

Vibrio vulnificus Oysters: Pearls and Perils

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***Vibrio vulnificus* is a naturally occurring bacterium found ubiquitously in coastal waters. Infection with this organism, which is often associated with eating raw oysters, is the leading cause of seafood-related deaths in the United States. This article reviews the current scientific literature on this potentially lethal pathogen and discusses the prognosis, treatment, and prevention of *V. vulnificus* infections.**

Vibrio vulnificus is a naturally occurring halophilic (salt-requiring) gram-negative rod that is ubiquitous in coastal waters. *V. vulnificus*, with a case-fatality rate exceeding 50%, is the leading cause of seafood-related deaths in the United States [1–4]. According to estimates from the Centers for Disease Control and Prevention (CDC), each year approximately 100 persons in the United States are infected with *V. vulnificus*, resulting in approximately 50 deaths per year [5].

Medical historians have hypothesized that Hippocrates may have reported the first case of *V. vulnificus* infection in the 5th century BC when he described a fatal foot wound infection characterized by black bullous skin lesions leading to sepsis and death within 48 h of the onset of infection in a man living by the Aegean Sea [6]. The first reported clinical case of *V. vulnificus* infection (although first erroneously reported as *Vibrio parahaemolyticus* infection) occurred in 1970 in a patient who presented with a leg wound infection with gangrene that necessitated below-the-knee amputation and endotoxin-related septic shock after exposure to New England coastal waters [7]. The laboratory characteristics of *V. vulnificus* were described by Hollis et al and the clinical characteristics by Blake et al; the pathogen was officially named in 1979 by Farmer [8–10].

V. vulnificus, similarly to other seafood-borne bacteria and viruses, lodges in the tissues of filter-feeding mollusks, such as oysters, clams, mussels, and crabs; most *Vibrio* species possess a chitinase, a digestive enzyme that breaks down glycosidic bonds in chitin, which allows *Vibrio* to embed themselves in the exoskeleton of most arthropods, particularly crustaceans. Infections are often acquired from eating raw oysters [11–13]. Since these infections are relatively uncommon, clinical awareness of these infections is also limited. This article reviews the current medical literature on this potentially lethal pathogen and discusses the prognosis and treatment of these infections and, more importantly, measures to prevent *V. vulnificus* infections.

EPIDEMIOLOGICAL CHARACTERISTICS

V. vulnificus infection is a nationally notifiable illness. The CDC and state and local public health departments established a voluntary surveillance system for *Vibrio* infections, first in 1988 among Gulf of Mexico Coast states and then nationally in 2007 [1, 11]. Although infections can occur throughout the year, most infections usually occur during the warmer months (May through October) [14]. The infectious dose for *V. vulnificus* infections is unknown, but circumstantial evidence suggests that it may be relatively high, because few infections occur during the cooler months of November through March, when *V. vulnificus* is still present in harvested oysters but at lower concentrations [15–17].

Oysters, the most common vehicle for *V. vulnificus* infections, are typically found in estuaries, sounds, and bays. Raw or undercooked shellfish has been implicated as the vehicle of transmission of several bacterial (such

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as *Salmonella enterica* serotype Typhi and *Vibrio* species) and viral pathogens (such as hepatitis A virus and caliciviruses), but *V. vulnificus* is the most lethal infection associated with the consumption of raw oysters. The highest density of *V. vulnificus* has been reported in oysters from the Gulf of Mexico, which has an overall higher mean water temperature compared with other coastal waters in the United States [18]. Gulf coast oysters are particularly hazardous during the summer months when water temperatures are highest. *V. vulnificus* grows best in warm waters (temperatures >22°C), and bacterial densities are highest when the water temperatures are high [11]. The organism has been isolated from all coastal geographic regions of the United States, including the Atlantic, Pacific, and Gulf of Mexico coasts.

Although wound infections have occurred in previously healthy individuals, *V. vulnificus* primary septicemia has been diagnosed almost exclusively in persons with underlying medical illness, with a predilection for patients with cirrhosis. *V. vulnificus* is an opportunistic human pathogen. The severity of *V. vulnificus* infections is directly related to specific characteristics of the agent and the host. *V. vulnificus* septicemia is most common in patients with suppressed immune systems. Patients with kidney disease, diabetes, cancer, hemochromatosis, achlorhydria occurring naturally or induced by medication, or any medical illness that weakens the body's immune system, and particularly those with cirrhosis, alcoholic liver disease, or chronic hepatitis B or C are at especially high risk for septicemia and death. Cirrhotic patients often have immune system dysfunction, decreased complement levels, and reduced phagocytic and chemotaxis capacity, making it difficult to counter the virulence of *V. vulnificus* [19]. Furthermore, in the presence of portal hypertension, *V. vulnificus* may directly enter the portal system, bypassing the hepatic reticuloendothelial system [19]. Elevated iron levels are often found in persons with liver disease, which predisposes these persons to invasive *V. vulnificus* infections, because the pathogen uses the iron stores for bacterial growth [19]. *V. vulnificus* also produces extracellular toxins, which destroy tissue and basement membranes in blood vessels, and has a bacterial capsule that makes an immune system response more difficult [19]. These fibrinolytic properties cause the hemorrhage and edematous skin changes commonly observed in the lower extremities of patients with disseminated infection. *V. vulnificus* infection should be considered in patients with sepsis and severe skin lesions; these patients should be asked about raw oyster consumption, seawater exposure, and history of liver disease.

CLINICAL CHARACTERISTICS

V. vulnificus causes primarily 3 distinct syndromes: wound infections, primary septicemia, and gastrointestinal tract–limited infections. Review of 1988–1996 data from the Gulf

Coast Surveillance System finds that 45% of reported cases were wound infections, 43% were primary septicemia (blood culture isolation), and 5% gastrointestinal tract–limited infections on the basis of the site of *V. vulnificus* isolation [11]. Review of data from the Cholera and Other *Vibrio* Illness Surveillance system, a national database of human illness, finds that approximately 60% of isolates come from blood and 30% from wound infections [20]. Atypical manifestations of *V. vulnificus* infection include meningitis, peritonitis, corneal ulcers, osteomyelitis, otitis, urinary tract infection, myositis, and rhabdomyolysis. The diagnosis is usually confirmed when organisms are isolated by means of routine blood culture or aspiration of material from bullous skin lesions. Stool cultures, similar to other *Vibrio* species, require thiosulfate–citrate–bile salts–sucrose agar for isolation.

In 96% of primary septicemia cases, the patient reported consumption of raw or undercooked oysters during the 7 days preceding illness onset [11]. The median age of patients with primary septicemia is 54 years, and 89% of the patients are men. Raw oyster consumers who have chronic liver disease (eg, cirrhosis) are 80 times more likely to develop this infection and 200 times more likely to die from this infection, compared with those without chronic liver disease [12].

Wound infections, which are often necrotizing, are usually acquired when an open wound is exposed to warm seawater or seafood drippings contaminated with *V. vulnificus*. *V. vulnificus* should be in the differential diagnosis of necrotizing soft-tissue infections along with other microbes, such as group A *Streptococcus*, *Staphylococcus aureus*, *Pseudomonas*, and *Clostridium perfringens* [21]. Typical symptoms of *V. vulnificus* infections include fever, chills, diarrhea, nausea, vomiting, septic shock, and characteristic skin lesions, which include lower extremity cellulitis with ecchymosis and bullae. Because the organism can cross the intestinal mucosa rapidly, development of bullous skin lesions of the lower extremities, which are thought to be an early manifestation of sepsis, can occur within the first 24 h after onset of illness [22]. Unlike illnesses caused by other *Vibrio* species, the gastrointestinal illness caused by *V. vulnificus* is usually self-limited, with very few deaths reported (approximately 10 deaths reported during the past 20 years) with *V. vulnificus* isolated from stool, and associated with diarrhea and vomiting.

TREATMENT

There are limited data on the usefulness of antimicrobial agents in treating *V. vulnificus* infections. One study often cited on the potential usefulness of antibiotics found that mortality was lowest for patients who were administered antibiotics within the first 24 h after onset of illness [22]. In the Florida case series, the mortality rate was 33% in patients given antibiotics within 24 h, 53% for patients given antibiotics between 24 and 48 h, and

100% for patients given antibiotics >72 h after illness onset [22]. This series combined both primary septicemia and wound-related infections, which may have reduced the overall mortality rates for septicemia, since *V. vulnificus*-related wound infections have been found to be less lethal, compared with primary septicemia cases [22]. There are no randomized controlled drug trials assessing the efficacy of treatment for *V. vulnificus* septicemia. It is generally believed that the early administration of antibiotics (within the first 24 h of infection) may help to reduce subsequent death rates. The usual clinical course of primary septicemia in patients with severe liver disease is rapid deterioration and death, despite the early administration of antibiotics and aggressive supportive intensive care. In a review by Shapiro et al, 61% of patients with primary septicemia died and a history of chronic liver disease was the strongest predictor associated with fatal outcome from *V. vulnificus* infection [11]. The case-fatality rate is >50% for primary septicemia and about 15% for wound infections [1, 11, 22]. The presence of leukopenia and hypotension early during hospitalization portends a worse prognosis and an increased risk of death, with a median duration from hospital admission to death of 2 days [22].

Since the incubation period is short and the mortality rate extremely high with invasive *V. vulnificus* infections, a high index of suspicion must be entertained by clinicians in a patient presenting with a compatible history and clinical syndrome. Patients often are critically ill or deceased by the time microbial culture results become available; therefore, the initiation of prompt antimicrobial therapy for *Vibrio* infection should begin immediately whenever patients are suspected of having a potential invasive *Vibrio* infection.

Treatment for *V. vulnificus* infections should include antibiotics and/or aggressive wound care if suspected in any person with chronic disease (which includes approximately 97% of patients with primary septicemia and 68% of patients with wound infections) [2]. Recommended antibiotic therapy for *V. vulnificus* infection includes doxycycline 100 mg intravenously or orally twice daily and ceftazidime 1–2 g intravenously every 8 h or other third-generation cephalosporin [1]. In addition to antibiotics, many patients require supportive therapy and intensive care; severe wound infections may require surgical debridement, fasciotomy, or limb amputation.

PREVENTION

The prevention of *V. vulnificus* infections should be emphasized in public health practice. Persons with chronic liver disease, who are particularly susceptible to these infections, should be advised to avoid raw or undercooked shellfish and to avoid contact with seawater. California was the first state, in 1991, to pass legislation requiring warning notices in English at point of retail sale for raw oysters for those at high risk for severe *Vibrio* infections.

Many other states, since 1994, have also required consumer warning labels about the hazards of shellfish to be displayed either on menus or at tables in restaurants. After a series of *V. vulnificus* infections was reported during the period April 1993 through May 1996 in California among primarily Spanish-speaking persons [13, 23], California required retailers to provide written warning of the health hazards associated with consumption of raw Gulf of Mexico oysters in both English and Spanish. Surveys show that the majority of high-risk patients are unaware of the risks associated with raw oyster consumption. Physicians should educate all patients with chronic liver disease about the risks associated with raw oyster consumption and counsel them not to eat raw or undercooked oysters. State health officials have often disseminated health information regarding *V. vulnificus* illness, through warning signs in restaurants and on menus, educational outreach efforts to doctors, health warnings on websites, and through the distribution of informational brochures, but these approaches have had little effect on the incidence of infection or on mortality rates. Since 2003, California has banned the importation of raw oysters from the Gulf of Mexico during the period 1 April through 31 October, which is the warmest time period in the Gulf, unless the oysters have been treated with a scientifically validated process to reduce the *V. vulnificus* to nondetectable levels [24]. Harvesting restriction, such as banning shellfish harvesting during the warmer months, is another strategy that could potentially reduce shellfish-related infections, since virtually all oysters during the summer months are positive for *V. vulnificus* [25]. Commercial fishermen and persons handling harvested shellfish should always wear protective gloves to decrease the risk of puncture wounds.

Most healthy individuals are not at risk of *V. vulnificus* infection or its complications, although deaths have occurred in otherwise healthy persons without evidence of hepatic disease [26]. Since the general population is at relatively low risk for *V. vulnificus* infection, public health policy on the retail sale of raw oysters has tried to balance the risk of infection from consumption of raw unprocessed oysters with interests in commercial fishing and recreational swimming in coastal waters. From a population survey, 3.5% of the United States population report having eaten raw oysters during the past 7 days [27]. Studies have shown that nearly all persons who develop *V. vulnificus* primary septicemia have underlying chronic liver disease; therefore, it is estimated that approximately 1.2% of the United States adult population is at high risk of developing *V. vulnificus* septicemia if they come into contact with the organism [28].

The Food and Drug Administration (FDA) recommends that persons at high risk should not consume oysters that have not been thoroughly cooked [29]. The FDA has supported point-of-purchase health advisories directed at persons at high risk. Many consumer advisories state that there is a risk in consuming raw oysters and warn that individuals with chronic illness or liver

disease are at greatest risk and should eat only oysters that have been fully cooked. *V. vulnificus* is readily killed by freezing or boiling. The FDA issued regulations in 1995 mandating the refrigeration of oysters from point of harvest to point of consumption to reduce postharvest proliferation of organisms, which occurs readily at room temperature (Figure 1). The FDA recognizes that innovative postharvest technologies may reduce or eliminate *V. vulnificus* from raw oysters. The FDA has approved several methods that can achieve reduction or elimination of *Vibrio* from raw oysters; technologies that have been shown to be effective include low-temperature pasteurization, high-pressure processing, and irradiation [30–32]. It is estimated that the potential FDA policy change of mandating Gulf Coast oysters be processed to eliminate *V. vulnificus* would affect approximately 25% of the total annual oyster harvest according to the FDA [33]. Pasteurization of oysters has been shown to reduce or eliminate *V. vulnificus* without altering the taste or consistency of oysters. A study of low-temperature pasteurization, using 50°C internal temperature for shell-stock oysters, reduced the presence of *V. vulnificus* organisms to nondetectable levels after 10 min, demonstrating the effectiveness of the technique. The use of such technologies as oyster pasteurization has become more widely available. The process used by AmeriPure, which is the leading American raw oyster processing company, can eliminate these deadly bacteria to nondetectable levels, defined as a most probable number of <3 organisms per gram of oyster meat. It remains unclear what effect the 2010 oil spill in the Gulf of Mexico will have on the oyster industry or on public health. Although there are oyster suppliers on both the Atlantic and Pacific coasts, an estimated 60%–70% of oysters harvested in the United States

come from the Gulf of Mexico, particularly from Louisiana. It is predicted that it may take many years for the oyster industry to recover from this environmental disaster. In addition to the oil spill's negative impact on the harvesting of oysters, AmeriPure, which runs the largest processing plant for eliminating *Vibrio* from oysters, was also forced to reduce staff and operations because of economic losses resulting from the oil spill.

Proposals to require a performance standard of “non-detectable” or zero tolerance for *V. vulnificus* in oysters have been discussed by the FDA, but regulations have not been enacted as a result of antiregulation lobbying by the oyster industry and political representatives [33]. The shellfish industry overall has not adopted technological measures to minimize the numbers of *V. vulnificus* organisms in oysters offered for raw consumption during the past decade, despite the approval of several bacteria-eliminating technologies, reportedly because of the additional cost of processing raw oysters to eliminate *Vibrio*. Public health advisories in both the scientific and lay media have attempted to publicize the risks of consuming raw or undercooked shellfish; however, despite these warnings, raw shellfish-associated illness and deaths continue to occur. Current prevention strategies have been ineffective in preventing *V. vulnificus* infections; therefore, enhanced preventive efforts making use of technologies to eliminate the organism before consumption are warranted as a public health strategy.

CONCLUSION

The appearance of bullous skin lesions on the lower extremities in patients with liver disease with an appropriate history of raw shellfish consumption should strongly suggest consideration of *V. vulnificus* infection, and immediate antibacterial treatment should be started whenever this infection is suspected. Awareness of *V. vulnificus* infections is extremely limited in the general population and among many medical professionals. Doctors who treat patients with chronic liver disease should educate these high-risk patients to avoid consuming raw or undercooked shellfish. Our public health approach should emphasize prevention of *V. vulnificus* infections rather than treatment, which is often unsuccessful in high-risk patients with primary septicemia. Strategies that have been implemented during the past few decades have been relatively unsuccessful in preventing infections and deaths. Consumer advisories, outreach to educate doctors, and education on treatment modalities have not changed the incidence of this infection. The FDA is considering increasing regulation of the oyster industry by requiring that all oysters be treated prior to consumption to eradicate *V. vulnificus*. The primary objective of any new oyster-related health policy should be to make raw oyster consumption safer. The increased use of scientifically validated technologies to eliminate *V. vulnificus* organisms from oysters after harvest and before

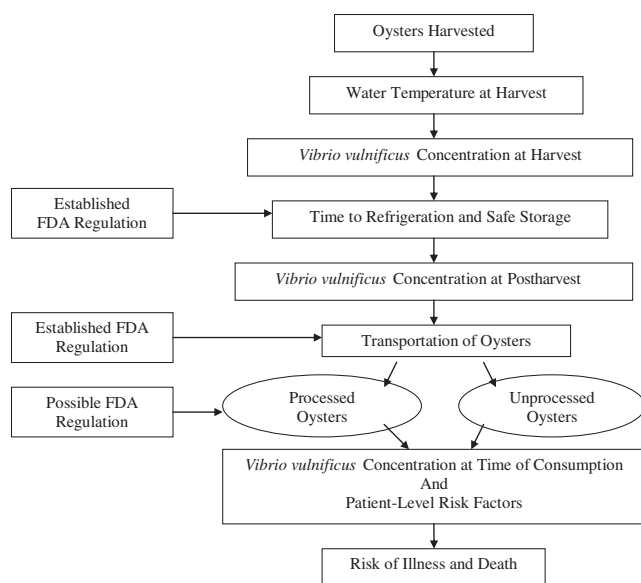


Figure 1. Factors associated with risk of infection from foodborne *Vibrio vulnificus* and Food and Drug Administration regulations.

consumption, as currently required in California during the warmer months, is warranted nationwide and may help substantially to reduce the morbidity and mortality associated with consumption of raw oysters.

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