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Review

A comprehensive review of *Vibrio vulnificus*: an important cause of severe sepsis and skin and soft-tissue infection

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SUMMARY

Vibrio vulnificus is a halophilic Gram-negative bacillus found worldwide in warm coastal waters. The pathogen has the ability to cause primary sepsis in certain high-risk populations, including patients with chronic liver disease, immunodeficiency, iron storage disorders, end-stage renal disease, and diabetes mellitus. Most reported cases of primary sepsis in the USA are associated with the ingestion of raw or undercooked oysters harvested from the Gulf Coast. The mortality rate for patients with severe sepsis is high, exceeding 50% in most reported series. Other clinical presentations include wound infection and gastroenteritis. Mild to moderate wound infection and gastroenteritis may occur in patients without obvious risk factors. Severe wound infection is often characterized by necrotizing skin and soft-tissue infection, including fasciitis and gangrene. *V. vulnificus* possesses several virulence factors, including the ability to evade destruction by stomach acid, capsular polysaccharide, lipopolysaccharide, cytotoxins, pili, and flagellum. The preferred antimicrobial therapy is doxycycline in combination with ceftazidime and surgery for necrotizing soft-tissue infection.

1. Introduction

Vibrio vulnificus is a halophilic, motile, Gram-negative bacillus capable of causing severe to life-threatening infection in susceptible individuals. The spectrum of illness can vary from gastroenteritis to 'primary sepsis' and necrotizing fasciitis. The case-fatality rate has been reported to exceed 50% in primary sepsis. Infection may result from consuming or handling contaminated seafood (usually shellfish such as oysters) or from exposing open wounds or broken skin to contaminated salt or brackish water.[1–5]

V. vulnificus is usually found worldwide in coastal or estuarine environments with water temperatures from 9 to 31 °C. The organisms preferred habitat, however, is considerably more selective and has been reported to be water temperatures in excess of 18 °C and salinities between 15 to 25 parts per thousand (ppt).[6–8] However, salinities at or greater than 30 ppt will substantially reduce the burden of *V. vulnificus* regardless of the water temperature.[8] As a result, most cases of infection can be traced to tropical or subtropical sources. Even so, small outbreaks related to local seawater or seafood exposure have occurred in temperate climates as far north as Denmark during the summer months.[6] A recent report from Israel described several cases of soft-tissue infection resulting from the handling and processing of fish (tilapia or carp) raised in freshwater aquaculture ponds.[9]

Three biotypes of *V. vulnificus* are known to cause severe human disease. Biotype 1 is found worldwide in salt or brackish water. Biotype 2 occupies a more specific niche and is found in saltwater used for eel (genus *Anguilla*) farming in the Far East and Western Europe.[6,7] Biotype 3 is the strain associated with freshwater fish farming in Israel. Genomic analyses of biotype 3 indicate it is a hybrid of biotypes 1 and 2.[9] Biotype 1 is the most common strain and is responsible for the entire spectrum of illness, including the primary sepsis associated with the often-quoted fatality rate in excess of 50%. Biotype 2 is usually a serious pathogen of eels, but on rare occasions may cause wound infections in humans.[3,6,7] Although biotype 3 can cause severe soft-tissue infections requiring amputation, the mortality rate appears to be less than 8%.[9]

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Most reported cases of infection with *V. vulnificus* have occurred in patients with chronic liver disease, immunodeficiencies, or hematological disorders characterized by elevated iron levels.[1–7,9–12] Contamination with *V. vulnificus* can be difficult to detect because the organism has no effect on the appearance, taste, or odor of seafood, particularly raw oysters.[13] Because *V. vulnificus* is ubiquitous in warm marine environments, water quality also has little impact on the risk of infection.[12]

In this report, we describe a severe case of soft-tissue infection and review much of the current literature concerning *V. vulnificus*. We also provide recommendations for treatment and prevention in populations at high risk of infection.

2. Illustrative case

A 53-year-old male was admitted to the emergency department (ED) with a 2-day history of pain in both arms, which he characterized as 10/10. The patient also complained of subjective chills and fever. Vital signs on admission included a temperature of 37.2 °C, heart rate of 73/min, respiratory rate of 20/min, blood pressure of 75/51 mmHg, and an oxygen saturation of 100% on room air. The patient was noted to be grimacing but alert, and oriented times 3 and cooperative. The left arm was erythematous with petechiae to the medial aspect of the lower arm. The right arm was erythematous to the anterior forearm with serosanginous bullae.

Pertinent laboratory data included a white blood cell count (WBC) of 8.6×10^9/l with 54% segmented neutrophils, 27% band neutrophils, 8% lymphocytes, 11% monocytes; hemoglobin of 11.5 g/dl (7.1 mmol/l), hematocrit of 34.1%, platelet count of 30×10^9/l; prothrombin time (PT) of 15.7 s; activated partial thrombin time (aPTT) of 35.1 s; international normalized ratio (INR) of 1.6; fibrinogen of 831 mg/dl (24.4 μmol/l), D-dimer of 6.3 mg/l FEU (fibrinogen equivalent units); serum creatinine of 5.8 mg/dl (512.7 μmol/l); blood urea nitrogen (BUN) of 52 mg/dl (18.6 mmol/l), sodium of 121 meq/l (121 mmol/l); potassium of 5.8 meq/l (5.8mmol/l); bicarbonate (HCO_3^-) of 11 mmol/l; glucose of 84 mg/dl (4.7 mmol/l); total bilirubin of 1.3 mg/dl (22.2 μmol/l); albumin of 2.6 g/dl; alkaline phosphatase of 203 U/l; acetaminophen of 47.6 μg/ml (315.1 μmol/l); pH of 7.25; pCO_2 of 21 mmHg; and a B-type natriuretic peptide (BNP) of 1007 pg/ml. Blood and blister fluid cultures were collected and sent to the laboratory for Gram stain, culture, and susceptibility testing.

Upon questioning, the patient provided no history of exposure to saltwater. He was placed on vancomycin 1 g every 12 h. Past medical history included hepatitis C (presumably from multiple transfusions), chronic renal insufficiency, cirrhosis, hypertension, congestive heart failure, and ethanol abuse (stopped 2.5 years prior to admission). The patient's toxicology screen was negative. While in the ED, he was given a bolus followed by a maintenance infusion of normal saline. The patient was also placed on a norepinephrine infusion and titrated to maintain a systolic blood pressure >90 mmHg.

He was transferred to the intensive care unit (ICU). Vancomycin was discontinued the next day following a nephrology consult and was replaced with clindamycin 900 mg every 8 h. Ertapenem 500 mg every 24 h was also added to the patient's antimicrobial regimen. Hemorrhagic bullae appeared within the first 24 h and the affected integument extended from both hands to the elbows, with the right hand (Figure 1) more involved than the left (Figure 2). Eventually much of the area encompassing both forearms became necrotic. The presumptive diagnosis was necrotizing fasciitis. Blood cultures were negative; however blister fluid cultures were positive at 48 h for *V. vulnificus*. The bacterium was susceptible at 72 h to ampicillin, ampicillin–sulbactam, aztreonam, cefazolin, ciprofloxacin, gentamicin, imipenem, piperacillin–tazobactam, and trimethoprim–sulfamethoxazole. When questioned about the laboratory finding, the patient admitted to shucking and eating at least 8 raw oysters a few days prior to admission. The antimicrobial regimen was changed to doxycycline 100 mg intravenous (IV) every 12 h and ceftazidime 1 g every 24 h (adjusted to renal function).

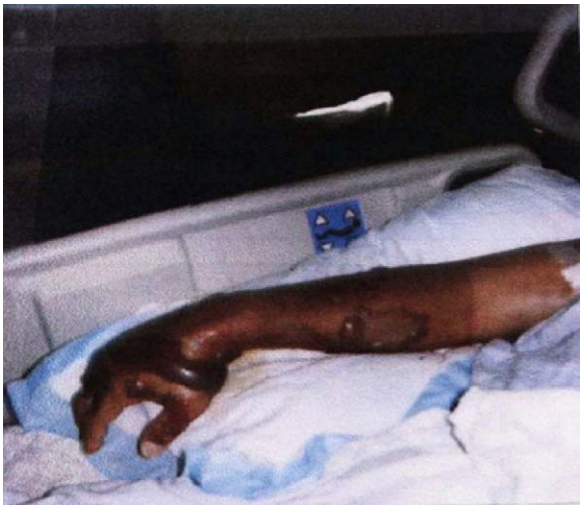

Figure 1. Right arm about 24 h after admission.

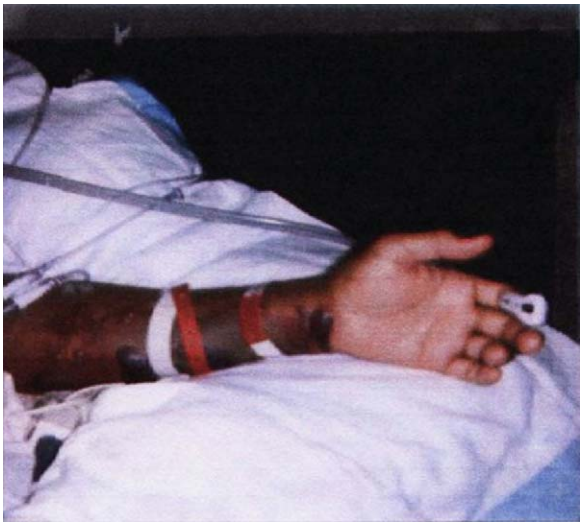

Figure 2. Left arm about 24 h after admission.

The patient's hypotension, metabolic acidosis, and thrombocytopenia responded to treatment and norepinephrine was discontinued by 48 h after admission. Hemodialysis was also initiated. A plastic surgery consult was requested when the patient stabilized, and debridement was performed on hospital days 6 and 15. The operative report indicated the infection was limited to the skin and subcutaneous fat and did not involve the fascia. The final diagnosis was therefore changed to necrotizing cellulitis. Skin grafts were performed on hospital days 36 and 39. The patient continued to improve, although he remained on hemodialysis post-discharge. He was discharged in stable condition on hospital day 40.

3. Epidemiology

V. vulnificus is found on all coastlines of the USA where water temperatures are sufficiently warm to support growth. It is one of