# Review Article

# Vibrio fluvialis: An Emerging Pathogen for Intestinal and Extraintestinal Infections

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## Abstract

*The genus Vibrio is a ubiquitous group of bacteria belonging in the family Vibrionaceae. More than 100 species have been discovered in the genus Vibrio and about 14 of them have been reported to cause several human infections. Vibrio fluvialis, a member of this group is widely distributed in the aquatic environment, mostly in the seas, brackish waters and coastal zones.[1]*

*V. fluvialis is a pathogenic bacterium more commonly found in coastal areas. It causes diarrhea and enterocolitis and a significant number of extra-intestinal infections. Due to increasing number of infections, it is considered as an emerging pathogen.1 Though this pathogen can be easily isolated by conventional staining and culture methods along with the biochemical properties, its identification is considered as a challenging problem due to its close phenotypic similarity of this species either with other vibrios and Aeromonas spp. By using automated BD Phoenix M50 techniques, it has become easier to identify V. fluvialis from clinical and different environmental samples. In this system biochemical properties of different 45 substrates are used to observe their fermentation reactions. Automated identification and antimicrobial susceptibility test systems are essential for modern clinical microbiology laboratories for rapid identification and proper selection of effective antibiotics. Several virulence factors of V. fluvialis have been identified.[2] The rule and mechanisms of action of these virulent factors causing pathogenesis and infection are yet to be clarified. In this review article, the epidemiology, identification, pathogenicity, intra- and extra-intestinal clinical features and management of V. fluvialis infections have been focused.*

***Key words:*** *Vibrio fluvialis, Emerging pathogen, Intestinal infections, Epidemiology, Virulence factors.*

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## Epidemiology

*V. fluvialis* is considered to be transmitted through oro-fecal route. It causes outbreaks and sporadic cases of diarrhea.[2,3] This organism naturally exists in warm, salty, and brackish water. It is able to survive in temperature from 9°C to 31°C, and optimally it grows when water temperature rises to 18°C or above.3 *V. fluvialis* infections show a seasonal pattern with the majority of clinical illnesses. The temperature and salinity factors may have some influence to the bacteria's proliferation.[4]

A large outbreak of V. fluvialis infection was reported in Bangladesh during October 1976 to November 1977. More than 500 patients were infected, of which 50% of them were young children.[5]

In the United States, enterocolitis in infants was reported in association with *V. fluvialis*.[6]

*V.fluvialis* causes a variety of infections in immune-competent/ HIV patients, including bacteremia, biliary tract infection and acute diarrhea.[7]

In the United States, the organism was isolated from a wound of a patient in Hawaii from water and sediment in the New York Bay[8] from shellfish in Louisiana and from water and shellfish in Pacific Northwest estuaries.[9]

Recently it was reported to be associated with acute diarrhea in Indonesia.[10] *V. fluvialis* has been recognized as an infectious importance because its clinical symptoms of gastroenteritis are very similar to that of *V. cholerae*.

Poor sanitation and hygienic conditions as well as lack of or little environmental awareness among people is considered the major cause of water contamination source. For example, agricultural practices that involve usage of sewage water and/or cattle manure on farms can effect the contamination procedure. Another practice is uncontrolled waste water effluents discharg

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es into waterbodies, which serve as raw water sources to municipal water treatment systems.[10] This is more common in developing or underdeveloped countries.

Considerable morbidity and mortality of enteric infections are observed worldwide, especially among children in developing countries. Infections due to *V. fluvialis* are common in areas that have high levels of fecal contamination of water, food supplies and consumption of raw seafood or seafood products.[10] Moreover, infection rates are highest where general standards of living, water supply, and sanitary conditions are low or inadequate. Microbial contamination of water remains the largest and most immediate health hazard, with surface water quality been subjected to frequent dramatic changes in microbial quality as a result of the variety of activities on the watershed.[11,12] These changes could be caused by discharges of municipal raw waters or treated effluent at a specific point-source into the receiving waters.[13]

In the wound infection or cellulitis that is related to direct inoculation of bacteria into the skin or exposure of a wound to contaminated water. In this case, the bacterium (and its associated toxins) rapidly cause local tissue necrosis associated with hemorrhagic bullae and erosions. Cellulitis may occur when an abrade area of skin is inoculated through bathing in marine waters where V. fluvialis thrives, or through exposure to liquid from harvested raw seafood.[14] This type of exposure typically occurs while sucking or handling raw oysters. Since the organism causes obliterating vasculitis and vascular necrosis, therapeutic levels of antibiotics may not reach the organism and rapid amputation may be necessary to prevent progression.

In primary septicemia syndrome patients show high fever and chills, often with vomiting, diarrhea, abdominal pain and extremities pain with no apparent focus of infection. Major diagnostic clues for V. fluvialis sepsis syndrome are heamorrhagic bullae which can be seen both in sepsis and cellulitis. It is believed that the bacteria most likely enter the circulation through the intestine.[15]

A number of host factors predisposed patients to severe infection with *V. fluvialis*. Known adverse host factors include liver disease (especially alcoholic cirrhosis), immunosuppressed states such as HIV/AIDS, iron overload (e.g., hemochromatosis), and diabetes mellitus.[15]

Recently, the organism was isolated from two patients suffering from chronic tonsilitis in a tertiary hospital in northern Bangladesh (KYAMCH) (unpublished data).

We also provide a literature review of reported cases of V. fluvialis extra-intestinal diseases including bacteremia.[16]

## Identification

Traditionally, for initial diagnosis of suspected infections caused by *V. fluvialis*, a big number of biochemical tests such as oxidase, catalase, Triple Sugar Iron (TSI) Agar, Kligler's Iron Agar (KIA), Sulfur–Indole–Motility (SIM), Bile Esculin Agar, Voges–Proskauer (VP), Lysine Decarboxylase, Arginine Dihydrolase, Ornithine Decarboxylase, Citrate, and ability to grow at different NaCl concentrations can be performed.

Minimal biochemical tests such as lysine decarboxylase, ornithine decarboxylase, arginine dihydrolase, and L-arabinose are mandatory for the identification of V. fluvialis. Without these minimal tests, the identification is incomplete and the isolate will be improperly classified as V. cholerae or Aeromonas spp.

Thiosulfate-citrate-bile salts-sucrose (TCBS) agar, is a selective agar culture plate that is used to isolate Vibrio species. Strains of Vibrio cholerae produce yellow colonies on TCBS agar plates due to the fermentation of sucrose. V. fluvialis produces a similar colony morphology like V. cholerae.It ferments sucrose and shows yellow color colonies after direct plating of environmental/ clinical specimens. Further identification is confirmed by its other biochemical features.[17]

In TSI agar, *V. fluvialis* shows positive reactions to glucose and sucrose. They are unable to produce gas and H2S. The organism is motile and on gram staining shows a curved bacillus. To arginine the reaction is positive and to ornithine, it shows a negative reaction.

Biochemical properties could be tested by a fully automated BD Phoenix M50 system. This automated microbiology system is carried out to confirm the result of the biochemical tests done conventionally.

Clinical samples were inoculated on MacConkey agar and 5% sheep blood agar. Gram negative organisms were analyzed for the BD Phoenix TM M50 Automated Microbiology System. In total,45 substrates including carbohydrates, amino acids and proteins are used for the observation of biochemical reactions of the organism on the substrates. About 5 hours required to get the result by using the device.

This equipment detects the organism automatically by revealing biochemical properties of the organisms.

**Biochemical properties of V. fluvialis**

Biochemical features of the isolated strains of *V. fluvialis* showed a similar character in our lab (unpublished data) like the studies elsewhere.[18]

Antibiotic susceptibility test

It Can be done manually by antibiotic susceptibility test by disc diffusion method.[19]

The Kirby-Bauer disk diffusion susceptibility test determines the sensitivity or resistance of pathogenic bacteria to various antimicrobial compounds in order to assist physicians in selecting treatment options of their patients.

BD PhoenixM50 automated machine can be used to detect the antimicrobial susceptibility test (AST). All the procedures were performed according to the manufacturer's instruction. A sealed and self-inoculating molded polystyrene tray with 136 micro-wells containing dried reagents, serves as the BD Phoenix disposable. The combination panel includes identifica

tion (ID) side with dried substrates for bacterial identification and an AST side with varying concentrations of antimicrobial agents, growth and fluorescent controls at appropriate well locations. The BD Phoenix system utilizes an optimized colorimetric redox indicator for AST and various colorimetric and fluorometric indicators for ID.[20]

## Virulence factors

In spite of a significant volume of research efforts have been published to narrate virulence factors of *V. fluvialis* that are responsible for the notable disease process, very little definitive information has been achieved. Several virulence factors have been identified in *V. fluvialis*, but the majority of them are only partially characterized and their precise role in virulence remains to be known.

1. Metalloendopeptidases produced by two human enteric pathogens, *V.fluvialis* and *Vibrio mimicus*, are structurally and/or catalytically related to vibriolysin from *V. vulnificus*.[19] Vibriolysin specifically hydrolyzes the peptide bond at the amino group side of the P10 amino acid residue, which is usually a hydrophobic amino acid residue (e.g. Phe, Tyr or Leu). Synthetic oligopeptides, such as Z-GlykPhe-NH2 and Z-GlykLeu-NH2, are thus commonly used as the suitable substrate. On the other hand, phosphoramidon and zincov are well-known competitive peptide inhibitors. Vibriolysin is also highly active on a wide variety of proteins. The enzyme exhibits significant proteolysis of casein, albumin, hemoglobin, type I and IV collagen, gelatin, elastin, fibrin and fibrinogen.

2. Cytolysin: It is a pore-forming exotoxin encoded in the hlyA(hemolysin A) gene of V. cholerae and V. fluvialis whose contribution to the pathogenesis is not fully understood.[20]

3. The virulence properties of a lacking of CT gene.

4. Heat-labile cytotoxin

5. Cytotonic toxin

6. Hemolysin

Hemolysin is an important virulence factor in the pathogenic processes of many clinical microorganisms, causing hemorrhagic septicemia and diarrhea. It can lyse erythrocytes and a variety of other cells including mast cells, neutrophils, and polymorphonuclear cells enhance the virulence activities by causing tissue damage or by dissolving protective material that would prevent spreading of the pathogen throughout the tissue. Other vibrio spp are also related to extracellular hemolysins. However, the role and biological properties of hemolysin from V. fluvialis have been studied by Han et al.[21] They found that hemolysin of V. fluvialis (VFH) forms pores in erythrocyte membrane and by using osmotic protectants.

7. Mucinase

8. Endotoxin activity of *V. fluvialis* has been demonstrated in vitro using Chinese hamster ovary (CHO) cells. Lockwood et al.[22] found that at least four biologically active substances could be found in culture supernatants of a reference strain of V. fluvialis.

9. Chinese hamster ovarian (CHO) cell elongation factor, CHO cell killing factor (CKF), and cytolysin are active against rabbit erythrocytes were identified when the bacterium was grown without antibiotic especially, lincomycin.

## Pathogenicity

## Wound infection

*V. fluvialis* causes wound infection very rarely.[23]

## Gastroenteritis

The clinical features of gastro-enteritis caused by *V.fluvialis* are similar to those caused by *Vibrio cholerae*.[24] Patients experienced with vomiting, abdominal pain along with typical watery diarrhea with, moderate to severe dehydration and fever. Bloody stools in *V. fluvialis* infections is frequently noted which is absent in cholera.[24]

From the enzyme-linked immunosorbent assay, Chikahira and Hamada[25] and Wall et al.[26] have reported that several *V. fluvialis* strains isolated from environmental and human sources produced an enterotoxin which is immunologically indistinguishable from cholera toxin (CT).

*V. fluvialis* produces several toxins that may be important in pathogenesis including an enterotoxin-like substance, lipase, protease, cytotoxin, and hemolysin.[27] Baffone et al.[28] reported that *V. fluvialis* has weak adhesiveness and no bacterial cytotoxicity, but Wong et al.[29] found it had strong haemolytic and proteolytic activity. Two cases of fatal infection due to V. fluvialis have been reported.[30] It accounted for 10% of Vibrio gastroenteritis cases in a US survey.[31] Unlike other Vibrio spp., which have commonly been reported to cause extra-intestinal infections, *V. fluvialis* is uniquely associated with gastroenteritis, with only rare reports of extra-intestinal infections such as hemorrhagic cellulitis with cerebritis, bacteremia, and peritonitis.[32]

## Clinical Manifestations

V. fluvialis-related illness is characterized by gastroenteritis, nausea, loss of appetite, vomiting, watery bloody diarrhea with abdominal cramps or significant fever. Moderate to severe dehydration, hypokalemia, metabolic acidosis, and occasionally, hypovolemic shock can occur in 4 to 12 hours if fluid losses are not replaced. Stools are colorless, with small flecks of mucus and contain high concentrations of sodium, potassium, chloride, and bicarbonate.

Wound infection (cellulitis) which is caused by direct inoculation of bacteria into the skin or exposure of a wound to contaminated water, the bacterium and its toxins rapidly cause local tissue necrosis associated with hemorrhagic. These consequences are more common when an abrade area of skin is inoculated through bathing in marine waters where V. fluvialis thrives, or through exposure to contaminated water from

harvested raw seafood.[33]

The septicemia due to *V. fluvialis* infection consists of high fever and chills, often with vomiting, diarrhea, abdominal pain and extremities pain with no apparent focus of infection. Major diagnostic clues for *V. fluvialis* sepsis syndrome are heamorrhagic bullae which can be seen both in sepsis and cellulitis. The bacteria might enter the circulation through the intestine.[34]

A number of host factors predisposed patients to severe infection with *V. fluvialis*. Known adverse host factors include liver disease (especially alcoholic cirrhosis), immunosuppressed states such as HIV/AIDS, iron overload (e.g., hemochromatosis), and diabetes mellitus.[34]

## Molecular tools

The genome sequences of *V. fluvialis* may promote the understanding of pathogenic mechanisms for this emerging pathogen. Another tool such as PCR are useful in the identification of many uncommon organisms like vibrios and most of these assays are comparable to the conventional identification methods.[1]

## Management

**Treatment**

An effective treatment of diarrheal disease has the potentiality to lower morbidity and mortality. The reduction of mortality from diarrhea is related to the effective management of dehydration. Usually, oral rehydration saline and bismuth subsalicylate or loperamide is used to treat for mild to moderate diarrhea (less than four stools per day).[35] The gastroenteritis syndrome is usually self-limited and does not require parenteral therapy. In the sepsis syndrome and the cellulitis that may cause life and limb threatening require extensive antibiotics therapy. Any delay in treatment of sepsis may lead to hypotension and septic shock. There are different opinions over which antibiotic regime is most effective given to multiple resistance pattern of V. fluvialis pathogen. Haq and Dayal[36], recommend 100 mg doxycycline intravenously every twelve hours, combined with two grams ceftazidime intravenously every eight hours. A group in Taiwan performed in vitro antibacterial testing and found several cephalosporin antibiotics effective in killing Vibrio infections including ceftazidime, ceftriaxone and cefotaxime.[37] They also found imipenem and a variety of quinolones to be equally effective. Several prophylactic and treatment have been described for Vibrio infections with quinolones.[37] Use of quinolones in the pediatric infections remains controversial. The combined therapy with doxycycline and ceftazidime is recommended by CDC. For treatment by doxycycline in children may remain contraindicated; in this case, the CDC recommends a combination of trimethoprim-sulfamethoxazole and aminoglycoside.[38]

In bacterial peritonitis antibiotic choice may be empiric, based on the most likely pathogens. Here the 3rd generation cephalosporin or ampicillin plus aminoglycoside are commonly used. In extra-intestinal Vibrio infections third-generation cephalosporins, doxycycline, amoxicillin / clavulanate, and fluoro quinolones were commonly used, especially with V. vulnificus infection.[39] The treatment guideline for extra-intestinal *V. fluvialis* infection are variable, and the antibiotics may differ in each case, i.e., cefuroxime and trimethoprim/sulfamethoxazole, gentamicin and ciprofloxacin, ceftazidime and oxytetracycline may be effective.[39] Further survey is needed to decide the appropriate treatment of choice for extra-intestinal infection by *V. fluvialis*.

## Conclusion

A number of factors could influence the emergence and re-emergence of different Vibrio species as significant pathogens in both developing and developed countries. Prevalence of *V. fluvialis* infection is significant public health hazard amongst bacterial pathogens as well as a contaminant in marine foods and food products, and causing impairment in both freshwater and marine environments. The barrier in preventing the spread of these pathogens is poverty, which goes with poor sanitization and hygiene. Proper surveillance of water, food and sanitation facilities may eradicate *V. fluvialis* infections. Occurrences of extraintestinal infection due to this organism becoming a challenging cause in the community as well as in the hospital. Proper identification of the bacteria in a short time from clinical specimen would enhance the management of the infected patients.

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