibrio* species from a human specimen (stool, vomitus, or blood). Only laboratory confirmed cases should be reported.

## Case Investigation

The purpose of investigation is to identify case(s), source(s) of infection and to institute appropriate control measures, i.e., public education, physician education regarding danger of severe infection in patients with some underlying diseases, monitoring seafood and/or closing oyster beds to harvesting.

- Upon receipt of a report of a cholera case, contact the physician or hospital to confirm the diagnosis. Request that the physician or hospital forward an isolate on the suspected case to the state laboratory for confirmation and serotyping.
- Identify the sources of infection:
  - Obtain food history: consumption of crustacean or molluscan shellfish, raw or cooked
  - Get occupation history
  - Determine recreational activities and contact with sea or brackish water
  - Elicit recent injury exposed to raw seafood or brackish waters.
- Identify co-primary cases: Collect stool or blood samples for testing of associates to the case,
- Collect clinical and epidemiologic information (CDC Vibrio Illness Investigation form) regarding the illness, personal health data that may be associated risks of *Vibrio* acquisition, traceback of *Vibrio* exposure source.
- Individual cases of *Vibrio* illnesses reportedly associated with raw shellfish consumption will be reported to the state shellfish control authority who in turn may notify the FDA Regional Shellfish Specialist.

### Outbreak Investigation:

*Vibrio* cases that cluster over specified time, place or persons warrant official outbreak investigative activities to be conducted by the Infectious Disease Epidemiology Section and in coordination with the State Shellfish Control Program.

## Reporting to the FDA is done by the Infectious Disease Epidemiology Section

The state shellfish control authority or their designated investigative agency provides a redacted (no name of patient or hospital) but detailed report to the FDA Regional Shellfish Specialist; this report should include the following information:

- Age, race, sex, home town/city, parish, home state of the patient(s)
- Suspect product consumed by the patient(s); how the product was prepared (raw, baked, boiled, fried, steamed, other, or unknown); whether or not the product was self-harvest or harvested by a friend; type of retail outlet the product was obtained
- Where the product was purchased (city & state) and where the product was eaten (city & state)
- Date and time the suspect product was consumed (exposure)
- Any additional food items within the 7 days prior to illness onset
- Date and time of illness onset
- Clinical manifestations of illness
- Duration of illness and outcome status of patient – include date of death, if applicable
- Whether the patient(s) was hospitalized or not
- Causative agent responsible for the illness and the source sample from which the agent was identified (blood, stool, wound, serum, etc.) in addition to whether this isolate was confirmed by a state or federal laboratory
- Pre-existing conditions and current medication usage of the patient
- Information as to whether the patient was advised of his health condition and was informed of the risks associated with consuming raw shellfish and other raw commodities
- Traceback information regarding the suspect product – obtain labels/shellstock ID tags or copies of labels/tags. For product consumed raw or partially cooked, or involved in an outbreak, obtain the harvest date and harvest location (harvest area and state, classification of harvest area); original shipper and date shipped; intermediate shippers and date purchased; retail outlets and date purchased; handling compliance (proper temperature, proper storage of the product by shippers and retail outlet); and environmental data from the harvest area at or near the time of harvest (ambient air temperature, surface water temperature, salinity, total rainfall in inches for the previous 5 days and fecal coliform count of the water in the area – state dates that the environmental data was collected)
- Any other information pertinent to the case that is obtained during the illness investigation

### **Harvest area closure:**

Harvest area closure is considered when the outbreak

- has been validated
- is not considered to be due to some post-harvest contamination
- is suspected to be associated with molluscan shellfish consumption from a specific harvest area

### **Case Management - Treatment**

The standard of care for cholera patients is to treat mild to moderate cholera with oral rehydration salts (ORS) solution or an oral electrolyte rehydration solution, and to treat severe cases with intravenous fluids (for example, Ringer lactate) and an antimicrobial agent. Prompt restoration of fluids and electrolytes should be the primary goal of treatment.

When an antibiotic is administered, purging stops within 48 hours and the Vibrios disappear from the stools. Without treatment, Vibrios would persist for about one week, rarely up to one year (convalescent carriers).

Antibiotics recommended for treatment of cholera in the absence of the results of an antibiotic sensitivity test are:

- Doxycycline is the antibiotic of choice for adults: 100 mg twice a day (total daily dose 200 mg) for 3 days or 300mg once a day for 3 days. In older children (>9 years) a dose of 6 mg/kg /day is recommended. Cyclines are contra indicated in children less than 9 years and pregnant women.
- Tetracycline, 500 mg four times a day (total daily dose of 2g) for 3 days, 2 hours away from food consumption. This regimen is not preferred because of the poor compliance resulting from the number of daily doses.
- Trimethoprim-Sulfamethoxazole or cotrimoxazole is the antibiotic of choice for children: Trimethoprim 160 mg -Sulfamethoxazole 800 mg twice a day (2 tablets of single strength 80/400 Septrin® twice per day) for 3 days. For children 4 mg/kg of Trimethoprim and 20 mg/kg of Sulfamethoxazole twice a day ( ½ tablet for 10 kg twice a day). The O 139 strains are often resistant to Trimethoprim sulfamethoxazole.
- Ampicillin 250 mg/day 4 times a day (total dose 1g/day) for 5 days is the safest regimen in pregnant women.
- Erythromycin 250 mg four times daily (daily dose of 1 g) for 3 days. For children 40 mg/kg/day in 4 divided doses.
- Ciprofloxacin 500mg twice a day (total 1 g/day) for 3 days. Ciprofloxacin should not be used for individuals <18 years old and pregnant women.

Chemoprophylaxis of household contacts is recommended. Refer family to private physician for treatment.

**Hospital precaution and isolation:** Contact precautions

## **Prevention**

1-Traditional epidemic control measures such as travel or trade restrictions are proven to be ineffective in preventing the spread of cholera. They only disrupt the economy of an area and, as a result, encourage the suppression of information which is extremely detrimental to early case finding.

2-No quarantine is necessary.

3-Routine bacteriological monitoring of diarrhea cases is necessary only in areas with sporadic cholera since any ordinary diarrhea may be due to cholera.

### 4-Contact Management:

The administration of doxycycline, tetracycline, ciprofloxacin, ofloxacin, or trimethoprim-sulfamethoxazole within 24 hours of identification of the index case may effectively prevent coprimary cases of cholera among household contacts. However, because secondary transmission of cholera is rare, chemoprophylaxis of contacts is not recommended in the United States, unless there is a high probability of fecal exposure.

Meal companions could be screened if necessary as indicated by the Epidemiology Unit to determine the extent of an outbreak but they are not systematic candidates for chemoprophylaxis.

5-Mass chemoprophylaxis of an extended community is not recommended.

6-Vaccines provide immunity of very short duration (6 months at most) and therefore is not very useful in the control of endemic cholera. It does not prevent asymptomatic infection and therefore its role in international travelers is reduced. It is no longer a requirement for international travel.

7-Control of cholera is based on sanitation and personal hygiene: This includes sanitary disposal of feces, hand washing after defecation, pure drinking water, uncontaminated food supply (particularly seafood and vegetables), sanitary preparation of food in commercial establishments and homes. Care in drinking and eating habits, safe disposal of excreta and personal cleanliness are the most effective ways in preventing and controlling outbreaks.