A Fish Hook and Liver Disease: Revisiting an Old Enemy

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Vibrio vulnificus is an uncommon but potentially devastating pathogen. Early recognition with prompt antimicrobial therapy and surgical treatment are key factors for a favorable outcome. Patients with diseases of the liver represent the group at highest risk of infection. However, clinicians are often unaware of underlying liver disease in these patients at the time of presentation. We present a case of fulminant V. vulnificus infection in a patient with previously undiagnosed liver disease.

CASE PRESENTATION

A 43-year-old man was swimming with friends in a local lake in the early summer when he caught his right leg on a stray fishhook. The patient removed the fishhook and resumed swimming. Six hours later, he noted swelling of his right lower extremity and blistering of the skin over the same area. The patient sought medical attention that evening and was prescribed cephalexin. Overnight, the swelling worsened with continued blistering, followed by sloughing of the skin over his right lower extremity. He presented to our hospital for further evaluation and management.

The patient denied past medical, surgical, or relevant family history. He had received a tetanus booster two years prior. He had a forty-pack year tobacco smoking history. He drank beer, but the exact quantification was not obtained. The patient denied any history of illicit drug use. His medications included the cephalexin prescribed one day prior and over-the-counter ibuprofen that he was taking for pain relief.

CME INFORMATION

TARGET AUDIENCE
The February Clinical Case of the Month is intended for family physicians, general internists, subspecialists in internal medicine, general practitioners, emergency medicine physicians, pathologists, and general surgeons.

EDUCATIONAL OBJECTIVES
After reading this article, physicians should understand the pathogenesis and epidemiology of Vibrio vulnificus infections. In addition, the physician should be able to discuss the recognition, diagnosis, and treatment of the clinical manifestations associated with V. vulnificus infections.

CREDIT
The LSMS Educational and Research Foundation designates this educational activity for a maximum of one (1) hour of category 1 credit toward the AMA Physician’s Recognition Award. Each physician should claim only those hours of credit that he/ she actually spent in the educational activity.

DISCLOSURE
Dr. Lillis has nothing to disclose. Dr. Dugan has nothing to disclose. Dr. Mills has nothing to disclose. Dr. Berner has nothing to disclose. Dr. Sanders has nothing to disclose. Dr. Hagensee has nothing to disclose. Dr. Lopez discloses that he is a member of the LSMS Journal Board and the LSMS Journal Editorial Board.

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Estimated time to complete this activity is 1 hour.
Vital signs included a temperature of 35.7° C, respirations of 28/ minute, blood pressure of 72/ 38 mmHg, and a pulse of 128/ minute. The patient was lethargic, diaphoretic, and in moderate distress, but oriented in all spheres. Examination was pertinent for icteric sclera, bibasilar pulmonary rhonchi, tachycardia, and a palpable liver edge that was described as nodular. His right lower extremity had a three-millimeter area of necrosis on the inner thigh and hemorrhagic bullae below the knee. There was also substantial right lower extremity pitting edema as well as a diminished dorsalis pedis pulse in the right foot.

Serum chemistries on presentation demonstrated a sodium of 128 mmol/ L (135-146mmol/ L), blood urea nitrogen of 39 mg/ dl (7-25 mg/ dl), creatinine of 4.2 mg/ dl (0.8-1.6mg/ dl), magnesium of 1.0 mg/ dl (1.5-2.6 mg/ dl), total protein of 4.3 g/ dl (6.0-8.0 g/ dl), albumin of 1.4 g/ dl (3.4-5.0 g/ dl), total bilirubin of 4.0 mg/ dl (<1.3 mg/ dl), direct bilirubin of 2.7 mg/ dl (0.0-0.3 mg/ dl), AST 108 u/ L (<45u/ L), ALT 37u/ L (<46 u/ L), alkaline phosphatase of 36u/ L (20-120 u/ L), and CPK 567 u/ L (50-290 u/ L). A complete blood count revealed a hemoglobin of 10.7 gm/ dl (13.5-17.5 gm/ dl), hematocrit 31.8% (40-51%), platelets 8000/ uL (130,000-400,000/ uL), and a white blood cell count of 4,400/ uL (6000-11000/ uL) with a differential of 54% neutrophils (35-65%), 18% bands (0-9%), and 5% metamyelocytes (0%). Urinalysis showed proteinuria, presence of urobilinogen, 6-10 WBC/ HPF and 0-2 fine and coarse granular casts/ HPF.

The patient was diagnosed with a necrotizing soft tissue infection and sepsis. He was intubated and required pressor support and broad spectrum intravenous antibiotics. He was immediately taken to the operating room for debridement. The following day, his right leg infection extended proximally, and a possible abdominal compartment syndrome developed. A right-above-the-knee amputation (Figure 1) and laparotomy were performed. During the latter procedure, a liver biopsy was obtained. On the second hospital day, culture of his wound from the initial debridement grew *Vibrio vulnificus*. Blood cultures taken throughout his hospitalization demonstrated no growth. The patient's antibiotics were streamlined to include doxycycline and cefepime. On the third hospital day, the patient's hepatitis panel revealed the presence of antibodies to hepatitis C. The liver biopsy (Figure 2) demonstrated mildly active, well-established cirrhosis, mild steatosis, and mild intracanalicular cholestasis. The patient’s hospital course was complicated by upper gastrointestinal bleeding and multisystem organ failure. On hospital day thirty-nine, the patient expired.

**DISCUSSION**

Although an extremely rare cause of infection, *V. vulnificus* is well recognized as a potentially devastating pathogen. Certain groups of patients are at increased risk for poor outcomes. The interrelating factors that determine the extent, severity, and scope of illness as well as the important role of prevention in the control of this infection will be the focus of this discussion.

**EPIDEMIOLOGY**

*V. vulnificus* is a naturally occurring, motile, gram-negative, curved, rod-shaped bacterium with a single polar flagellum. It is free living in estuarine and marine environments and has also been isolated from brackish inland waters. More common in tropical waters, this bacterium thrives best at temperatures greater than 18° C.1

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**Figure 1.** Right, lower leg, acute fascitis: A heavy, acute inflammatory infiltrate courses through the skeletal muscle and adipose tissue. Necrotic muscle cells with their loss of nuclei and indistinct cell borders are prominent. Hematoxylin and Eosin, 100x.

**Figure 2.** Liver, cirrhosis: Thick bands of connective tissue divide the hepatic lobules into small, regenerative nodules and distort the normal architecture. The fibrous connective tissue extends from portal tract to portal tract and also from portal tract to central vein. A mononuclear cellular infiltrate is present.
The organism has been found in many parts of the world, including Europe, Australia, South America, and Korea. In the United States, it is most prevalent in the southeastern Gulf Coast waters, but can also be found off the New England and northern Pacific coasts. *V. vulnificus* lives best in low to moderate salinities and concentrates in the gut of scallops, clams, mussels and oysters (1 X 10^3 to 1 X 10^6 bacteria per gm of oyster). It can also be found in the intestines of estuarine fish that inhabit oyster reefs off the US Gulf Coast. Thorough cooking of seafood is the only definitive method of killing these bacteria.

*V. vulnificus* causes three types of infections: an invasive septicemia from ingestion of raw or undercooked seafood, a necrotizing wound infection from contact with contaminated shellfish or marine waters, and a gastroenteritis from eating raw shellfish. In 1999, there were 11 cases of wound infection and two cases of primary septicemia reported in Louisiana. These statistics differ from national statistics. From 1988-1996, 422 *V. vulnificus* infections were reported to the CDC from 23 states. Of these, 45% were wound infections, 43% were primary septicemia, 3% were gastroenteritis, and 7% were unknown. On average, 50 cases per year are reported nationally. The warmer summer months from May to October are prime times for infection. These are also the months of highest recreational water exposure, which undoubtedly played a role in the case of our patient who acquired the infection in late June.

*V. vulnificus* is the leading cause of seafood-related fatalities in the US, a reflection of the severity of septicemia and necrotizing fasciitis infections. Overall, septicemia causes 58% of infections, but 83% of all fatalities. Furthermore, 96% of patients with primary septicemia consumed raw oysters, and of these, 61% died. Wound infections comprised approximately one-third of the reported cases, but only caused 8% of the fatalities. The overall incidence of infection, however, remains rare. Of 100,000 inhabitants per year. For example, in Florida there are only 5-10 infections per year despite the 70,000 people at risk (ie, liver disease, etc.) who eat raw oysters.

There is a clear male prevalence to this infectious disease, with a male to female ratio of 6:1. In fact, cases reported to the Centers for Disease Control revealed an 86% male predominance. Much of this can be explained by lifestyle. Exposure to *V. vulnificus* occurs in high-risk occupations which include any exposure to seawater or shellfish. Fishermen, shrimpers, oyster shuckers, those who do crabbing, shellfish cleaners, and shipyard workers are at increased risk. Recreational activities such as swimming, boating, and wading also result in exposure to the bacterium. Sixty-nine percent of cases reported either fishing or handling raw seafood in the 7 days prior to symptom onset. Another hypothesis is that the higher iron content found in the blood of men provides a more favorable environment for *Vibrio* proliferation. In summary, males consume more raw oysters, have increased rates of liver disease and alcoholism, have increased iron stores, and have increased occupational exposure to raw seafood and seawater, all possibly contributing to the increased risk for infections with *V. vulnificus*.

**HOST FACTORS**

As in many infectious diseases, host factors play a critical role in outcome. With *V. vulnificus*, predisposing medical conditions determine whether there is simple exposure without illness at one end of the spectrum to fulminant, lethal infection at the other end. Susceptible hosts include patients with chronic diseases, hematologic conditions, and compromised immune systems. The greatest predisposition occurs with liver conditions such as cirrhosis, alcoholic liver disease, hepatitis, metastatic liver disease, hepatoma, or transplanted livers. In patients with primary septicemia, liver disease is the most common risk factor, present in up to 80% of patients and in 87% of fatalities. Liver disease was also a predictor of fatal outcome for wound infections, reported present in 80% of fatal versus 35% of nonfatal cases. Undoubtedly, our patient's course was greatly influenced by his underlying liver disease as he had both cirrhosis and hepatitis C. Hematological conditions like hemochromatosis and thalassemia major that increase serum iron levels are also predisposing factors. Patients with a compromised immune system such as those with AIDS, a history of splenectomy, chronic steroid use, and those undergoing chemotherapy are also at increased risk of infection with *V. vulnificus*. Other chronic conditions such as diabetes mellitus, renal disease, chronic intestinal disease, and low gastric acid level (natural or therapeutically-induced) also have been implicated in predisposing patients to infection.

A study by Hor et al links survival of *V. vulnificus* not only to the presence of liver disease, but also to increased serum ferritin concentration and percent of transferrin iron saturation. Low phagocytic activity by neutrophils and a high ferritin level were statistically significant independent predictors for *V. vulnificus* survival in blood. In this study, patients with cirrhosis and hepatocellular cancer demonstrated a decrease in phagocytic activity. Thus, it appears that *V. vulnificus* survives and multiplies more rapidly when phagocytosis is hampered and serum ferritin levels are elevated. Shapiro et al also found an increased transferrin iron saturation in 86% of patients with primary septicemia who had liver disease or a history of alcohol abuse, suggesting the un-
derlying problem may be one of iron regulation. Another reported potential risk factor is peptic ulcer disease, which results in disruption of the gastric mucosa and increased rates of bacteremia after ingestion of raw shellfish.

**VIRULENCE FACTORS**

The lethal dose of this bacterium is unknown. When grown on a variety of media, three types of colonies predominate: opaque, translucent, and mixed colonies. The opaque colonies show serum resistance, antiphagocytic activity, tissue invasiveness, and increased lethality. The presence of an acidic, polysaccharide capsule is associated with increased virulence, and is present only in the opaque colonies. Furthermore, these opaque colonies are also able to utilize transferrin-bound iron. Translucent cells have a much higher 50% lethal dose and cannot utilize transferrin-bound iron. These colonies also will not revert to the more virulent cell type, suggesting that perhaps there is some selection or mutation that favors the less virulent translucent colony type. This speculation would explain the relatively low incidence of *V. vulnificus* infections.

Though encapsulation is the most critical virulence factor of *V. vulnificus*, other factors deserve mention. Iron availability in human serum is essential. This bacterium also produces a cytolysin that lyses red blood cells and enhances vascular permeability in animal models, consistent with the clinical picture of sepsis and diffuse intravascular coagulation seen in humans. Organism-associated proteases (like collagenase and elastase), phospholipases and chondroitin-sulphatase also contribute to cell destruction. *V. vulnificus* can also adhere to epithelial cell surfaces.

**CLINICAL SYNDROMES**

Illnesses associated with *Vibrio vulnificus* can be categorized as primary septicemia, wound infection, or self-limited gastroenteritis. The severity of each of these relies on the presence of underlying medical illnesses. Primary septicemia is defined as a systemic illness characterized by fever and shock where *V. vulnificus* is isolated from blood or other normally sterile site(s) in a patient with a history of raw shellfish consumption but no wound infection preceding the illness. This syndrome represented 43% of *V. vulnificus* presentations in a review of cases between 1988 and 1996. The majority of the enteric exposure was from raw oysters, but raw clams, and raw crabs also have been implicated.

Ninety percent of patients with primary septicemia will present with sudden onset of fever and chills. Gastrointestinal symptoms such as nausea, vomiting, or diarrhea are only apparent 50% of the time. Shock will ensue in 60% of patients and mental status changes in 50%. Most characteristic are skin manifestations that can vary from maculae, petechiae, and purpura to the more ominous signs of ecchymoses and hemorrhagic bullae. These bullae can rapidly develop into cellulitis, necrotizing fasciitis, gangrene, and pyomyositis. Skin changes are usually apparent on admission or within 24 hours thereafter. It is hypothesized that they result from hematogenous spread of the organism. In one study, *Vibrio* was cultured from skin lesions in 21% of patients with primary septicemia. Hematologic abnormalities noted upon presentation include a leukopenia or leukocytosis, thrombocytopenia, or diffuse intravascular coagulation.

Mortality ranges from 60% to 75% in patients with primary septicemia. Most patients who die will do so within the first 48 hours. Mortality rates are greatly affected by early recognition, antibiotic therapy, and prompt surgical intervention. The patient that presents with hypotension within 12 hours of admission has a 90% mortality rate, twice that of patients who remain hemodynamically stable.

*V. vulnificus* may also present as a wound infection in the patient who has incurred a wound before or during exposure to seawater or seafood drippings. This most likely was the source of our patient’s infection. He had been swimming in brackish water, was injured by a fishhook during that time, and subsequently, developed a necrotizing soft tissue infection. Wound infections represented 45% of 422 *V. vulnificus* infections reviewed between 1988-1996 by the CDC. Of these 189 cases, 50% sustained the wound at the time of exposure, 21% had a preexisting wound such as venous stasis ulcers, and 29% could not time the presentation of the wound. Frequently, the exposure was occupationally-related, ie, initiated by a minor wound suffered while shucking oysters, cleaning crabs, or peeling shrimp.

A wound infection from *V. vulnificus* is acquired through direct inoculation of contaminated seawater or seafood into an acute or preexisting wound. The wound can be mild and limited or present with associated fever, chills, and painful swelling. It can progress rapidly with three recognized stages that may advance in as short as 18 hours from time of contact to tissue necrosis and secondary septicemia. Erythema, localized swelling, and evidence of infiltration with polymorphonuclear cells and extravasation of red blood cells mark the inflammatory stage. The second (or bullous) stage manifests as subepidermal bullae and vasculitis. The third (or gangrenous) stage consists of necrosis of the entire skin surface, transmural necrotizing vasculitis, and small vessel thrombosis. One-third of these patients will develop a secondary bacteremia, often with hemodynamic compromise. The secondary bacteremia is thought to be responsible for secondary skin lesions that develop at a site distant from the original wound. Mortality is greater in those with underlying liver disease, because they are more likely to develop secondary
bacteremia. Wound infections associated with *V. vulnificus* generally have a 20% to 30% mortality rate.9

Gastroenteritis is defined as illness with abdominal cramps, vomiting, or diarrhea with no evidence of wound infection and where *V. vulnificus* is isolated from the stool alone. Five percent of 422 cases associated with *Vibrio vulnificus* infection reviewed between 1988-1996 by the CDC presented in this manner.2 Vomiting, diarrhea and abdominal pain are common symptoms. Isolating the organism from the stool is considered diagnostic. There is some debate as to whether this syndrome exists since other causes of infectious gastroenteritis are often not pursued in the cases reported in the literature.2 Most cases are self-limited so it is also thought that this syndrome is greatly underreported, as patients may not present for evaluation or require hospitalization.

**DIAGNOSIS**

A high degree of suspicion is warranted when patients present with necrotizing skin infections or sepsis after ingestion or exposure to seawater or seafood. *V. vulnificus* infections are usually observed in the warm summer months between May and October.13 In the emergency room, a Gram stain of the fluid aspirated from the bullous skin lesions may reveal curved gram-negative rods suggestive of the diagnosis. Blood cultures are positive in 70% to 100% of patients with primary sepsisemia and in 30% of those with wound infections and secondary bacteremia.9

**TREATMENT**

Because death usually occurs in the first 48 hours, a high degree of suspicion must be maintained so that early recognition, antibiotic therapy, and surgical intervention can occur. Mortality rates of 33% associated with a delay in initiation of antibiotic therapy of 24 hours were increased to as high as 100% in cases when the delay of antibiotic therapy was greater than 72 hours.10

*V. vulnificus* is susceptible to many antibiotics in vitro. A Taiwanese report of 28 cases of *Vibrio vulnificus* recommended combined therapy with a third generation cephalosporin or ampicillin and an aminoglycoside in addition to appropriate surgical therapy.14 However, some authorities advocate the use of doxycycline and cefazidime as first line therapy.15 Optimal supportive care for shock and fluid loss is imperative.

It has been observed that widespread obliteration of vasculitis and vascular necrosis limit the effective penetration of antibiotics to affected areas, mandating the need for early surgical debridement.16 A small prospective series of 7 cases of primary *Vibrio* skin infections evaluated the outcomes associated with early and late surgical intervention (less than or greater than 72 hours, respectively).12 Four of seven patients had evidence preoperatively of skin necrosis, but all had necrosis of the underlying subcutaneous tissue. Small vessel thrombosis was also present in the subcutaneous tissue. In this small series, early surgical debridement decreased mortality and duration of ICU and hospital stay. In other series, mortality rates vary from 25% to 100% in those who did not undergo debridement.10 Forty percent to 100% mortality rates are reported in patients with underlying chronic illness who do not undergo debridement.6

**PREVENTION**

Several methods have been proposed to reduce the incidence of *V. vulnificus* infections. One study by Shapiro et al demonstrated an association between *Vibrio* infections and summer oyster harvesting.4 Although not economically feasible, the practical implication is to avoid harvesting oysters in the summer. Epidemiological studies have consistently shown that certain groups of patients are at greatly increased risk of infection with *V. vulnificus*. With this in mind, certain states have passed laws requiring restaurants and other businesses that sell Gulf Coast oysters to post warnings about the possible risk of infection in people with liver disease, cancer and chronic illnesses. A study published in 1997 examined the efficacy of these posted warnings in Los Angeles County.17 During the 27-month study period, eleven cases of *Vibrio vulnificus* were diagnosed despite this preventative strategy. The investigators found that warning signs were not posted in 25% of stores and 50% of restaurants implicated in the infections. This preventative strategy does not address patients such as ours who obtain the infection through recreational swimming. In Louisiana in 1999, 54% patients with *V. vulnificus* wound infections reported no history of shellfish consumption, but only exposure to seawater.3

Additional steps must be taken to warn patients at risk of the possible consequences of raw oyster consumption and exposure to potentially contaminated seawater. Because patients with liver disease, a history of excess alcohol consumption, diabetes, renal disease, peptic ulcer disease, and malignancy represent the population at greatest risk, healthcare providers should include educating these patients about the risk of *V. vulnificus* infection through exposure to seawater or consumption of raw oysters as part of routine preventative medical practice, particularly in endemic areas such as Louisiana.

**REFERENCES**

2. Strom MS, Paranjpye RN. Epidemiology and pathogenesis of *Vibrio vulnificus*. Mirobes and Infection 2000; 177-188.
Clinical Case of the Month


The Clinical Case of the Month is a regular educational feature presented by the Louisiana State University Department of Medicine in New Orleans. Medical students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these discussions.

CME QUESTIONS

To earn CME credit, read the CME article and complete the registration, evaluation, and answer form on page 47. Mail or fax the registration, evaluation, and answer form to the ERF. Answers must be postmarked or faxed prior to February 28, 2003. Participants must attain a minimum score of 70% to receive credit.

For each question, choose the one answer that is most correct.

1. True or False: Vibrio vulnificus grows best in waters that are cooler than 18 degrees Celsius.
2. True or False: V. vulnificus infections are found only in the southeastern United States.
3. True or False: V. vulnificus is the leading cause of seafood-related fatalities in the US.
4. True or False: V. vulnificus infection is greatest during the winter months.
5. Vibrio vulnificus typically causes all of the following syndromes except:
   a) Septicemia
   b) Meningitis
   c) Diarrhea/gastroenteritis
   d) Wound infections
6. Which of the following clinical syndromes of V. vulnificus infection has the highest case fatality rate:
   a) Septicemia
   b) Wound infections
7. Risk factors for the development of V. vulnificus infection commonly include all of the following except:
   a) Liver disease
   b) Hemachromatosis
   c) Achlohydria
   d) Unprotected sexual activity
8. Healthcare practitioners should warn which of the following groups of patients about the risk of infection with V. vulnificus with raw shellfish consumption:
   a) Patients with liver disease
   b) Patients with Thalassemia major
   c) Patients without a spleen
   d) Patients on chronic steroid therapy
   e) All of the above

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