

Vibrio vulnificus— A Significant Public Health Problem

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Abstract

Vibrio vulnificus can cause three types of human illness including a sepsis syndrome most often seen in patients with chronic liver disease. Severe wound infection and gastroenteritis are other syndromes associated with the organism. The bacteria flourish in United States' Gulf Coast waters between May and October. While the bacteria live in waters off California, Australia, Europe, and Asia as well, this paper will concentrate on the problem in the Gulf Coast area. Filter-feeding shellfish, particularly oysters, concentrate *Vibrio vulnificus* in their tissues. Ingestion of raw oysters is the most common mechanism of life-threatening human infection. This paper discusses the epidemiology of the organism, the pathogenesis and clinical manifestations of human *Vibrio vulnificus* infection, and then explores public health measures and post-harvest industrial technologies aimed at reducing the incidence of clinical illness.

Introduction

Vibrio vulnificus, a flagellated, rod-shaped, gram-negative bacterium prevalent in warm marine and estuarine waters along the Gulf Coast, is the leading cause of death from seafood consumption in the United States.¹ By one report, it accounts for 95% of all human seafood ingestion fatalities.² An extremely virulent organism, *Vibrio vulnificus* was first described as a significant human pathogen by the U.S. Centers for Disease Control and Prevention (CDC) in 1979.³ Since the first documented case, *Vibrio vulnificus* has been identified as the cause of an average of 95 cases per year in the United States with a case hospitalization rate of 90% and an overall case fatality rate of 37%.¹

Given its public health implications, *Vibrio vulnificus* has been the subject of intensive study for the last 20 years, yet many questions remain unanswered about

its microbiological characteristics, virulence-engendering features, and possible methods of attenuation. This review will discuss the epidemiology of the organism followed by the clinical manifestations and pathogenesis of *Vibrio vulnificus* infection. Subsequently, the paper will review strategies and make recommendations to mitigate the problem.

Epidemiology

Existing naturally in warm, salty, and brackish water, *Vibrio vulnificus* exists in temperatures between 9°C and 31°C, but thrives when water temperatures rise above 18°C. The bacteria prefer lower salinity levels between 15 and 25 parts per thousand (ppt);⁴ these temperature and salinity characteristics are typical of U.S. Gulf Coast waters in the summertime.⁵ They live in waters off Europe, Asia and Australia, and New Zealand⁶ but this paper concentrates on the U.S. Gulf Coast problem. *Vibrio vulnificus* infections demonstrate a seasonal pattern with the majority of clinical illnesses along the coastal areas of the Gulf of Mexico occurring between May and October,⁷ when temperature and salinity factors are most favorable to the bacteria's proliferation. It is interesting that this pattern mirrors to some degree the "old wives' tale" that one should not eat raw oysters in months with no "r" (an idea originally attributed to William Butler in the 16th Century⁸).

Filter-feeding shellfish, especially oysters (*Crassostrea virginica*), concentrate *Vibrio vulnificus* naturally through feeding, and can accumulate significant numbers in their gut and tissues,—approximately 10^3 - 10^4 bacteria per gram of oyster meat during peak periods of warm water.⁵ Unfortunately, presence of the organism cannot be detected by smell, taste, or appearance of the shellfish product, nor can the harvest location or the degree of freshness act as accurate predictors. Therefore, one must assume that *Vibrio vulnificus* is present in all Gulf Coast filter-feeding mollusks, and that adequate

cooking is necessary to kill the bacteria. In fact, the vast majority of *Vibrio vulnificus* infections in the United States occur through ingestion of raw oysters.

Clinical Manifestations

Vibrio vulnificus can cause three types of human clinical illness—primary sepsis syndrome, wound infection (cellulitis), and gastroenteritis. The primary sepsis syndrome consists of high fever and chills, often with vomiting, diarrhea, abdominal pain, and extremities pain⁵ with no apparent focus of infection. Major diagnostic clues for *Vibrio vulnificus* sepsis syndrome are hemorrhagic bullae which can be seen both in sepsis and cellulitis. It is believed that the bacteria most likely enter the circulation through the intestine.⁹ There is a case fatality rate of 50-60% for the sepsis syndrome^{6,7,8} while the overall case fatality rate for all three syndromes is 37%.¹

The second clinical picture is that of wound infection (cellulitis) that is caused by direct inoculation of the bacteria into the skin. The bacterium (and its associated toxins) rapidly cause local tissue necrosis associated with hemorrhagic bullae and erosions. Cellulitis may occur when an abraded area of skin is inoculated through bathing in marine waters where *Vibrio vulnificus* thrives, or through exposure to liquid from harvested raw seafood (drippings).¹⁰ This type of exposure typically occurs while shucking 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 one case series of 189 patients, 50% of patients with wound infections reported sustaining a wound at the time of exposure, 21% reported a pre-existing wound, and 29% were unable to correlate the time of the wound with exposure to *Vibrio vulnificus*.⁵ In the same case series, 69% of infections occurred due to exposure during fishing or raw oyster shucking in the previous week.⁵

The third *Vibrio vulnificus*-related illness, gastroenteritis, causes nausea, vomiting, diarrhea, and abdominal cramps. In this condition, the causative organism can be cultured from the stool but not the blood.⁹ The true incidence of *Vibrio vulnificus* gastroenteritis may not be known. It is most likely underreported because the illness is usually self-limited and medical care is not sought.⁵

The CDC⁷ reported 125 cases of *Vibrio vulnificus* infection in Florida between 1981 and 1992. Of these, 44 died, 72 had primary sepsis syndrome, 35 had wound infection/cellulitis, and 18 suffered gastroenteritis. In patients with primary sepsis syndrome, the vast majority (81%) had consumed raw oysters in the week prior to becoming ill. Of the 40 deaths associated with primary sepsis syndrome (56% sepsis case fatality rate), 35 had eaten raw oysters within the prior week. The average age of the septicemic patients was 60 years (range 33-90, standard deviation 12.9 years) and the majority were male (88%). Of the patients who developed gastroenteritis, 78% had eaten raw oysters. Their average age was 49 years (range 19-89, standard deviation 25.7 years) and 50% were male.

A number of host factors predispose patients to severe infection with *Vibrio vulnificus*. Known adverse host factors include liver disease (especially alcoholic cirrhosis), immunocompromised states such as HIV/AIDS, iron overload (e.g. hemochromatosis), and diabetes mellitus.¹⁰ By far, the most important of these predisposing factors is liver disease, whether primary or secondary to other causes. In the CDC Florida case series⁵ described above, the annual death rate for *Vibrio vulnificus* in liver disease patients was 45 per million compared with only 0.2 per million in patients unaffected by liver disease—a greater than 200 fold increase in the risk of death. Other studies have found at least a 50% case fatality rate in chronic liver disease patients who develop the sepsis syndrome.⁸

Pathogenesis

A number of factors appear related to the extreme virulence of *Vibrio vulnificus*. The bacterium secretes a lipopolysaccharide (LPS), a capsular polysaccharide (CPS), and various enzymes and toxins including metalloprotease and cytolysin.⁹ The LPS is a potent mediator of septic shock by inducing host pyrogenic reaction, especially tissue necrosis factor-alpha (TNF-a).⁵ The CPS is the most important virulence factor because it confers resistance to phagocytosis by macrophages and protects against serum bactericidal activity.⁵ The metalloprotease is an extracellular enzyme produced by *Vibrio vulnificus*, which displays elastolytic and collagenolytic activity. It appears to induce hemorrhagic damage, leading to enhanced vascular permeability and edema. The cytolysin enzyme mediates increases in intracellular cyclic GMP that leads to vasodilatation. It causes significant damage to endothelial cells and dis-

plays cytotoxic activity toward a variety of other cell types.⁵ Each of the above factors contributes to the virulence of the organism.

Iron plays a critical role in the pathogenesis of *Vibrio vulnificus* infection in humans. The organism is dependent on host iron for growth and secretes siderophores, which scavenge host iron from iron transport proteins such as transferrin. Raising the serum iron substantially reduces the number of bacteria required to cause systemic infection.⁹ This is why patients with hemochromatosis (and other iron overload states) are at higher risk for severe *Vibrio vulnificus* infection—the bacteria thrive in iron-rich environments.

Release of the various toxins mentioned above is associated with the primary sepsis syndrome. The primary sepsis syndrome also involves release of TNF- α , various interleukins and other systemically active cytokines.⁹ Once this syndrome becomes fully established, it is difficult to intervene medically, even with aggressive therapy. Therefore, the earlier effective therapy begins (with antibiotics and, if necessary, surgery), the more likely the patient will recover.

Strategies for Reduction in Incidence of *Vibrio vulnificus* Infection

Because *Vibrio vulnificus* is the main cause of seafood-related bacterial death in the United States, public health strategies to reduce the incidence of infection are important. There are population-based and industrial strategies to reduce infection. Educational strategies to improve public awareness of the problem will be considered first.

Educational Initiatives

As mentioned in Section I, patients with certain chronic conditions are at significantly increased risk of inva-

Table 1 Medical Conditions Associated with Risk for *Vibrio vulnificus*

Chronic Liver Disease	Heart Disease
Alcoholism	Hemochromatosis
Diabetes mellitus	Immunodeficiency
Previous Gastrointestinal Surgery	Malignancy
Peptic Ulcer Disease	Renal Disease (esp. end stage)

sive, lethal infection by *Vibrio vulnificus*. Table 1⁴ provides a list of these conditions:

In order to promote appropriate public health and practice preventive medicine, clinicians who care for such at-risk patients must teach them never to eat or shuck raw shellfish, especially oysters.⁸ In addition, these patients should be counseled not to bathe in Gulf Coast waters between May and October when *Vibrio vulnificus* levels are highest.⁶ While family physicians who see these patients on a regular basis are in a unique position to reduce the incidence of *Vibrio vulnificus* infection through effective patient teaching,¹¹ all involved healthcare providers should discuss these issues with at-risk patients. Unfortunately, many clinicians are unaware of *Vibrio vulnificus* because they have never received any continuing medical education about it. Recently, the Interstate Shellfish Sanitation Conference (ISSC) has developed an excellent online training video for physicians; it is available at the website: http://www.issc.org/Vibrio_vulnificus_Education/Vv_Infection_Course/main.htm)

Good teaching pamphlets in both English and Spanish are available through the ISSC website (www.issc.org) and should be given to at-risk patients.

The above prohibition on raw shellfish does not mean that at-risk patients cannot enjoy oysters, which are perfectly safe when properly cooked.¹² Consequently, such patients should order oysters and other shellfish “fully cooked” in restaurants. Alternatively, they can buy raw oysters and follow the cooking directions below in Box 1:¹²

Box 1: Cooking Directions for Oysters

- Uncooked oysters should have closed shells—discard any uncooked oysters with open shells
- Boil live oysters for another 3-5 minutes after the shells open – do not cook too many oysters in one pot as the ones in the middle may not cook thoroughly
- In a steamer – add oysters to steaming water and cook for 4-9 minutes
- If oysters are already shucked – boil for at least 3 minutes – edges will curl indicating “fully cooked”
- Fry shucked oysters at 375° for at least 3 minutes
- Broil shucked oysters 3” from heat for 3 minutes
- Bake shucked oysters at 450° for 10 minutes

Following these directions will effectively kill *Vibrio vulnificus* in oysters rendering them safe to eat (similar directions should work for clams and mussels as well).

Mitra² makes other food safety recommendations for at-risk individuals in addition to proper cooking: eat shellfish promptly after cooking, refrigerate leftover shellfish, avoid cross-contamination of cooked and raw shellfish, and wear protective clothing (gloves and eye protection) when handling raw shellfish.

In 1991, California led the nation by mandating an educational initiative to teach the public about the risk of *Vibrio vulnificus* because California imports a significant amount of raw oysters from the Gulf Coast. Among other mandates, the initiative requires the placement of the following warning signs in prominent places of restaurants serving raw oysters: "Eating raw oysters may cause severe illness and even death in persons who have liver disease...cancer or other chronic illnesses" (1991 California Code of Regulations, Title 17, Article 10.5. 10) Unfortunately, the signs were only required in English.

A group at the CDC¹³ studied this educational strategy in Los Angeles County and found its impact to be less than adequate. Reasons for this policy failure included improper posting of warning signs in more than 50% of cases; one-third of posted notices were in English only; warnings were not placed on tables; and only rarely was the notice placed in the menus. As an indication of the need for culturally sensitive notices, one should note that between 1993 and 1996 there were 16 cases of invasive *Vibrio vulnificus* infection in Los Angeles County and all but one were in Hispanic consumers. Seventy-five percent had pre-existing liver disease. None had been made aware of the dangers of eating raw oysters.¹⁴ Epidemiologic tracing of the oysters in these cases found they had been harvested either in Galveston Bay, Texas, or in Louisiana. It became apparent that better educational methods were necessary; in particular, educational signs and materials needed to be in both English and Spanish.

Since the late 1990's, the Interstate Shellfish Sanitation Conference (www.issc.org) has taken the lead in providing educational materials to the general public concerning *Vibrio vulnificus*. In 2001, the ISSC in concert with the FDA mandated that any state with two or more cases of *Vibrio vulnificus* infection must develop and implement a state education program targeting both at-risk populations and the medical community.

The state plan should include distribution of ISSC educational materials (available at www.issc.org), placement of articles in newspapers and magazines, continuing education courses for health professionals (including emergency department personnel), signage in retail/food service areas, TV ads, and marketing events such as seafood festivals. The FDA has authority to oversee and enforce the state educational plan.¹⁵ The ISSC has created a comprehensive tool kit for distributing educational material directly to patients at their local pharmacies and has used this approach effectively in Florida and California (The educational tool kit is available at www.issc.org).

Shapiro and coworkers⁴ recommend better enforcement of the existing requirement to post educational warnings in California, Louisiana, and Florida. Further, they call for other states to mandate similar warning signs. They also suggest that Gulf Coast oysters only be sold cooked or otherwise processed in order to kill *Vibrio vulnificus* between May and October. In April 2003, California banned the import of raw oysters from the Gulf of Mexico Coast between April and October unless the oysters were treated to reduce *Vibrio vulnificus* to undetectable levels.

Post-Harvest Risk Reduction

The ISSC recommends accomplishing a 60% reduction in shellfish-related *Vibrio vulnificus* infections by the year 2007.¹⁶ Achieving this goal will require, in addition to educational programs and pre-consumption treatment, post harvest treatments and testing for the bacteria. The ISSC proposes that oysters for human consumption contain no more than three colony forming units of *Vibrio vulnificus* per gram of oyster meat by 2007.¹⁶

Cook demonstrated that the bacteria did not multiply in post-harvest oysters cooled to 13°C or less. In contrast, oysters kept at 18°C or at ambient air temperature showed statistically significant increases in *Vibrio vulnificus* growth ($p < 0.05$).¹⁷ The next logical step would be to evaluate whether icing the oysters would diminish the bacterial prevalence in the post-harvest oysters. Unfortunately, ice immersion of oysters for three hours post-harvest has not been successful—the declines in *Vibrio vulnificus* levels were modest at best. The ice immersion process did have one unexpected effect—a trend toward increased counts of fecal col-

iform and heterotrophic bacteria.¹⁸ Therefore, icing post-harvest oysters cannot be recommended.

Tamplin and Capers¹⁹ used ultraviolet light to treat the seawater in which oysters were being held. At ambient temperatures greater than 23°C there was no significant inhibition of the organism. However, when seawater temperature was below 15°C, the bacterium was undetectable in the water. This finding supports the known temperature preferences of *Vibrio vulnificus* discussed previously but does not support any role for UV radiation of seawater.

Several post-harvest, commercially practical processes appear to be successful in destroying *Vibrio vulnificus* in the oyster without altering the palatability of the oyster meat. Low temperature pasteurization (at 50°C for 15 minutes—this temperature is considered low for pasteurization) not only lowers *Vibrio vulnificus* to undetectable levels, it also reduced spoilage bacteria significantly and prolongs the safe “shelf life” seven days compared with untreated oysters.²⁰

A variant of the above method used a commercial heat-shock process which increases the oyster meat temperature to >50°C for 1-4 minutes. This process diminished *Vibrio vulnificus* and total bacterial counts significantly but not to undetectable levels.²¹ Another method mentioned in the literature and approved by the FDA utilizes high pressure to destroy the bacteria in the oysters.¹

Improved technology to detect the presence and quantity of *Vibrio vulnificus* in both ambient seawater and post-harvest oysters will also facilitate the ISSC goal of reducing infection from shellfish. Older bacteriologic methods using “most probable number” of bacteria were lengthy, imprecise, and impractical. The development and application of polymerase chain reaction (PCR) testing for the presence and amount of *Vibrio vulnificus* DNA has revolutionized the shellfish industry and is now the standard for measurement. It is commercially practical, requiring about eight hours to complete as compared to the several days required by older techniques.^{16,22,23,24} Using PCR technology, the shellfish industry can demonstrate compliance with the ISSC 2007 goal of <3 colony forming units (CFUs) of *Vibrio vulnificus* per gram of oyster meat. Since voluntary industry compliance is unlikely to succeed, the FDA should mandate regular, random PCR testing of oyster catches with spot inspections by federal officers to ensure adherence to policy.

The FDA maintains an online registry of interstate cer-

tified shellfish shippers—appropriately called the Interstate Certified Shellfish Shippers List.²⁵ These shipping companies must rigorously maintain quality controls to reduce post-harvest multiplication of *Vibrio vulnificus*. The list is updated monthly and is available at <http://vm.cfsan.fda.gov/~ear/shellfis.html>.

Having discussed the educational and post-harvest strategies to limit infection of *Vibrio vulnificus*, treatments available to patients with established infection will now be discussed.

Treatment

As soon as a clinician makes a presumptive diagnosis of *Vibrio vulnificus* invasive infection, antibiotic therapy must begin immediately. While the gastroenteritis syndrome is usually self-limited and does not require parenteral therapy, the sepsis syndrome and the cellulitis syndrome are potentially life and limb threatening and require aggressive antibiotic therapy. Any delay in treatment in the latter two syndromes increases the likelihood of poor outcome for the patient, especially if hypotension ensues. There is debate over which antibiotic regime is most effective. Haq and Dayal¹ 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 vulnificus* including ceftazidime, ceftriaxone, and cefotaxime.⁹ They also found imipenem and a variety of quinolones (including ciprofloxacin and levofloxacin) to be equally efficacious. The combined therapy with doxycycline and ceftazidime is the recommended therapy according to the CDC website.²⁶ For treatment of children in whom doxycycline is contraindicated, the CDC website recommends a combination of trimethoprim-sulfamethoxazole and an aminoglycoside.²⁶

In combination with antibiotics, aggressive surgical debridement of infected wounds and intravenous hydration are necessary for patients suffering from the sepsis syndrome or cellulitis.⁹ Fasciotomy may also be required. Unfortunately, limb amputation is frequently necessary; the infection spreads rapidly because of the endothelial destruction and edema caused by the various toxins and enzymes released by the bacteria. Supportive care, including hospitalization for invasive monitoring in an intensive care unit, is critical for improved outcomes, especially for patients with the primary sepsis syndrome.

Recommendations

Because *Vibrio vulnificus* poses a significant public health threat, mitigation and treatment methods require delineation. Any plan to reduce the incidence of *Vibrio vulnificus* infection must be multi-factorial. Public and industrial educational strategies must be mandated in every state where raw shellfish (especially oysters) is harvested, processed, or sold. These must include warning signs (in English, Spanish, and any other locally prevalent language) in the places of business of restaurants and seafood vendors, with additional warning signs on restaurant tables and in menus. Public education through television ads, newspapers, magazine articles, and signs in liquor/beer stores must be funded. Educational outreach to health-care professionals should include required continuing medical education programs granting credit hours to nurses, mid-level providers, and physicians. Educational pamphlets in English and Spanish should be available in health practitioners' offices and primary care providers should be encouraged to discuss the risks of eating raw shellfish (or bathing in the Gulf of Mexico between May and October) with at-risk patients. So strong is the correlation between death due to *Vibrio vulnificus* infection and liver disease, that public health programs should be instituted to educate at-risk patients to abstain from eating or shucking raw oysters from the Gulf of Mexico.

During warm water months (generally May-October), Gulf Coast oysters must be treated after harvest to reduce *Vibrio vulnificus* to <3 CFUs per gram of oyster meat. Treatment either can be with low temperature pasteurization or with high-pressure methods described above. Only companies listed on the FDA's Interstate Certified Shellfish Shippers List should be allowed to transport shellfish. The harvesters of shellfish must be educated, their ships and facilities regulated and tested for bacteriological safety and approved lists of wholesalers, storage, and processing businesses must be established, based on regular inspection and testing. There must be frequent lot testing of oysters and other shellfish for levels of *Vibrio vulnificus* using PCR DNA probe technology. These programs will be meaningless without enforcement. Those not in compliance must be prohibited from dealing with raw shellfish for commercial purposes.

Treatment for established infection should include aggressive hydration, surgical debridement, and antibiotic therapy. Patients with primary sepsis syn-

drome should be aggressively treated in an intensive care unit.

Conclusion

Vibrio vulnificus is prevalent in Gulf Coast waters and in shellfish harvested from there during warm summer months. In patients with chronic illnesses, especially liver disease, the organism can cause a life-threatening sepsis syndrome. In other cases, it can cause an aggressive cellulitis or a milder syndrome of gastroenteritis. The cellulitis syndrome, like the sepsis syndrome, seems more prevalent in patients with chronic medical problems. This paper explored strategies to reduce the incidence of human infection from this organism. With appropriate resolve and formation of strategic partnerships, the ISSC goal of 60% reduction in infection is attainable by 2007.

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