Vibrio vulnificus Sepsis Successfully Treated with Antibiotics, Surgical Debridement, and Recombinant Human Activated Protein C

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A 43-year-old Vietnamese man presented in the morning to a local hospital with a chief complaint of left lower extremity pain and redness of the ankle and calf for 2 days. The patient was evaluated, given a prescription for cephalexin, and discharged home with a diagnosis of cellulitis. Later the same day, the patient presented to another hospital with the development of black bullae on his left leg. The patient's pain had increased in severity and was exacerbated with movement of the left foot. He also complained of fevers and chills. He denied any history of recent trauma, spider or insect bites, or wading in water. Three days prior to his admission, he had consumed partially cooked oysters.

The patient's medical history was significant for type 2 diabetes mellitus, chronic hepatitides B & C, cirrhosis, alcohol abuse, and hypertension.

Physical examination in the emergency room revealed a blood pressure of 99/45 mmHg, a heart rate of 111 beats/minute, a respiratory rate of 20 breaths/minute, and a temperature of 37.4° Celsius. Crackles were auscultated at the base of the right lung. Multiple spider hemangiomata were present on the trunk. The liver was palpated 1cm below the right costal margin. The spleen tip was palpable 3 cm below the left costal margin. The left lower extremity had multiple, large, coalescing purpuric and bullous skin lesions over the anterolateral tibial region (Figure 1). The right lower extremity was normal.

Abnormal laboratory studies included a white blood cell count of 15.4 $x10^3/mm^3$ (normal range, 4.5-11.0 $x10^3/mm^3$) with 25% bands, a platelet count of 37 $x\ 10^3/mm^3$ (normal range, 130-400 $x10^3/mm^3$), an MCV of 104.1 (normal range, 80-100 FL), a serum iron of 30 μg/dl (normal range, 40-160 ug/dL), and a total iron binding capacity of 139 ug/dL (250-425 ug/dL). Gram stains of the bullous skin lesions revealed Gram negative rods. Blood cultures 24 hours after admission revealed the growth of Gram-negative rods (Figures 2 & 3).

The patient was admitted to the medical intensive care unit with a diagnosis of Gram-negative sepsis. He was immediately started on broad-spectrum antibiotics and subsequently required vasopressor support. *Vibrio vulnificus* was isolated from all admission blood cultures.

CME INFORMATION

TARGET AUDIENCE

The May/June Clinical Case of the Month is intended for family physicians, general internists, medicine subspecialists, general practitioners, critical care specialists, obstetricians-gynecologists, emergency medicine physicians, pediatricians, dermatologists, radiologists, and psychiatrists.

EDUCATIONAL OBJECTIVES

The Clinical Case of the Month is a regular educational feature from the Department of Medicine at the LSU Health Care Sciences Center. Medical students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these discussions. After reading this article, physicians should be able to better identify and understand the pathophysiology, microbiology, clinical presentation and treatment of sepsis due to *Vibrio vulnificus*.

CREDIT

The LSMS Educational and Research Foundation designates this educational activity for a maximum of one (1) 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. Anand has nothing to disclose.
Dr. Lopez discloses that he is a member of the LSMS *Journal* Board and the LSMS *Journal* Editorial Board.
Dr. deBoisblanc has nothing to disclose.

ORIGINAL RELEASE DATE	EXPIRATION DATE
6/1/2004	6/30/2005

Estimated time to complete this activity is 1 hour.

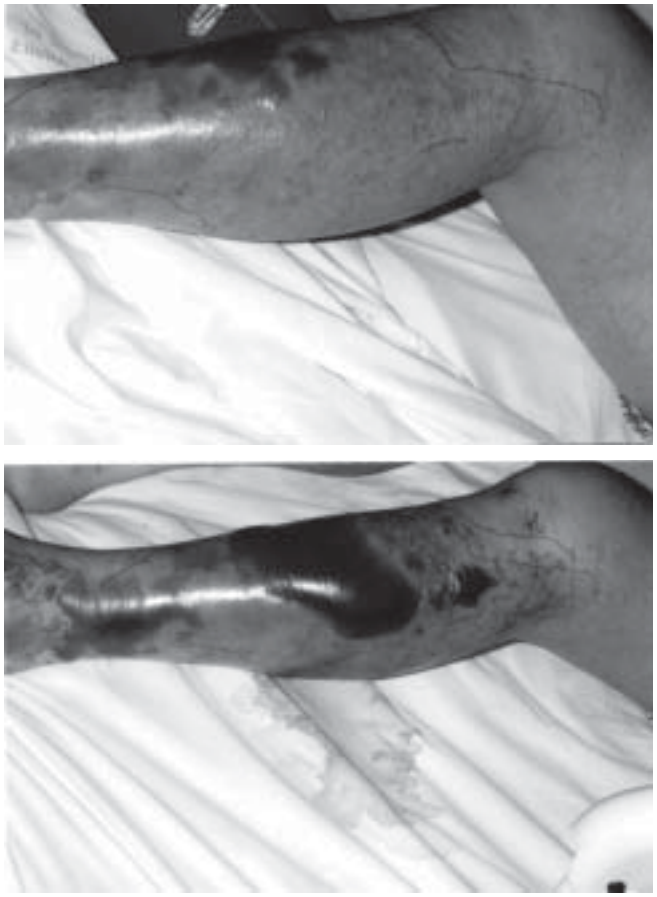

Figure 1. The top photograph is of the patient's leg at the time of admission. The bottom photograph demonstrates rapid progression of the lesions after only 10 hours.

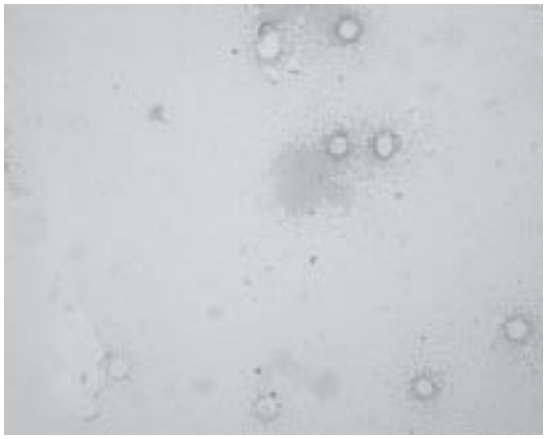

Figure 2. Gram stain of wound demonstrating Gram-negative rods.

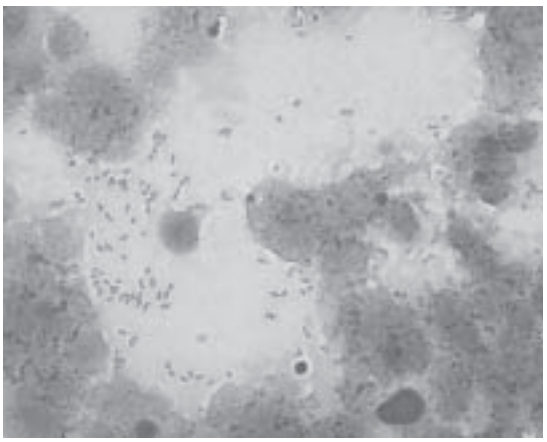

Figure 3. Gram stain of blood culture demonstrating numerous Gram-negative rods.

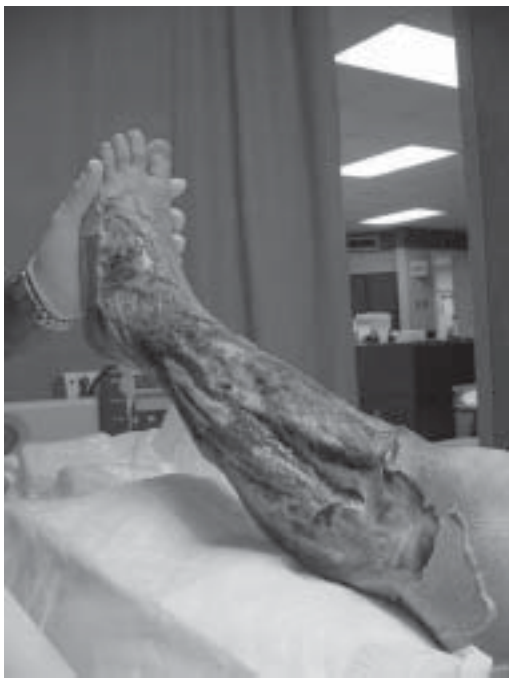

Figure 4. Post-operative photograph demonstrating extent of surgical debridement.

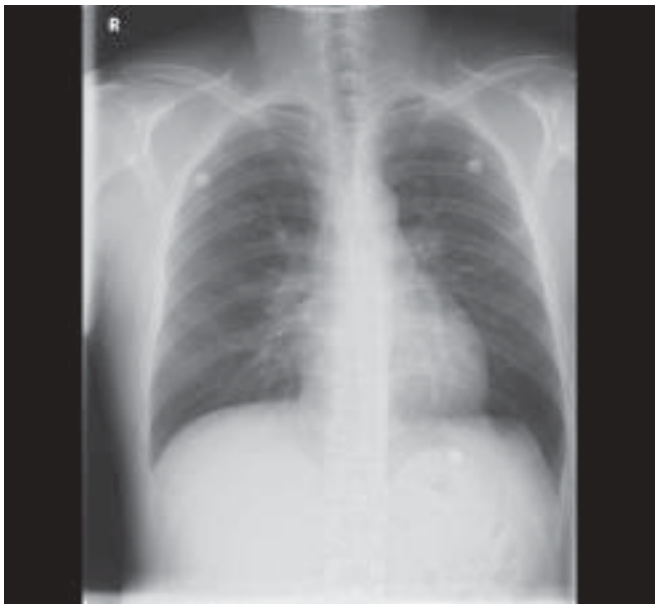

Figure 5a. Admission Chest x-ray is normal.

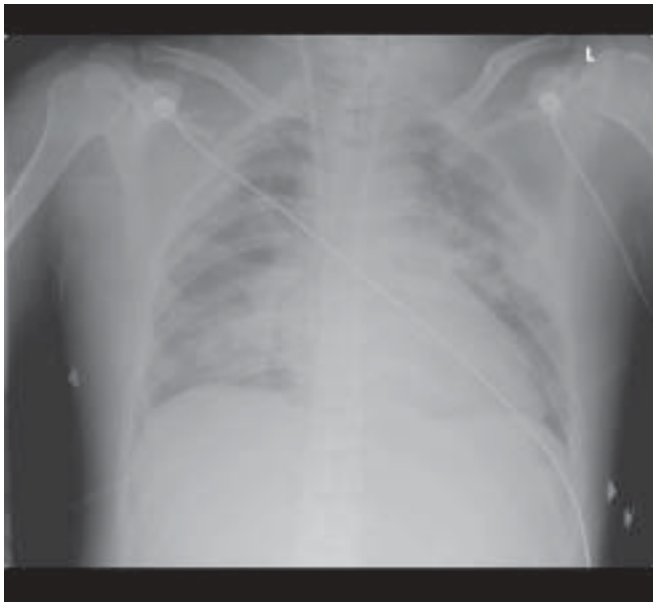

Figure 5b. Chest x-ray after surgical debridement demonstrating diffuse airspace opacities consistent with a pattern of acute lung injury.

Antibiotic coverage was tailored to include cefepime and doxycycline. Surgical debridement of the extremity was required (Figure 4). Immediately after surgery, the patient developed the acute respiratory distress syndrome (Figure 5a & 5b), acute renal failure, disseminated intravascular coagulation, and an episode of reversible asystole. Because of the patient's multi-system failure, recombinant human activated protein C (drotrecogin alfa activated, Xigris®) was initiated at an infusion rate of 24μg/kg/hr for a total duration of 96 hours. The patient's septic shock and multi-system organ dysfunction slowly improved over the subsequent 24 hours. Within 7 days, the patient was extubated and transferred from the intensive care unit to continue long-term surgical care of his wounds.

DISCUSSION

Historically, only antibiotics, surgical interventions, and supportive care could be offered to patients suffering from sepsis of any cause. Even with early antibiotic and surgical intervention, *Vibrio vulnificus* sepsis carries a 50% mortality rate, that increases to greater than 90% in the presence of hypotension.[1,2,3] In the face of such a poor prognosis, the use of recombinant human activated protein C can be advocated for patients with *Vibrio vulnificus* sepsis.

Vibrio vulnificus is a Gram-negative bacterium whose virulence is strongly associated with a polysaccharide capsule that triggers the release of proinflammatory cytokines such as TNF-a and interleukin-6.[4,5] Prior studies have demonstrated that the inflammatory and the procoagulant host responses to infection are closely related.[6] The end result of activating the inflammatory and coagulation cascades is endovascular injury, multiorgan dysfunction, and eventually death.

A reduced level of activated protein C has been associated with an increased risk for death in patients with sepsis.[8] Boehme and colleagues demonstrated that during sepsis, levels of endogenous activated protein C may be impaired via down-regulation of thrombomodulin by inflammatory cytokines.[7] In the normal host, the coupling of thrombin to thrombomodulin is responsible for the conversion of protein C to activated protein C.

In a placebo-controlled, phase 2 trial an infusion of recombinant human activated protein C in patients with sepsis resulted in dose-dependent reductions in the plasma levels of D-dimer and serum levels of interleukin-6, markers of coagulopathy and inflammation, respectively.[9] Thus, it appears that recombinant human activated protein C is a drug with significant antithrombotic, anti-inflammatroy, and profibrinolytic properties.

A recent trial published by the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis study group evaluated whether the administration of recombinant human activated protein C would reduce mortality from all causes at 28 days in patients with severe sepsis due to different organisms and have an acceptable safety profile. Severe sepsis was defined as sepsis associated with acute organ dysfunction. Treatment with recombinant human activated protein C was associated with a 6.1% ($P = 0.005$) absolute reduction in the risk of death and a 19.4% (95% confidence interval, 6.6-30.5%) reduction in the relative risk of death from any cause in patients with severe sepsis. The incidence of serious bleeding with recombinant human activated protein C was increased over the placebo rate (3.5% vs. 2.0%, $P = 0.06$).[10]

Vibrio vulnificus sepsis is a morbid and potentially fatal condition. It appears that recombinant human activated protein C is a drug well designed to address the proinflammatory and prothrombotic complications that are characteristic of *Vibrio vulnificus* sepsis.

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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 preceding CME article and complete the registration, evaluation, and answer form on page 167. Mail or fax the registration, evaluation, and answer form to the Educational and Research Foundation. Answers must be postmarked or faxed prior to June 30, 2005. Participants must attain a minimum score of 75% to receive credit.

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

1. The mortality rate for sepsis due to *Vibrio vulnificus* is:
   a) 5-15%
   b) 20-30%
   c) >50%

2. Therapeutic approaches to *Vibrio vulnificus* sepsis potentially include all of the following except:
   a) Supportive care including intravenous fluids as needed
   b) Antibiotics
   c) Vibrio antitoxin
   d) Surgical debridement for necrotizing skin lesions

3. True or False. Recombinant human activated protein C is indicated for use only in patients with severe sepsis due to Gram-negative bacteria.

4. All of the following are true statements except:
   a) *Vibrio vulnificus* is a Gram-negative bacterium whose virulence is associated with a polysaccharide capsule.
   b) Serious bleeding is not an adverse event associated with the administration of recombinant human activated protein C.
   c) Recombinant human activated protein C is a drug with significant antithrombotic, anti-inflammatroy, and profibrinolytic properties.
   d) Treatment of patients with severe sepsis with recombinant human activated protein C reduces the risk of death from any cause.