Conferences and Reviews

Vibrio vulnificus
Hazard on the Half Shell

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Vibrio vulnificus is an extremely invasive gram-negative bacillus that causes bacteremia and shock. It should be suspected in any patient who is immunocompromised or has liver disease or hemochromatosis. Reduced gastric acidity may also increase the risk of infection if a patient presents with a history of ingesting raw shellfish (especially oysters) or trauma in brackish waters and skin lesions. Patients most commonly present with one of three clinical syndromes: primary septicemia, wound infection, or gastroenteritis. Treatment includes aggressive wound debridement, antibiotic therapy, and supportive care. Rapidly diagnosing and promptly initiating therapy are critical because _V vulnificus_ infection is rapidly progressive and mortality approaches 100% if septic shock occurs.

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Vibrio vulnificus is an increasingly recognized cause of sepsis that occurs in patients with preexisting liver disease or immunocompromised states who have recently ingested raw seafood. Because of dietary trends, this at-risk patient population may be eating increasing amounts of shellfish without awareness of the associated risks. *V vulnificus* infection is rapidly progressive and deadly if not recognized promptly and treated aggressively.

This review was prompted by the case of a patient who presented with *V vulnificus* sepsis after ingesting raw oysters shipped from Louisiana to her home in northern California.

History

Vulnificus comes from the Latin word for "wounding"—an appropriate name, as this species of *Vibrio* may cause extensive soft tissue damage. Hippocrates described what may be the first case in the medical literature. A patient named Criton from the island of Thasos presented with "violent pain in foot," fever, delirium, and black blisters of his skin.[1] Despite state-of-the-art therapy, he died on the second day after the onset of symptoms. As Criton was a fisherman, it is likely that he was exposed to the organism in seawater.

The first recent report of clinical infection was in 1970, with the case of a previously healthy man in whom leg gangrene, a generalized hemorrhagic rash, thrombocytopenia, hypotension, and vomiting and diarrhea developed two days after he bathed and clammed in the seawater of Narragansett Bay.[2] Although *Vibrio vulnificus* was first isolated by the Centers for Disease Control in 1964,[3] the patient's symptom complex was initially mistakenly attributed to *Vibrio parahaemolyticus. Vibrio vulnificus* was first given its name in 1979.[4,5]

Epidemiology

The peak incidence of cases is in the summer months, with a range from March to November.[6-8] The male-to-female ratio is 4 to 1; more than 90% of patients are older than 40 years; and more than 90% of patients have eaten raw or undercooked oysters within 24 to 48 hours of clinical infection (range 7 hours to 4 days).[9,10] The amount of oysters consumed ranges from 3 to 48.

The organism is halophilic (salt-loving); it will not grow in a saltfree environment. *V vulnificus* is most frequently isolated from seawater with a temperature greater than 20°C (68°F) and a salinity of 0.7% to 1.6%, and it is rarely found in seawater cooler than 17°C (62.6°F).

Surveys have shown that more than 50% of oysters and 10% of crabs are culture-positive for this organism.[11,12] Culture-positivity is highly seasonal, with oysters most likely to be positive during warm summer months.[13] The incidence of *V vulnificus* infection is not increased with fecal contamination of seawater, and, in fact, the organism may grow better in the absence of enteric bacteria. It will proliferate in seafood kept at room temperature but will be killed by boiling or freezing.[9]

Vibrio vulnificus has been found in virtually every geographic location in the United States, including seawater in the Gulf of Mexico, off both coasts, as far north as Cape Cod, and off the islands of Hawaii.[14] It has been found in lakes in New Mexico and Oklahoma and from the Great Salt Lake in Utah. In general, Pacific shellfish have not been implicated as causes of disease in humans. Cases have been reported from Japan, Belgium, and Australia, but most reported cases are from the United States.

Pathophysiology

Vibrios are motile, curved, rod-shaped, gram-negative bacteria. *Vibrio vulnificus* is an extremely invasive organism that commonly causes bacteremia and shock. It may invade vascular endothelium and create a necrotizing vasculitis[15-17] leading to endothelial hypoplasia and septic thrombosis.

Bullae are common and result from dermal necrosis, which is thought to be due to the extracellular toxins produced by this bacterium.[18] Subcutaneous tissue, muscle, and nerves may be completely destroyed in the course of this infection.

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Iron appears to be needed for the growth of *V vulnificus*.[6,19,20] Studies using animals show the median lethal dose for organisms producing sepsis will be lowered if iron is given as a premedication. *Vibrio* species are able to extract iron from hemoglobin and use it as a nutrient. The elevated serum and tissue iron levels, with the saturation of transferrin, found in patients with liver disease may provide a nutrient substrate for the proliferation of *Vibrio* organisms.

Several other theories exist as to why morbidity is increased in the presence of liver disease. The shunting of portal blood containing *V vulnificus* infection around a diseased liver may lead to septicemia.[13] Poor opsonization and a reduced activity of polymorphonuclear leukocytes and Kupffer's cells in the diseased liver may lead to a decreased clearance of bacteria from the portal circulation.

The common occurrence of hypotension is thought to be due to several toxins produced by the pathogenic *V vulnificus*. A cytolysin has been shown to be hemolytic in animals and causes a disruption of collagen and damage to capillary endothelium.[21] The organism is also known to produce elastase,[22] collagenase,[23] and phospholipase.[24] A capsule is present that resists phagocytosis and bactericidal activity of human serum. This is genetically determined, and its presence correlates directly with the virulence of the organism. Strains can undergo phase variation, shifting between encapsulated and unencapsulated forms.

The organism may occasionally be identified in wound or bullae fluid and stool, as well as blood specimens, in patients with sepsis.[25] The use of a selective medium such as thiosulfate citrate bile salts is usually necessary. The laboratory should be notified that *V vulnificus* is suspected because identification of the organism can be difficult (especially from stool specimens).[26,27]

Risk Factors

Certain groups of patients have been shown to be at greater risk for complications after exposure to *V vulnificus*. It is rare for a person without a risk factor to be affected.

High-risk patients include those with:

- Liver disease and other diseases with possible hepatic involvement or elevated serum iron levels (including cirrhosis, alcoholism, malignancy, hemochromatosis, or thalassemia major)[3,28-30];
- Therapeutically induced or naturally low gastric acid (achlorhydria or antacid or H_2 blocker use)[26,31];
- Compromised immune systems (patients with the acquired immunodeficiency syndrome [AIDS] or AIDS-related complex; patients with cancer, especially during treatment; patients with diabetes mellitus; and patients with renal disease, chronic intestinal disease, or steroid dependency).[29,30]

In one study, only 17% of patients in high-risk groups were aware of the danger associated with ingesting raw seafood.[32] This emphasizes the important role of physicians in educating certain patient populations.

Clinical Presentation

Three clinical syndromes have been reported: primary septicemia, wound infection, and gastroenteritis.[7,14,19,33] In the largest review to date,[7] a report of 62 cases in Florida between 1981 and 1987, the group of patients with septicemia was the largest (62% of the total). The patients' mean age was 62, and 87% were male. This syndrome was characterized by the abrupt onset of fever and chills with secondary skin lesions arising within 24 hours in more than half of the patients. Intense lower extremity pain, vomiting, diarrhea, and abdominal pain were all common complaints. Cultures of blood were positive for *V vulnificus* in 97% of these patients. Various other cultures were also positive, including cultures of cerebrospinal fluid. The overall mortality for these patients was 55%, although the mortality in patients with hypotension during the first 48 hours of illness was 92%. Of these patients, 66% had underlying liver disease and 5% had hemochromatosis. Liver disease or other chronic illness was diagnosed in 95%.

The other two syndromes made up a relatively minor percentage of cases. Wound infections were evident in 27%

TABLE 1.—*Signs and Symptoms of* Vibrio vulnificus *Infections**

Signs and Symptoms	Patients, %: Primary Septicemia, 62%	Wound Infection, 27%	Gastroenteritis, 11%
Systemic	100†	70†	70†
Fever	94	75	57
Chills	91	39	43
Mental status changes	50	18	0
Hypotension (systolic blood pressure <90 mm of mercury)	35	14	0
Gastrointestinal	71†	12†	100†
Nausea	58	NA	NA
Vomiting	35	12	29
Abdominal pain	34	0	100
Diarrhea	30	3	100
Cutaneous Lesions	75†	100†	0†
Cellulitis	50	90	0
Bullae	40	38	0
Ecchymosis	32	20	0
Bacteremia	100	30	NA
Mortality	55‡	25	0

NA = data not available

*Modified from Klontz et al.[7]
†Percent of patients with at least one of the listed signs or symptoms.
‡More than 90% of patients are in shock.

TABLE 2.—*Bullous Skin Lesions With Sepsis: Differential Diagnosis*

Group A streptococcal erysipelas with necrotizing fasciitis (gangrenous erysipelas)
Ecthyma gangrenosum (due to *Pseudomonas aeruginosa* or *Aeromonas*)
Vibrio infections, including *Vibrio vulnificus*
Staphyloccocal cellulitis
Streptococcal cellulitis
Toxic epidermal necrolysis (staphylococcal scalded skin syndrome, infections, medications)

TABLE 3.—*Management of* Vibrio vulnificus *Infections*

History: Raw shellfish ingestion? Contact with seawater? Risk factors?
Cultures: Take specimens of blood, wounds, and stool for culture; notify laboratory of suspected *V vulnificus* infection
Antibiotics: Tetracycline (with or without gentamicin or chloramphenicol) therapy promptly
Supportive care: Monitoring in intensive care unit, fluids, watch for complications (disseminated intravascular coagulation, bleeding, shock)
Surgical treatment: Aggressive debridement of wounds, consider amputation
Reporting: Legally notifiable condition to public health department

TABLE 4.—*Educational Instructions for the Prevention of* Vibrio vulnificus *Infection*

Immunocompromised patients: Avoid raw or improperly cooked shellfish
Patients with cutaneous lesions: Avoid contact with seawater
Public: Warning labels on shellfish containers and menus, public health brochures

of the patients. More than 80% of these had direct contact with seawater on open wounds. Blood cultures were positive in only 30% of these patients, with a correspondingly lower mortality of 24%.

Only 11% of patients presented with the third clinical syndrome: gastroenteritis characterized by vomiting, diarrhea, and abdominal pain with a stool culture positive for *V vulnificus*. None of the patients in this group died.

Two other large reviews of 39[13] and 23 patients[19] yielded similar results to those of the series described above. There are about 20 other case reports in the literature that emphasize the wide spectrum of disease processes caused by *V vulnificus*. These include pneumonia and septicemia following the aspiration of seawater,[34] meningitis,[7] spontaneous bacterial peritonitis,[35,36] endometritis after intercourse in seawater,[37] necrotizing fasciitis[15,16] presenting with compartment syndrome,[17] corneal ulcers,[38] epiglottitis,[39] and infections of the testes, spleen, and heart valves.[6,14]

Overall, 94% of patients present with fever, 91% with chills, 75% with skin lesions, and 58% with nausea (Table 1).[1] A third of patients are in shock when they are first seen, or hypotension develops within 12 hours of admission,[4] and more than 90% of these will die.[11] Patients may present with severe, localized pain that precedes the onset of skin lesions by hours to days.[1,13]

Distinct bullous skin lesions, which develop secondary to sepsis, are present in about 40% of patients.[4,11,40] The differential diagnosis of these lesions includes group A streptococcal erysipelas with necrotizing fasciitis (gangrenous erysipelas), ecthyma gangrenosum secondary to *Pseudomonas aeruginosa* or *Aeromonas* species, other *Vibrio* species infections, brown recluse spider bites, and staphylococcal or streptococcal cellulitis (Table 2).[6,41]

Thrombocytopenia is common, and there is often evidence of disseminated intravascular coagulation.[4,12,35] Leukopenia is more common than leukocytosis. Other complications include the respiratory distress syndrome and heart block.

Management

Once *Vibrio vulnificus* is suspected, appropriate cultures (of blood, wound or bullae, and stool specimens) should be done and aggressive management begun immediately. Supportive care with intravenous fluids (and pressors if needed) and monitoring in an intensive care unit are essential. Careful observation for possible complications such as disseminated intravascular coagulation is crucial.

Treatment with antibiotics must be initiated promptly. The organism is susceptible to a wide variety of antibiotics in vitro (tetracycline, erythromycin, ampicillin, cephalosporin, chloramphenicol, norfloxacin, and gentamicin). In studies of mice, however, ampicillin, cephalosporin, erythromycin, and gentamicin are not as effective as tetracycline.[42] Tetracycline is currently recommended as the drug of choice.[10,20] The addition of an aminoglycoside[7] or chloramphenicol[19] is often advised.

It has been shown that case-fatality rates for patients with septicemia increase with greater delays between the onset of illness and the initiation of antibiotic treatment or if tetracycline is not used in the regimen.[7]

Along with supportive care and the prompt administration of antibiotics, the third component of treatment is aggressive wound care. Debridement of wounds is essential,[12] and amputation of the affected limb may be life-saving in some cases (Table 3).[43]

As of May 1, 1988, infection due to *Vibrio* species is a legally notifiable condition in California.[9]

Clinical Implications

Although early treatment with antibiotics has some efficacy, the mortality associated with septicemia remains high, emphasizing the need for education to prevent this disease

from occurring (Table 4). Clinicians should warn immunocompromised patients (including those infected with the human immunodeficiency virus) to avoid eating raw seafood.

If the prevention of *Vibrio* infection is not possible, physicians must maintain a high index of suspicion to identify patients at risk. The diagnosis should be entertained when a high-risk patient presents with upper or lower extremity skin lesions, especially if a history of eating shellfish is elicited. The disease is rapidly progressive and must be treated aggressively. Appropriate specimens for culture should be obtained, antibiotic therapy begun, and blood pressure support initiated.

Summary

There are two major syndromes of *Vibrio vulnificus* infection. One of these is primary septicemia, which is usually seen in patients with underlying liver disease who have eaten raw oysters 24 to 48 hours earlier. The syndrome is characterized by fever, chills, nausea, and characteristic lower extremity lesions. Hypotension is present on admission in more than a third of bacteremic patients. Skin lesions are present in 75%, usually consisting of bullae, although pustules, petechiae, and purpura may also be seen. The syndrome of septicemia carries a mortality rate in excess of 50%,[26,27] which approaches 100% if hypotension occurs within 12 hours of admission.[35]

The second major syndrome is that of a wound infection, usually seen in a healthy person in whom a wound develops while cleaning shellfish or who has an existing wound that is exposed to seawater. Only a third of these patients have positive blood cultures,[1] and the mortality is about 25%. Patients who have underlying health problems such as liver disease or malignancy are more likely than healthy persons to have disseminated infection develop.

The early recognition of these syndromes and appropriate antibiotic therapy followed by local supportive measures are the key to reducing the impressive mortality associated with *V vulnificus* infection.

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