Vibrio vulnificus: Review of Mild to Life-threatening Skin Infections

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PRACTICE **POINTS**

- *Vibrio vulnificus* infection should be high on the differential for patients who present with chronic liver disease and immunosuppression; a history of raw seafood consumption or exposure to brackish water; and bullae, cellulitis, necrotic lesions, or sepsis.
- Time to treatment is directly proportional to mortality rates in *V vulnificus* infections, and prompt treatment with antibiotics, wound care, debridement, and supportive measures is necessary to decrease mortality rates.
- The incidence of *V vulnificus* infection is rising in the United States, likely due to a combination of factors, including an aging population with multiple comorbidities, improvements in diagnosis, and climate change.

Vibrio vulnificus is a motile, gram-negative, halophilic, aquatic bacterium that is part of the normal estuarine microbiome and typically is found in warm coastal waters. Infection with the pathogen typically is due to consumption of contaminated seafood or exposure to contaminated seawater. *Vibrio vulnificus* has a mortality rate of almost 33% in the United States and is responsible for more than 95% of seafood-related deaths in the United States. *Vibrio vulnificus* can cause a vast spectrum of diseases, such as gastroenteritis, cellulitis, necrotizing fasciitis, and sepsis. Gastroenteritis is self-limited, whereas septicemia often is fatal. Gastroenteritis and septicemia are caused by ingestion of contaminated shellfish, whereas wound infections and necrotizing fasciitis are caused by exposure to contaminated seawater or handling of contaminated seafood. Septicemia is the most common presentation of *V vulnificus* and accounts for the most fatalities from the bacteria. Prompt diagnosis and treatment are vital to prevent mortality. It is important to keep *V vulnificus* on the differential when a patient presents with bullae or cellulitis or has a history of raw seafood consumption or exposure to brackish water, as missing the diagnosis could lead to necrotizing fasciitis, sepsis, and death.

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Vibrio vulnificus is a member of the *Vibrio* genus. Most *Vibrio* species are nonpathogenic in humans; however, *V vulnificus* is one of the pathogenic strains.[1] In Latin, the term *vulnificus* means "wounding," and *V vulnificus* can cause life-threatening infections in patients. The mortality rate of *V vulnificus* infections is approximately 33% in the United States.[2] *Vibrio vulnificus* is a gram-negative bacterium that was first isolated by the Centers for Disease Control and Prevention in 1964 and was given its current name in 1979.[3-6] It has been found in numerous organisms, including oysters, crabs, clams, shrimp, mussels, mullets, and sea bass.[4] The vast majority of infections in the United States are due to oyster exposure and consumption.[2,7] *Vibrio vulnificus* is responsible for more than 95% of seafood-related deaths in the United States and has the highest mortality rate of all food-borne illness in the United States.[2,5] It also has the highest per-case economic impact of all food-related diseases in the United States.[1]

What distinguishes a pathogenic vs nonpathogenic *Vibrio* isolate remains unknown; *Vibrio* species rapidly undergo horizontal gene transfer, making DNA isolation difficult.[1] Some characteristics of *V vulnificus* that may confer virulence are the capsular polysaccharide, lipopolysaccharide, binding proteins, and tissue-degrading enzymes.[1,5] First, encapsulated strains are more virulent

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and invasive than unencapsulated strains.[1] The mucopolysaccharide capsule protects the bacterium from the immune system, allowing it to evade immune surveillance, cause more severe infection, and invade into the subcutaneous tissue.[3,5] Second, production of sialic acid–like molecules alter the lipopolysaccharide, allowing for motility and biofilm formation.[1] This allows the bacterium to survive in marine waters and within the bloodstream, the latter leading to sepsis in humans. Third, production of N-acetylglucosamine–binding protein A allows for adhesion to chitin. Shellfish consume chitin, and chitin accumulates in shellfish. N-acetylglucosamine–binding protein A also binds mucin; this may be how *V vulnificus* binds to mucin in the gastrointestinal tract in humans, causing gastroenteritis.[1] Binding to the human mucosae also may allow the bacteria to gain access to the blood supply, leading to septicemia.[4] Finally, tissue-degrading enzymes such as proteases are responsible for necrotizing wound infections associated with *V vulnificus*, as the enzymes allow for invasion into the skin and subcutaneous tissues. Proteases also increase vascular permeability and lead to edema.[3] Hence, these virulence factors may provide *V vulnificus* the pathogenicity to cause infection in humans.

Three biotypes of *V vulnificus* have been discovered. Biotype 1 is the most common and is found worldwide in brackish water.[8] It can cause the entire spectrum of illnesses, and it has a case fatality rate of 50% in humans. Biotype 1 is presumably responsible for all infections in the United States. Biotype 2 is found in the Far East and Western Europe; it inhabits a unique niche—saltwater used for eel farming. It typically causes infection in eels, but rarely it can cause wound infections in humans. Biotype 3 is found in freshwater fish farming in Israel, and it is a hybrid of biotypes 1 and 2. It can cause severe soft tissue infections in humans, sometimes requiring amputation.[8]

Epidemiology

Vibrio vulnificus is a motile, gram-negative, halophilic, aquatic bacterium.[1,4,5,8,9] It is part of the normal estuarine microbiome and typically is found in warm coastal waters.[1,5,10] The ideal conditions for growth and survival of *V vulnificus* are water temperatures at 18 °C (64.4 °F) and water salinities between 15 to 25 parts per thousand.[2,8,9] These conditions are found in tropical and subtropical regions.[2] *Vibrio vulnificus* is found all over the world, including Denmark, Italy, Japan, Australia, Brazil, and the United States,[2] where most infections come from oyster exposure and consumption in the Gulf of Mexico.[2,8,11] The incidence of infection in the United States is highest between April and October.[8,11]

Some populations are at a higher risk of infection. Risk factors include male sex, liver cirrhosis, hemochromatosis, end-stage renal disease, immunosuppression, and diabetes mellitus.[1,8,11] Healthy patients with no risk factors account for less than 5% of US *V vulnificus* infections.[8]

Male Predilection—Men are 6 times more likely to be affected by *V vulnificus* than women. Some hypotheses for this discrepancy are that estrogen is protective against *V vulnificus* and that women may be less likely to engage in risky water activities and seafood handling.[5] Additionally, older males (aged >60 years) are most often affected,[1,8] likely due to the association between increasing age with number of comorbidities, such as diabetes mellitus, heart disease, and chronic disease.[8]

Iron Levels—Iron appears to play an important role in *V vulnificus* infection. Iron is essential for bacterial growth, and the ability to obtain iron from a host increases the organism's pathogenicity.[3] *Vibrio vulnificus* rapidly grows when transferrin saturation exceeds 70%.[8] Additionally, iron overload decreases the inoculum needed to cause sepsis in animal studies, which could play a role in human pathogenesis.[4] Iron levels are elevated in patients with hemochromatosis due to increased iron absorption, cirrhosis and chronic liver disease due to impaired iron metabolism, and end-stage renal disease, especially in patients receiving parenteral iron.[8]

Immunosuppression—Patients who are immunocompromised and those with chronic liver disease are at an increased risk of infection because of neutrophils having decreased phagocytic activity.[4]

Diabetes Mellitus—Patients with diabetes mellitus may have peripheral neuropathy and may be unaware of preexisting wounds that serve as entry points for *V vulnificus.*[12]

Etiology

Vibrio vulnificus infects humans via seafood consumption and handling as well as exposure to contaminated water.[2,5] With respect to seafood consumption, raw shellfish are the primary type of seafood that harbor high levels of *V vulnificus.*[5] Oysters are the most common etiology, but consumption of crabs, clams, and shrimp also can lead to infection.[5,7] *Vibrio vulnificus* contamination does not change the appearance, taste, or odor of shellfish, making it hard to detect.[8] An inoculate of 1 million bacteria typically is necessary for infection after consumption.[5] Contaminated seawater is another primary cause of *V vulnificus* infection. When open wounds are exposed to seawater harboring the bacteria, wound infections can arise.[7] Infections can be acquired when swimming, fishing, or participating in water sports. Wound infections also occur while handling contaminated seafood, such as oyster shucking.[5] There is a short incubation period for *V vulnificus* infections; the onset of symptoms and clinical outcome typically occur within 24 hours.[5]

Clinical Presentation

Vibrio vulnificus infections can have numerous clinical presentations, including gastroenteritis, wound infections, necrotizing fasciitis, and sepsis.[1,8] There also is a spectrum of clinical outcomes; for instance, gastroenteritis typically is self-limited, whereas necrotizing fasciitis or sepsis can be fatal.[2]

Gastroenteritis—*Vibrio vulnificus* gastroenteritis is due to ingestion of contaminated shellfish.[2,9] Symptoms typically are mild to moderate and include nausea, vomiting, diarrhea, fever, chills, abdominal pain, and cramping.[2,4,8] Cases likely are underreported in the United States because gastroenteritis is self-limited, and many patients do not seek treatment.[2,11]

Wound Infections—Wound infections with *V vulnificus* have a cutaneous port of entry. Exposure to contaminated seawater or seafood can inoculate an open wound, leading to infection.[7,8] Wound infections usually stem from 1 of 2 routes: (1) a pre-existing open wound gets infected while the patient is swimming in contaminated water, or (2) a traumatic injury occurs while the patient is handling contaminated shellfish, knives, or fishhooks. Many shellfish, such as oysters, have sharp points on their shells that can lacerate the skin.[8] A wound on the hand can be contaminated by *V vulnificus* while handling contaminated seafood (eg, oyster shucking).[13] Minor abrasions should not be dismissed; in fact, a small puncture or skin break often acts as the port of entry.[9,11] Wound infections tend to arise within 7 days of exposure, though they can manifest up to 12 days after exposure.[8] Wound infections can present as cellulitis, bullae, or ecchymoses.[7] Lesions are exquisitely tender, and the skin is erythematous with marked surrounding soft tissue edema.[3,4,8] Cellulitis typically arises first, with hemorrhagic bullae rapidly following.[14] Lesions are limited to the affected extremity or area of inoculation.[8] Systemic symptoms are rare, but fever and chills may accompany the infection.[8,14] Unfortunately, lesions can become necrotic and progress rapidly to necrotizing fasciitis if left untreated.[4,7,11] In these cases, secondary sepsis can occur.[8]

Necrotizing Fasciitis—Wound infections caused by *V vulnificus* can progress to necrotizing skin and soft tissue infections, such as necrotizing fasciitis and gangrene.[5] Necrotizing fasciitis accounts for approximately one-third of *V vulnificus* infections.[9] It usually stems from an open wound that is inoculated by contact with contaminated seafood or seawater.[2,9] The wound infection begins as cellulitis with extreme tenderness, erythematous skin, and marked soft tissue edema, then rapidly progresses, becoming necrotic. These necrotic lesions present as black and purple eschars as the skin, blood supply, and subcutaneous tissues are infiltrated by the bacteria and destroyed. Lesions may have blistering or exudation. Many patients have accompanying systemic symptoms, including fever, chills, abdominal pain, diarrhea, hypotension, and sepsis.[11,14] However, some patients may not present with systemic symptoms, so it is important to maintain a high index of suspicion even in the absence of these symptoms. The infection typically is limited to the affected extremity; necrotizing infections can lead to amputation and even death, depending on the extent of destruction and spread of the bacteria.[11,13] The infection may spread beyond the inoculated extremity if the bacteria gains access to the bloodstream.[8,9] In these cases, fulminant purpura or secondary septicemia can occur.[8,15] Fatality rates in the United States for necrotizing *V vulnificus* infections approach 30%.[2] Necrotizing fasciitis accounts for approximately 8% of deaths associated with the pathogen in the United States.[9]

Interestingly, one reported case of necrotizing fasciitis associated with *V vulnificus* infection was triggered by acupuncture.[16] The patient worked in a fish hatchery, where he was exposed to *V vulnificus,* and subsequent acupuncture led to the inoculation of bacteria into his bloodstream. This case raises the important point that we typically sequence the pathogenesis of *V vulnificus* infection as a patient having an open wound that is subsequently exposed to contaminated water; however, it also can follow the reverse sequence. Thus, proper cleansing of the skin after swimming in brackish water or handling shellfish is important to prevent *V vulnificus* infection.[16] Additionally, dermatologists should be sure to cleanse patients' skin thoroughly before performing procedures that could cause breaks in the skin.

Septicemia—Primary septicemia is the most common presentation of *V vulnificus* infection.[2,8] Septicemia accounts for approximately 58% of *V vulnificus* infections in the United States.[9] Infection typically occurs after ingestion of contaminated oysters, with subsequent absorption into the bloodstream through the ileum or cecum.[2,8,9] Patients with chronic liver disease are 80 times more likely to develop primary sepsis than healthy individuals.[8] Patients typically present with sudden-onset fever and chills, vomiting, diarrhea, and pain in the abdomen and/or extremities within hours to days of ingestion.[4,8,9] The median time from ingestion to symptom onset is 18 hours.[4,16] However, symptoms can be delayed up to 14 days.[2] Progression is rapid; secondary lesions such as bullae, ecchymoses, cellulitis, purpura, macular or maculopapular eruptions, pustules, vasculitis, urticaria, and erythema multiforme–like lesions appear on the extremities within 24 hours of symptom onset.[2,3,4,8,17] Hemorrhagic bullae are the most common cutaneous manifestation of sepsis.[4] Lesions are extremely tender to palpation.[3] Cutaneous lesions can progress to necrotic ulcers, necrotizing fasciitis, gangrene, necrotizing vasculitis, or myonecrosis.[4,8] Evidence of petechiae may indicate progression to disseminated intravascular coagulation (DIC). Elevated D-dimer and fibrin split products also may indicate DIC, and elevated creatine kinase may signify rhabdomyolysis.[3] Unfortunately, septicemia has the worst outcomes of all *V vulnificus* presentations, with morality rates greater than 50% in the United States.[1,2,4] *Vibrio vulnificus* septicemia has a similar case-fatality rate to pathogens such as anthrax, Ebola virus disease, and the bubonic plague.[5] Septicemia accounts for approximately 80% of the deaths associated with *V vulnificus* in the United States.[8,9]

Septicemia due to *V vulnificus* progresses to septic shock in two-thirds of cases.[8] Septic shock presents with hypotension, mental status changes, and

thrombocytopenia.[2,8,17] Patients can become tachycardic, tachypneic, and hypoxic. Intubation may be required for resuscitation. In cases of septic shock secondary to *V vulnificus* infection, mortality rates reach 92%.[3] Hypotension with a systolic blood pressure less than 90 mm Hg is a poor prognostic factor; patients presenting with hypotension secondary to *V vulnificus* infection have a fatality rate approaching 75% within 12 hours.[2]

Atypical Presentations—Rare atypical presentations of *V vulnificus* infection that have been reported in the literature include meningitis, corneal ulcers, epiglottitis, tonsillitis, spontaneous bacterial peritonitis, pneumonia, endometritis, septic arthritis, osteomyelitis, rhabdomyolysis endophthalmitis, and keratitis.[2,4,6,13,18,19]

Diagnosis

When diagnosing *V vulnificus*, providers need to obtain a thorough patient history, including any history of consumption or handling of raw seafood and recent water activities. Providers practicing in tropical climates or in warm summer months should keep *V vulnificus* in mind, as it is the ideal climate for the pathogen.[9] Vital signs can range from unremarkable to fever, hypotension, tachycardia, and/or hypoxia. Skin examination may show exquisitely tender, erythematous skin with marked soft tissue edema, hemorrhagic bullae, ecchymoses, and/or necrosis. As physical examination findings can be nonspecific, wound cultures, blood cultures, and skin biopsies should be taken.

A wound culture and blood culture should be taken immediately if *V vulnificus* is suspected.[8,11] A wound culture using discharge or fluid from necrotic or bullous lesions should be analyzed via gram stain.[8,9] Gram stains of *V vulnificus* show short, slim, curved gram-negative rods under light microscopy.[9,20] Special stains also can be done on cultures; *V vulnificus* is an oxidase-positive, lactose-positive, lysine-positive, salicin-positive, and arginine-negative organism. This knowledge can help differentiate *V vulnificus* from other gram-negative rods.[13] Blood cultures will be positive in approximately 97% of patients with primary septicemia and 30% of patients with septicemia secondary to *V vulnificus* wound infections.[3,9]

Histologically, perilesional skin biopsies show epidermal necrosis with dermal and subcutaneous inflammation.[12,17] There typically is an inflammatory infiltrate with neutrophilic abscesses and extensive tissue destruction in the subcutaneous tissue extending into the deep dermis.[12,17] The superficial dermis is edematous but can lack the inflammatory infiltrate found in the subcutaneous tissue.[17] Subepidermal bullae can form with numerous organisms within the fluid of the bullae. There also may be evidence of leukocytoclastic vasculitis with accompanying vessel wall necrosis. Fibrin clot formation and extravasated red blood cells may be visualized with few inflammatory cells but numerous organisms around the involved vessels.[17]

Management

Early diagnosis and treatment are vital.[5,17] Cultures should be taken before aggressive treatment is started.[3] Treatment is multifaceted; it requires antibiotics and wound care, except in cases of self-limited gastroenteritis.[2,11] Aggressive debridement, fasciotomy, amputation, and supportive measures also may be necessary depending on the patient's presentation.[2,3,8,9] Establishing 2 peripheral intravenous lines is important in case rapid resuscitation becomes necessary.

Antibiotics—Primary cellulitis wound infections should be treated with doxycycline or a quinolone. If untreated, the wound can rapidly progress to necrotizing fasciitis.[11] For necrotizing fasciitis and septicemia, broader-spectrum antibiotics are needed. For adults, ceftazidime plus doxycycline is the mainstay of antibiotic treatment for *V vulnificus*.[2,9,11] For children, trimethoprim-sulfamethoxazole plus an aminoglycoside is preferred (Table).[2,11]

Antibiotic Recommendations for Treatment of *Vibrio vulnificus* Infection

Clinical manifestation	Adult: Recommended[9,11]	Adult: Alternative[2,9,11]	Child: Recommended[a,9,11]
Non-necrotizing wound infection	Oral doxycycline 100 mg once daily + oral moxifloxacin 400 mg once daily for 10–14 d	N/A	Trimethoprim-sulfamethoxazole 320 mg daily IV or orally, both divided every 12 h + gentamicin (or other aminoglycoside) 2–2.5 mg/kg IV or IM every 8 h
Necrotizing fasciitis	IV ceftazidime 1–2 g every 8 h + IV doxycycline 100 mg every 12 h for 10–14 d	IV moxifloxacin 400 mg every 24 h for 10–14 d	
Sepsis	IV ceftazidime 1–2 g every 8 h + IV doxycycline 100 mg every 12 h for 10–14 d	IV cefotaxime 2 g every 8 h + IV ciprofloxacin 400 mg every 8 h for 10–14 d; IV moxifloxacin 400 mg once daily	

Abbreviations: N/A, not applicable; IV, intravenous; IM, intramuscular.
[a]Recommended treatment for children applies to all clinical manifestations.

Antibiotic treatment has become more difficult as resistance arises. Antibiotic resistance likely is due to extensive antibiotic use in health care along with the agriculture and aquaculture industries using prophylactic and therapeutic antibiotics that wash into or are directly added to marine waters, where *V vulnificus* resides. Thus, antibiotic treatment should be tailored to the resistance profile of *V vulnificus* in various regions; for example, ceftazidime has an intermediate resistance profile in the United States, so cefotaxime and ceftriaxone may be better options.[2]

Wound Care—Wound infections must be extensively irrigated.[9,21] For mild wound infections, proper wound care and oral antibiotics are appropriate (Table).[21] Mild wounds should be irrigated thoroughly and followed by wound coverage to prevent progression, secondary infection, and necrosis. The dressing of choice will depend on the presenting lesion and provider preference; nonadherent, occlusive, or wet-to-dry dressings often are the best choices.[22] Nonadherent dressings, such as petrolatum-covered gauze, do not pull off the newly formed epithelium when removed, making them beneficial to the skin's healing process. Another option is occlusive dressings, which maintain a moist environment to hasten healing. They also enhance the autodigestion of necrotic tissue, which can be beneficial for necrotizing *V vulnificus* infections. Wet-to-dry dressings also may be used; these typically are comprised of gauze soaked with water, an astringent, and an antimicrobial or antiseptic solution. These dressings help to treat acute inflammation and also remove any exudate from the wound.[22]

Soft tissue and necrotizing infections require debridement.[2,8] Early debridement decreases mortality rates.[2,8,9] Necrotizing fasciitis often requires serial debridement to clear all the dead tissue and reduce the bacterial burden.[8,9] Debridement prevents contiguous spread and metastatic seeding of the bacteria; it is important to prevent spread to the blood vessels, as vasculitis can necrose vessels, preventing antibiotics from reaching the dead tissue.[17] Providers also should monitor for compartment syndrome, which should be treated with fasciotomy to decrease mortality.[9,23] Many physicians leave *V vulnificus*–infected wounds open in order to heal by secondary intention.[9] Hyperbaric oxygen therapy may be helpful as an adjunct to aggressive antimicrobial treatment for wound healing.[8]

Supportive Measures—Supportive care for dehydration, sepsis, DIC, and septic shock may be necessary, depending on the patient's course. Treatment for severe *V vulnificus* infection includes intravenous fluids, crystalloids, oxygen, and/or intubation. Furthermore, if DIC develops, fresh frozen plasma, cryoprecipitate, a packed red blood cell transfusion, and/or anticoagulation may be required for resuscitation.[3]

Timing—Time to treatment and fatality rate are directly proportional in *V vulnificus* infection; the greater the delay in treatment, the higher the fatality rate.[2] A 24-hour delay in antibiotic treatment is associated with a 33% case-fatality rate, and a 72-hour delay is associated with a 100% case-fatality rate.[9] Even with early, appropriate treatment, mortality rates remain high.[4]

Prevention

Prevention of *V vulnificus* infections is an important consideration, especially for patients with chronic liver disease, immunosuppression, and hemochromatosis. Public education about the risks of eating raw shellfish is important.[4] Oysters need to be treated properly to prevent growth and survival of *V vulnificus.*[2] The most reliable method for destroying the bacteria is cooking shellfish.[8,13] Only 15% of high-risk patients in the United States are aware of the risks associated with raw oyster consumption.[3] High-risk patients should avoid eating raw oysters and shellfish and should cook seafood thoroughly before consumption.[2,8] They also should wear protective clothing (ie, gloves) and eye protection when handling seafood and protective footwear (ie, wading shoes) while in seawater.[2,8,13] It also is important to avoid contact with brackish water if one has any open wounds and to cleanse properly after exposure to brackish water or shellfish.[2,8,16] Because severe *V vulnificus* infections can lead to death, prevention should be strongly encouraged by providers.[2]

Conclusion

Vibrio vulnificus infection typically occurs due to consumption of contaminated seafood or exposure to contaminated seawater. It most frequently affects older male patients with chronic liver disease, immunosuppression, hemochromatosis, or diabetes mellitus. *Vibrio vulnificus* can cause a vast spectrum of diseases, including gastroenteritis, wound infections, necrotizing fasciitis, and sepsis. Septicemia is the most common presentation of *V vulnificus* infection and accounts for the most fatalities from the bacteria. Septicemia often presents with fever, chills, vomiting, diarrhea, and hemorrhagic bullae. *Vibrio vulnificus* also commonly causes necrotizing fasciitis, which initially presents as cellulitis and rapidly progresses to hemorrhagic bullae or necrosis with accompanying systemic symptoms. Prompt diagnosis and treatment are vital to prevent mortality.

Interestingly, regions impacted by *V vulnificus* are expanding because of global warming.[5,7] *Vibrio vulnificus* thrives in warm waters, and increasing water temperatures are enhancing *V vulnificus* growth and survival.[1,9] As global warming continues, the incidence of *V vulnificus* infections may rise. In fact, the number of infections increased by 78% between 1996 and 2006 in the United States.[5] This rise likely was due to a combination of factors, including an aging population with more comorbidities, improvements in diagnosis, and climate change. Thus, as the number of *V vulnificus* infections rises, so too must providers' suspicion for the pathogen.

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