Rapidly Progressive Hemorrhagic Cellulitis of Bilateral Lower Extremities with Subsequent Septic Shock and Death

Ellen E. Connor, MD, PhD; Nicole R. Jackson, MD, MPH; Robin R. McGoey, MD

A 51-year-old man presented to a community based emergency department with bilateral lower extremity swelling that began four days prior and that had evolved into recent blister formation on the left lower extremity. Medical history was significant only for hypertension and a recent self-described episode of “food poisoning” five days earlier characterized by diarrhea, nausea, and vomiting that quickly resolved. Physical exam revealed marked bilateral lower extremity edema and an ecchymotic rash below the knee. In addition to the rash, there were large flaccid bullae on the left leg, mostly intact but some notable for draining of scanty serosanguinous fluid. The patient was tachycardic with a rate of 114 bpm and initial labs showed thrombocytopenia (platelets 56 x 10^3/uL [140-440 x 10^3/uL]), hypoglycemia (15mg/dl [70-105mg/dl]), an elevated creatinine (2.7mg/dL [0.7-1.25mg/dL]), and aspartate aminotransferase (AST 156U/L [5-34U/L]). Two sets of blood cultures were drawn, broad spectrum antibiotics including doxycycline were empirically initiated and then he was subsequently transported to a tertiary care hospital for escalation of care. Within hours of presentation to the tertiary care facility, the rash appeared progressively hemorrhagic and bullous, lactic acidosis and coagulopathy developed and hemodynamic instability and septic shock necessitated endotracheal intubation and vasopressors. He was taken to the operating room for skin debridement but was emergently converted to bilateral above the knee lower extremity amputations due to the extent of the soft tissue necrosis. The patient remained intubated and in critical condition following surgery and the ecchymotic rash reappeared at the amputation sites. A newly developed ecchymotic rash with bullae formation was noted on the right upper extremity forearm. At that time, the clinicians were notified that four out of four blood culture bottles from admission were rapidly growing a microorganism. The family elected for withdrawal of care, and the patient died approximately 72 hours following presentation. A full and unrestricted autopsy was authorized by the Coroner’s Office. A representative image from the decedent’s newly erupted right upper extremity skin lesions, a gross image of the liver at autopsy and an image of the microorganisms growing on MacConkey agar are shown right in Figures 1A-C.

Based on the clinical case description, the liver disease and the microorganism morphology, what is the diagnosis?
Cellulitis with ecchymoses and bullae. When half of patients develop the characteristic skin lesions of severe presentation. Within 24 hours of symptom onset, more than half of patients are in septic shock at the time of presentation. Within 24 hours of symptom onset, more than half of patients are in septic shock at the time of presentation. Within 24 hours of symptom onset, more than half of patients are in septic shock at the time of presentation. Within 24 hours of symptom onset, more than half of patients are in septic shock at the time of presentation. Within 24 hours of symptom onset, more than half of patients are in septic shock at the time of presentation. Within 24 hours of symptom onset, more than half of patients are in septic shock at the time of presentation. Within 24 hours of symptom onset, more than half of patients are in septic shock at the time of presentation. Within 24 hours of symptom onset, more than half of patients are in septic shock at the time of presentation. Within 24 hours of symptom onset, more than half of patients are in septic shock at the time of presentation. Within 24 hours of symptom onset, more than half of patients are in septic shock at the time of presentation. Within 24 hours of symptom onset, more than half of patients are in septic shock at the time of presentation. Within 24 hours of symptom onset, more than half of patients are in septic shock at the time of presentation. Within 24 hours of symptom onset, more than half of patients are in septic shock at the time of presentation. Within 24 hours of symptom onset, more than half of patients are in septic shock at the time of presentation. Within 24 hours of symptom onset, more than half of patients are in septic shock at the time of presentation.

Individuals who ingest inoculated seafood often complain of fever, diarrhea, nausea and vomiting. The differential diagnosis of aggressive soft tissue infection is usually polymicrobial necrotizing fasciitis or other bacterial organisms such as group A Streptococcus, Staphylococcus aureus, Pseudomonas, and Clostridium perfringes.

The initial laboratory workup for patients with Vibrio is nonspecific but includes a left shift in the white count and a rising serum creatinine. Computed tomography of affected soft tissues will most often show primarily edema. For microbial culture, not only should sets of blood cultures be obtained, but fluid-filled bullae and/or surgical tissue can be considered for rapid gram stain analysis and subsequent culture such that quick coverage preferably with doxycycline and a third-generation cephalosporin can be initiated. The differential diagnosis of aggressive soft tissue infection is usually polymicrobial necrotizing fasciitis or other bacterial organisms such as group A Streptococcus, Staphylococcus aureus, Pseudomonas, and Clostridium perfringes.

The overall mortality rate for V. vulnificus is reported to be 20-30%; though for those presenting in shock, the mortality can approach 50%. And, due in large part to the rapid replication rate, death frequently occurs within the initial 48 hours of presentation. Underlying comorbidities that are associated with mortality from V. vulnificus infection include cirrhosis, hepatitis, hemochromatosis, thalassemia, metastatic cancer, transplant, AIDS, chemotherapy, and chronic steroid use. Notably though, liver disease has repeatedly been reported as the strongest independent predictor of a fatal outcome presumably due to poor nutritional status, decreased serum bactericidal activity, and a defective white blood cell function.

As was shown in the case presented here, it is not uncommon for patients to have an unrecognized exposure to Vibrio whether that be from an obscure small wound in contaminated waters or from poor recall for consumption of uncooked at-risk seafood. Furthermore, and again seen here, it is also not uncommon to uncover additional comorbid conditions that place infected individuals at a higher mortality risk, such as liver disease or other immunodeficiency. Given Vibrio’s predilection to inhabit both the mollusk community of oysters, shrimp and other shellfish as primary wound infection, the mode of transfer is from contaminated water often through an open wound. Exposure typically occurs during water related activities such as boating, fishing, or swimming but can also be occupationally linked to those who work in the seafood industry and are involved in shrimp cleaning, oyster shucking, and crabbing. Local cellulitis can rapidly progress to large, coalescent hemorrhagic bullae with necrosis, necessitating surgical debridement and possible amputation. Almost one half of these cases also have Vibrio bacteremia and nearly all have fever and chills. Rare cases of Vibrio with unusual presentations have been recorded and include self-limiting watery, non-bloody diarrheal disease and other mucosal site infections after exposure to seawater, sometimes in immunocompromised patients.

Vibrio vulnificus is a halophilic, motile, curve-shaped, gram-negative rod whose preferred habitat is a considerably warm, estuarine environment. As such, in the United States, V. vulnificus predominates along the coast lines of those states that border the Gulf of Mexico particularly during the more seasonal months of April through September. Though V. vulnificus can be found free-living, it is commonly taken up by filter-feeding mollusks such as oysters, clams, mussels and scallops, with the highest density being localized to those oysters that are harvested from the state of Louisiana.

The Vibronaceae family of gram negative rods consist of roughly a dozen or so species divided clinically into generally two categories of infection: cholera due to V. cholera and vibriosis due either to V. parahaemolyticus or V. vulnificus. First isolated and differentiated as its own species in the mid-1970s, V. vulnificus has a specific propensity to cause either a foodborne illness or a highly lethal necrotizing wound infection.

Now, there are three known biotypes of V. vulnificus shown to cause human disease. While biotypes 2 and 3 are found only in niche regions of Western Europe-East Asia and Israel, respectively, biotype 1 is found worldwide making it the most common Vibrio strain.

The annual incidence of infections associated with Vibrio appears to be rising, thought by some to be due to global warming and increasing sea water temperatures. The Centers for Disease Control estimates that the average annual incidence of all Vibrio infections increased by 41% between 1996 and 2005. In 2011, V. Vulnificus was confirmed in approximately 100 cases in the United States worldwide, with the majority of infections attributed to consumption of raw oysters harvested from the Gulf of Mexico during the summer.

V. vulnificus generally causes diseases via two main modalities. Approximately 75% of cases are due to a foodborne illness with nearly all of the remaining cases accounted for by a primary soft tissue wound infection. As a foodborne illness, V. vulnificus infection occurs following consumption of undercooked or raw seafood such as clams, oysters and scallops. The Vibrio organism does not change the taste, appearance or odor of the seafood; and proper cooking methods are the only reliable method for killing the organism. Individuals who ingest inoculated seafood often complain of fever, diarrhea, nausea and vomiting. Of those who seek medical attention, roughly 50% have mental status changes and nearly 1/3 are in septic shock at the time of presentation. Within 24 hours of symptom onset, more than half of patients develop the characteristic skin lesions of severe cellulitis with ecchymoses and bullae. When Vibrio occurs via

Diagnosis and Answer: Vibrio vulnificus

DISCUSSION

V. vulnificus is a halophilic, motile, curve-shaped, gram-negative rod whose preferred habitat is a considerably warm, estuarine environment. As such, in the United States, V. vulnificus predominates along the coast lines of those states that border the Gulf of Mexico particularly during the more seasonal months of April through September. Though V. vulnificus can be found free-living, it is commonly taken up by filter-feeding mollusks such as oysters, clams, mussels and scallops, with the highest density being localized to those oysters that are harvested from the state of Louisiana.

The Vibronaceae family of gram negative rods consist of roughly a dozen or so species divided clinically into generally two categories of infection: cholera due to V. cholera and vibriosis due either to V. parahaemolyticus or V. vulnificus. First isolated and differentiated as its own species in the mid-1970s, V. vulnificus has a specific propensity to cause either a foodborne illness or a highly lethal necrotizing wound infection. Now, there are three known biotypes of V. vulnificus shown to cause human disease. While biotypes 2 and 3 are found only in niche regions of Western Europe-East Asia and Israel, respectively, biotype 1 is found worldwide making it the most common Vibrio strain.

The annual incidence of infections associated with Vibrio appears to be rising, thought by some to be due to global warming and increasing sea water temperatures. The Centers for Disease Control estimates that the average annual incidence of all Vibrio infections increased by 41% between 1996 and 2005. In 2011, V. Vulnificus was confirmed in approximately 100 cases in the United States worldwide, with the majority of infections attributed to consumption of raw oysters harvested from the Gulf of Mexico during the summer.

V. vulnificus generally causes diseases via two main modalities. Approximately 75% of cases are due to a foodborne illness with nearly all of the remaining cases accounted for by a primary soft tissue wound infection. As a foodborne illness, V. vulnificus infection occurs following consumption of undercooked or raw seafood such as clams, oysters and scallops. The Vibrio organism does not change the taste, appearance or odor of the seafood; and proper cooking methods are the only reliable method for killing the organism. Individuals who ingest inoculated seafood often complain of fever, diarrhea, nausea and vomiting. Of those who seek medical attention, roughly 50% have mental status changes and nearly 1/3 are in septic shock at the time of presentation. Within 24 hours of symptom onset, more than half of patients develop the characteristic skin lesions of severe cellulitis with ecchymoses and bullae. When Vibrio occurs via primary wound infection, the mode of transfer is from contaminated water often through an open wound. Exposure typically occurs during water related activities such as boating, fishing, or swimming but can also be occupationally linked to those who work in the seafood industry and are involved in shrimp cleaning, oyster shucking, and crabbing. Local cellulitis can rapidly progress to large, coalescent hemorrhagic bullae with necrosis, necessitating surgical debridement and possible amputation. Almost one half of these cases also have Vibrio bacteremia and nearly all have fever and chills. Rare cases of Vibrio with unusual presentations have been recorded and include self-limiting watery, non-bloody diarrheal disease and other mucosal site infections after exposure to seawater, sometimes in immunocompromised patients.

V. vulnificus is reported to be 20-30%; though for those presenting in shock, the mortality can approach 50%. And, due in large part to the rapid replication rate, death frequently occurs within the initial 48 hours of presentation. Underlying comorbidities that are associated with mortality from V. vulnificus infection include cirrhosis, hepatitis, hemochromatosis, thalassemia, metastatic cancer, transplant, AIDS, chemotherapy, and chronic steroid use. Notably though, liver disease has repeatedly been reported as the strongest independent predictor of a fatal outcome presumably due to poor nutritional status, decreased serum bactericidal activity, and a defective white blood cell function.

As was shown in the case presented here, it is not uncommon for patients to have an unrecognized exposure to Vibrio whether that be from an obscure small wound in contaminated waters or from poor recall for consumption of uncooked at-risk seafood. Furthermore, and again seen here, it is also not uncommon to uncover additional comorbid conditions that place infected individuals at a higher mortality risk, such as liver disease or other immunodeficiency. Given Vibrio’s predilection to inhabit both the mollusk community of oysters, shrimp and other shellfish as
well as its propensity for warm brackish waters, clinicians practicing in Louisiana and near the Gulf of Mexico should maintain a heightened index of suspicion for vibriosis. Particular attention should be made to patients presenting in the warmer months, those who work in and around the sea waters and to those with underlying comorbid medical conditions, in particular liver disease. And, albeit rare from a worldwide perspective, *V. vulnificus* certainly affects our local community in a unique way. With a mortality rate approaching 50% and with extreme survivor morbidity that can include amputations, surgical debridement and long hospital stay, continued clinical awareness is imperative such that early recognition of symptoms is coupled with not only immediate and aggressive surgical management but also prompt initiation of antimicrobial therapy.

REFERENCES

1. Strom MS, Paranjpye RN. Epidemiology and pathogenesis of *Vibrio vulnificus*. Microbes and Infection, 2000;177-188.

In the Department of Pathology at Louisiana State University School of Medicine in New Orleans: **Dr. Connor** is a third year pathology resident, **Dr. Jackson** is a first year pathology resident, and **Dr. McGoey** is an Associate Professor of Pathology and Residency Program Director.

The authors would like to gratefully acknowledge the support of University Medical Center New Orleans and the Orleans Parish Coroner’s Office for providing the case material for this report.