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Leptospirosis During Adventure Travel

SPECIAL FEATURE

On aug. 20, 2000, the ecochallenge sabah 2000 expedition race began in Malaysian Borneo. This event attracted 76 four-person teams from 26 countries, and included 36 teams from the United States and five teams from Canada. The EcoChallenge race is an intense, multisport event requiring participants to trek through jungles, swim in open water, canoe and kayak in rivers and oceans, mountain bike, scuba dive, spelunk, and climb their way through 320 miles of Borneo wilderness. In the words of the EcoChallenge promotional material "competitors will navigate through ancient caves and paddle along winding rivers in indigenous Sampan canoes where herds of elephants, monkeys, crocodiles, and even the rare Sumatran rhino can be seen. Teams will trek and mountain bike along dense rain forest trails while orangutans and ancient tribes of once fierce headhunters will curiously watch their passing. Teams will sail through tropical seas to magical coral-fringed islands using the native Perahu outrigger canoes and even dive down to an underwater coral reef checkpoint. Teams will negotiate swift jungle rivers and rappel down cascading waterfalls using fixed ropes."[1] The event ran from Aug. 20 to Sept. 3 with participants taking anywhere from 6-12 days to complete the course, racing nonstop. Forty-four teams completed the race. Further details about EcoChallenge can be found at www.ecochallenge.com.

Beginning in early September, racers began to present with an acute febrile illness to health care professionals in their home countries. Reports to the GeoSentinel network[2] and to the Centers for Disease Control (CDC)[3] quickly began to accumulate, and helped to describe the nature of the illness and the extent of involvement. Of 153 athletes interviewed by the CDC up to late October, 68 (44%) met the case definition of an illness characterized by fever with at least two of the following symptoms: chills, myalgias, headache, diarrhea, or conjunctivitis (M Cetron, CDC, personal communication). Thirty-seven percent of case patients

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were hospitalized with no deaths occurring. The typical clinical syndrome included fever and myalgias with proteinuria, mildly elevated liver enzymes, and an increased serum CK level. Based on the characteristic clinical syndrome combined with positive serology in 13 of 27 (48%) U.S. case patients, a diagnosis of leptospirosis was made. Other clinically similar tropical diseases, including malaria, were ruled out. Among multiple potential exposures, participants encountered severely flooded rivers beginning on Aug. 25. Exposure during the river swim was significantly associated with illness.

COMMENT BY DAVID R. HILL, MD, DTM&H

Leptospirosis is an uncommon, but well-recognized cause of acute febrile illness in both travelers and native inhabitants of temperate and tropical areas of the world.[4-9] *Leptospira* spp. are motile spirochetes that infect both domestic and wild animals. Dogs, livestock, and rats are the most commonly infected animals throughout the world. Organisms can survive for long periods in the kidneys of animals and then are excreted in urine, contaminating water, mud, or moist soil. When humans come into contact with the organism by swimming in or drinking contaminated water, or being covered with mud, as can easily occur during adventure travel, organisms penetrate mucous membranes or cuts and abrasions and establish infection. Heavy rainfall facilitates the spread of organisms, because as water saturates the environment, leptospires become washed into surface water. During times of flooding, there have been well-documented increases in leptospirosis. Fiji and Thailand are currently experiencing outbreaks. Flooding in Nicaragua in 1995[10,11] and in Guatemala, Honduras, and Nicaragua in 1998, in association with Hurricane Mitch, led to a marked increase in cases. Leptospirosis is also well-recorded in adventure travelers occurring in river rafters in Thailand[7] and Costa Rica.[12] In the summer of 1998, triathletes in Illinois experienced leptospirosis following their swim in a rain-swollen lake.[5,13] The outbreak in triathletes affected 11% of participants; based on preliminary information, this current outbreak in Sabah had an extremely high attack rate of more than 40%.

Following an incubation period of four days to 2-3 weeks, the illness begins abruptly and is characterized by fever, chills, myalgias, and headache. Conjunctivitis, abdominal pain, vomiting, and diarrhea are also seen. A severe illness known as Weil's disease with renal and hepatic, and rarely pulmonary involvement, can be life threatening.

Although treatment of mild illness is controversial, the CDC was recommending therapy of mild disease with doxycycline 100 mg twice daily for a week.[3] Severely ill, hospitalized patients should be treated with intravenous penicillin.[14] Evidence from U.S. troops stationed in Panama indicated that prophylaxis with 200 mg of doxycycline weekly is effective.[15]

There are several points for travel medicine experts. The first point is to consider leptospirosis in the differential diagnosis of an acute febrile illness in returned travelers, particularly if they have had fresh water exposure through recreational activities such as diving, swimming, or river rafting, or through occupational exposure with work in rice fields, sewer systems, or with handling of potentially infected animals.

The second is to inform travelers of leptospirosis if their plans would put them at risk and to become involved as advisors to tour groups or adventure racing promoters to provide accurate information about tropical disease risk. There has to be improved communica-

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tion between the travel industry and travel medicine providers. Organizers of adventure travel may not emphasize the risk of disease in favor of promoting the exciting nature of their trip. Indeed, leptospirosis had occurred several times previously in adventure racers, some of whom were racing again in 2000 EcoChallenge, but it does not appear that this disease was adequately considered by race organizers.[16] Racers may not focus on tropical disease risk during their period of intense training and be more concerned about accident or injury.

Third, if a traveler will be at great risk for leptospirosis, they should consider prophylaxis with doxycycline 200 mg weekly. It will be of interest to see if EcoChallenge racers who may have been taking doxycycline either for chemoprophylaxis of leptospirosis or malaria were protected from illness.

Finally, the benefits of a global surveillance system for tropical or travel-related disease with rapid dissemination of information are clearly illustrated with this outbreak. Within days, the GeoSentinel network had identified cases presenting to three sites in three different countries. In conjunction with CDC and WHO, information was provided via tropical and travel medicine e-mail list serves and the Internet (CDC web site [www.cdc.gov/travel/], EcoChallenge web site, and ProMed[17]), so that physicians could identify illness and participants could receive appropriate evaluation and treatment. Earlier in 2000, this surveillance system helped to rapidly identify an outbreak of W-135 meningococcal disease in religious pilgrims who traveled to Mecca for the annual Hajj.[18] Thus, travel medicine health professionals should consider joining the American Society of Tropical Medicine and Hygiene (www.astmh.org) and/or the International Society of Travel Medicine (www.istm.org) so that they can participate in this global information network. (*Dr. Hill is Associate Professor of Medicine; Director, International Travelers' Medical Service, University of Connecticut, Storrs, Conn.*) ❖

References

1. EcoChallenge 2000. Field notes about the 2000 race. http://www.ecochallenge.com/borneo/borneo.htm. Accessed on Oct. 13, 2000.
2. The GeoSentinel network is a global surveillance system with 26 sites throughout the world, coordinated by the Centers for Disease Control and the International Society of Travel Medicine. It can be contacted via e-mail at istm@geomed.dom.uab.edu.
3. Centers for Disease Control and Prevention. Outbreak of acute febrile illness among participants in EcoChallenge Sabah 2000—Malaysia, 2000. *MMWR Morb Mortal Wkly Rep* 2000;40:816-817.
4. Hill DR. Leptospirosis in Nicaragua. *Travel Medicine Advisor Update* 1996;6:10-12.
5. Hill DR. Waterborne infectious disease outbreaks: Cryptosporidiosis and leptospirosis. *Travel Medicine Advisor Update* 1998;8:42-45.
6. Bia F. Symposium: Leptospirosis—a re-emerging disease. *Travel Medicine Advisor Update* 1998;8:5-7.
7. van Crevel R, et al. Leptospirosis in travelers. *Clin Infect Dis* 1994;19:132-134.
8. Farr RW. Leptospirosis. *Clin Infect Dis* 1995;21:1-8.
9. World Health Organization. Leptospirosis worldwide, 1999. *Wkly Epidemiol Rec* 1999;74:237-242.
10. Centers for Disease Control and Prevention. Outbreak of acute febrile illness and pulmonary hemorrhage—Nicaragua, 1995. *MMWR Morb Mortal Wkly Rep* 1995; 44:841-843.
11. Trevejo RT, et al. Epidemic leptospirosis associated with pulmonary hemorrhage—Nicaragua, 1995. *J Infect Dis* 1998;178:1457-1463.
12. Centers for Disease Control and Prevention. Outbreak of leptospirosis among white-water rafters—Costa Rica, 1996. *MMWR Morb Mortal Wkly Rep* 1997;46: 577-579.
13. Centers for Disease Control and Prevention. Update: Leptospirosis and unexplained acute febrile illness among athletes participating in triathlons—Illinois and Wisconsin, 1998. *MMWR Morb Mortal Wkly Rep* 1998;47:673-676.
14. Watt G, et al. Placebo-controlled trial of intravenous penicillin for severe and late leptospirosis. *Lancet* 1988;1:433-435.
15. Takafuji ET, et al. An efficacy trial of doxycycline chemoprophylaxis against leptospirosis. *N Engl J Med* 1984;310:497-500.
16. Levy B. Lurking dangers. Risk and reward in adventure racing. MountainZone.com. http://adventure.mountainzone.com/2000/afiles/risk/html/index_1.html. Accessed Oct. 13, 2000.
17. ProMed (Program for Monitoring Infectious Diseases) is an e-mail list serve alerting subscribers to developments in infectious disease throughout the world. To subscribe send a message to: Majordomo@usa.healthnet.org, followed by: subscribe ProMed digest. It can also be accessed on the Internet at: http://www.promedmail.org.
18. Centers for Disease Control and Prevention. Serogroup W-135 meningococcal disease among travelers returning from Saudi Arabia—United States, 2000. *MMWR Morb Mortal Wkly Rep* 2000;49:345-346.

The Chief Resident Presenting with a Coral Cut Injury: Infections From the Sea

CASE REPORT

By Marc A. Ciampi, MD, and Andre N. Sofair, MD, MPH

A 30-year-old previously healthy male presented with pain in his left knee and left groin. Five days prior to presentation, he had scraped his exposed left knee against a large brain coral while snorkeling in the Caribbean, near the island of Aruba. He noted local erythema, slight pruritus, and a small abrasion. After irrigating the wound, the patient used topical antibacterial cream daily. He remained afebrile with no evidence of local or systemic complaints. He denied significant pain, increasing erythema, or wound drainage. On the day of presentation, the patient developed notable groin tenderness and mild left-sided lumbar pain along with increasing knee pain. He denied fever, chills, night sweats, or fatigue. He had no significant past medical history and was taking no medications. He had no known allergies and denied recent ingestion of shellfish.

The patient was afebrile with normal vital signs and general appearance. Physical examination of his knee was notable for the presence of a raised, slightly erythematous rash showing a dermatograph of brain coral, and a 2 mm abrasion with no significant drainage or fluctuance. The joint was normal with no evidence of effusion or inflammation. The left leg revealed tender inguinal lymphadenopathy without lymphangitis. Abdominal examination showed mild left upper quadrant and left costovertebral angle tenderness; a spleen tip was not palpated.

He was empirically started on an oral fluoroquinolone antibiotic, levofloxacin, to treat his soft tissue infection. Oral doxycycline was added one day later to ensure adequate coverage of various marine microorganisms. He was treated for 10 days with resolution of his groin tenderness and back pain after two days of therapy. Over three weeks, the rash resolved completely without complications.

Discussion

Contact with coral or "coral cuts" may produce significant and sometimes dramatic cutaneous reactions.[1,2] Manifestations include localized erythema, urticara, and occasional pruritus.[3] The local reaction can be a response to coral nematocysts, contamination of the wound site with microparticulate coral and calcium carbonate, possible bacterial infection, or toxin effects.

Although on a worldwide basis staphylococci and streptococci remain the most common causes of soft tissue infections, vibrios, and some *Aeromonas* spp. are virulent waterborne organisms that may infect wounds sustained in a marine environment.[1-8] *Erysipelothrix rhusiopathiae*, coliforms such as *Escherichia coli*, and *Mycobacterium marinum*, *M. balnei*, or *Pseudomonas* spp. are also capable of producing localized infections after exposure to salt water.[6] Wound infections acquired in this environment may also be polymicrobial.[7,9]

Ecology and Epidemiology

The halophilic *Vibrio* spp. are naturally free-living aerobic inhabitants of marine environments. These organisms have been found in Europe, Asia, Australia, South America, and North America.[10] In North America, they have been recovered from the waters of the Gulf coast, the entire East Coast from Florida to Maine, the California and Washington State coasts, and from the waters around Hawaii. Halophilic vibrios have been found in both water and marine sediments, adherent to plankton, or absorbed onto mollusks and crustaceans.[11] *Vibrio* spp. are taken up by filter-feeding molluscs such as oysters, clams, mussels, and scallops achieving concentrations as high as 10^6 bacteria per gram of oyster during periods of warm water temperatures. Bacteria are also found in the intestines of some estuarine fish, which may transport them between oyster beds or serve as a source of wound infections.[12]

Vibrio spp. reside in ocean water or marine estuaries within a wide range of salinity (1-34 parts per thousand). Organisms have been isolated from brackish lakes and even from the Great Salt Lake.[13] A salinity greater than 25 parts per thousand has adverse effects on their survival.

Intolerant of cold conditions, *Vibrio* spp. thrive during the summer and fall months, but they may also survive the winter months in marine sediment.[5,14-18] *Vibrio* spp. are found in zones where there is decreased dissolved oxygen concentrations, possibly reflecting increased nutrient concentrations in such areas. Vibrios are rarely found in the open ocean, likely due to colder water temperatures, the absence of nutrients, the higher hydrostatic pressures, and the relatively higher salinity.[18]

Vibrio infections are acquired either by the consumption of contaminated food and water or through skin and soft tissue injuries.[4] The primary food sources for acqui-

sition are raw/undercooked oysters or other seafoods.[4,19] In those with skin and soft-tissue infections, nearly all report prior recreational or occupational exposure to sea water or marine organisms.[9]

Clinical Presentations

Three major presenting clinical syndromes have been described for vibrios including gastroenteritis, soft tissue infection, and septicemia. There have been additional case reports of vibrio-associated otitis media, pneumonitis, keratitis, meningitis, and endometritis.[4,13]

Soft tissue infections caused by noncholera vibrios may present as one of two distinct clinical entities, primary vibrio cellulitis, or secondary cellulitis following primary bacteremia.[4] Direct cutaneous inoculation from abrasions, lacerations, or puncture wounds may result in primary vibrio cellulitis. With the exception of *V. cholerae* O1, primary vibrio cellulitis has been associated with all known *Vibrio* spp.[1,5,20-23] In hospitalized patients with vibrio wound infections, the majority are caused by *V. vulnificus* (43%), followed by *V. parahaemolyticus* (29%) and *V. alginolyticus* (18%). The case fatality for *V. vulnificus* was 11%, and for *V. parahaemolyticus* it was 5%.[9]

Wound infections range from mild, limited disease to rapidly progressive, necrotizing infections.[9,10,13,19] Virulence may be related to the organisms' capsular polysaccharide and lipopolysaccharide. Many vibrios also produce degradative toxins and enzymes. These include chitinases, which allow vibrios to colonize the exoskeletons of marine zooplankton, as well as hemolysins and metalloproteases, which break down tissues at the site of colonization. Vibrios also produce siderophores that scavenge iron from host transport proteins, transferrin and lactoferrin. This may account for the increased virulence of *Vibrio* spp. in patients with iron overload states.[12]

Cellulitis usually occurs within 24-48 hours but can occur as early as four hours, or as late as 12 days after exposure.[20,24,25] Fever occurs in 45-80% of primary cellulitis cases.[4] Infected wounds are usually erythematous or ecchymotic, swollen and notably tender with little to no purulent discharge.[4,24] Vesicles or bullae with secondary necrotic centers and necrotizing fasciitis have also been described.[9,12,16,24,26]

Patients with a history of liver disease, renal disease, chronic illness or immunodeficient states are at considerably increased risk of generalized sepsis following cellulitis.[4,9,19,20,27-30] In cirrhosis, it has been suggested that porto-systemic shunting may allow vibrios to bypass the hepatic reticuloendothelial system. Additionally, liver disease predisposes such patients to complement deficiencies, impaired chemotaxis, and phagocytosis.[31] Iron overload states also contribute to fulminant vibrio infection. Increased bioavailability of free iron, found in patients with hemochromatosis, may stimulate bacterial growth and metabolism. In addition, iron overload may impair normal host phagocytic activity, increasing susceptibility to infections.[12,31,32] Septicemia occurs in 15% of patients with primary soft tissue infections and contributes to the high case-fatality rates. In those with bacteremia, the rate is 32%; without hematogenous involvement, the case fatality rate is only 1%.[9]

Secondary cellulitis in the setting of primary septicemia associated with *Vibrio* spp. carries a 32-50% mortality rate.[4,9,10,19,33] In these cases, there is usually a preceding history of having eaten raw/undercooked oysters or other seafood ingestion.[4,19] These individuals develop generalized, metastatic, macular, or papular lesions in the setting of primary bacteremia. Culture-positive cutaneous lesions have been reported with bacteremia caused by *V. vulnificus, V. cholerae* non-O1, *V. parahaemolyticus*, and rarely *V. alginolyticus*.[4,34]

Treatment of Coral-related Soft Tissue Infection

Local wound care should include soap and water, followed by aggressive irrigation and debridement with saline solution and hydrogen peroxide to remove foreign material from the site and prevent secondary infection or granuloma formation.[35]

Given the potential polymicrobial nature of coral-related infections, broad-spectrum antibiotics should be considered. For those with obvious cellulitis, or as a prophylactic measure in those with abnormal immune systems, antibiotics with a spectrum of activity against staphylococci and streptococci should be used. In addition, antibiotics that are effective against halophilic *Vibrio* spp. should be administered.

Vibrio spp. frequently produce beta-lactamases and are often resistant to various beta-lactam antibiotics. The beta-lactam inhibitor, sulbactam, does not completely render these organisms susceptible to ampicillin. They are often resistant to cephalothin, cefuroxime, and cefoperazone, but sensitive to cefotaxime, ceftazidime, aztreonam, and imipenem.

Although the fluoroquinolones, ofloxacin and norfloxacin, are effective against these organisms, ciprofloxacin appears to have the greatest activity with an MIC_{90} of approximately 0.25 mg/L. Trimethoprim/sulfamethoxazole is effective, as are the tetracyclines and chloramphenicol.[36] For those with devitalized tissue or fasciitis, surgical intervention is

indicated. This may be particularly important when dealing with infections caused by *Vibrio damsela*.[16,21,37] (*Dr. Ciampi is a Clinical Instructor in Medicine at Yale University and Dr. Sofair is an Assistant Clinical Professor of Medicine at Yale University with the Emerging Pathogens Program, New Haven, Conn.*) ❖

References

1. Patterson TF, et al. *Vibrio alginolyticus* cellulitis following coral injury. *Yale J Biol Med* 1988;61:507-512.
2. Brown CK, Shepherd SM. Marine trauma, envenomations, and intoxications. *Emerg Med Clin North Am* 1992;10:385-408.
3. Habif TP, Habie TP. A color guide to diagnosis and therapy. *Clin Dermatol* 1996;3:2005.
4. Blake PA, et al. Disease caused by a marine vibrio. *N Engl J Med* 1979;300:1-5.
5. Morris JG, Black RE. Cholera and other vibrioses in the United States. *N Engl J Med* 1985;312:343-350.
6. Bateman JL, et al. *Aeromonas hydrophilia* cellulitis and wound infections caused by waterborne organisms. *Heart Lung* 1988;17:99-102.
7. Pien FD, et al. Bacterial flora of marine penetrating injuries. *Diagn Microbiol Infect Dis* 1983;1:229-232.
8. Kelly KA, et al. Spectrum of extraintestinal disease due to *Aeromonas* species in tropical Queensland, Australia. *Clin Infect Dis* 1993;16:574-579.
9. Hlady WG, Klontz KC. The epidemiology of vibrio infections in Florida, 1981-1993. *J Infect Dis* 1996; 17:1176-1183.
10. Howard RJ, et al. Necrotizing soft-tissue infections caused by marine vibrios. *Surgery* 1985;98:126-130.
11. Limpert GH, Peacock JE Jr. Soft tissue infections due to noncholerae vibrios. *Am Fam Physician* 1988; 37:193-198.
12. Strom MS, Paranjpye RN. Epidemiology and pathogenesis of *Vibrio vulnificus*. *Microbes and Infection* 2000; 2:177-188.
13. Hill MK, Sanders CV. Localized and systemic infection due to *Vibrio* species. *Infect Dis Clin North Am* 1987; 1:687-707.
14. Oliver JD, et al. Distribution of *Vibrio vulnificus* and other lactose-fermenting vibrios in the marine environment. *Appl Environ Microbiol* 1983;45:985-998.
15. Linkous DA, Oliver JD. Pathogenesis of *Vibrio vulnificus*. *FEMS Microbiol Lett* 1999;174:207-214.
16. Yuen KY, et al. Fatal necrotizing fasciitis due to *Vibrio damsela*. *Scand J Infect Dis* 1993;25:659-661.
17. Penman AD, et al. *Vibrio vulnificus* wound infections from the Mississippi Gulf coastal waters: June to August 1993. *South Med J* 1995;88:531-533.
18. Joseph SW, et al. *Vibrio parahaemolyticus* and related halophilic vibrios. *Crit Rev Microbiol* 1982;10:77-124.
19. Klontz KC, et al. Syndromes of *Vibrio vulnificus* infections. Clinical and epidemiologic features in Florida cases, 1981-1987. *Ann Intern Med* 1988;109:318-323.
20. Howard RJ, Lieb S. Soft tissue infections caused by halophilic marine vibrios. *Arch Surg* 1988;123: 245-249.
21. Tang WM, Wong JW. Necrotizing fasciitis caused by *Vibrio damsela*. *Orthopedics* 1999;22:443-444.
22. Ien F, et al. *Vibrio alginolyticus* infections in Hawaii. *J Clin Microbiol* 1977;5:670-672.
23. Porres JM, Fuchs LA. Isolation of *Vibrio parahaemolyticus* from a knee wound. *Clin Orthop* 1975; 106:245-247.
24. Johnston JM, et al. *Vibrio vulnificus*. Man and the sea. *JAMA* 1985;253:2850-2853.
25. Ho PL, et al. Necrotizing fasciitis due to *Vibrio alginolyticus* following an injury inflicted by a stingray. *Scand J Infect Dis* 1998;30:192-194.
26. Farina C, et al. *Vibrio cholerae* O_2 as a cause of a skin lesion in a tourist returning from Tunisia. *Journal of Travel Medicine* 2000;7:92-94.
27. Brennt CE, et al. Growth of *Vibrio vulnificus* in serum from alcoholics: Association with high transferrin iron saturation. *J Infect Dis* 1991;164:1030-1032.
28. Stabellini N. Fatal sepsis from *Vibrio vulnificus* in a hemodialyzed patient. *Nephron* 1998;78:221-224.
29. Ali A, et al. *Vibrio vulnificus* sepsis in solid organ transplantation: A medical nemesis. *J Heart Lung Transplant* 1995;14:598-600.
30. Ko WC, et al. Infections due to non-O1 *Vibrio cholerae* in southern Taiwan: Predominance in cirrhotic patients. *Clin Infect Dis* 1998;4:774-780.
31. Hor LI, et al. Survival of *Vibrio vulnificus* in whole blood from patients with chronic liver diseases: Association with phagocytosis by neutrophils and serum ferritin levels. *J Infect Dis* 1999;179:275-278.
32. Bullen JJ, et al. Hemochromatosis, iron and septicemia caused by *Vibrio vulnificus*. *Arch Intern Med* 1991; 151:1606 -1609.
33. Chuang YC, et al. *Vibrio vulnificus* infection in Taiwan: Report of 28 cases and review of clinical manifestations and treatment. *Clin Infect Dis* 1992;15: 271-276.
34. Bonner JR, et al. Spectrum of *Vibrio* infections in a gulf coast community. *Ann Intern Med* 1983;99: 464-469.
35. Rosson Cl, Tolle SW. Management of marine stings and scrapes. *West J Med* 1989;150:97-100.
36. French GL, et al. Antimicrobial susceptibilities of halophilic vibrios. *J Antimicrob Chemother* 1989; 24:183-194.

37. Bia FJ. On damsels and distress from a vibrio species. *Travel Medicine Advisor Update* 2000;10:31-32.

Effect of Norepinephrine on the Outcome of Septic Shock

ABSTRACT & COMMENTARY

Synopsis: *In a prospective, comparative trial of norepinephrine against high-dose dopamine, norepinephrine, as a part of the hemodynamic management of patients in septic shock, was associated with a highly significant decrease in hospital mortality.*

Source: Martin C, et al. Effect of norepinephrine on the outcome of septic shock. *Crit Care Med* 2000;28:2758-2765.

Martin and colleagues used a prospective observational design to identify factors associated with outcome in a cohort of 97 consecutive critically ill patients with septic shock at a major referral center in France. Nineteen clinical, biological, and hemodynamic variables were analyzed using stepwise logistic regression analysis and a model building strategy to identify variables independently and significantly associated with outcome. Septic shock was defined according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference on Sepsis and Organ Failure: sepsis-induced hypotension, persisting despite adequate fluid resuscitation, along with the presence of hypoperfusion abnormalities, or organ dysfunction (oliguria < 30 mL/hr, lactic acidosis, and alteration in mental status evaluated without use of sedative drugs).

All patients in the study received a protocol of broad-spectrum antibiotic coverage, mechanical ventilation, and pulmonary artery catheterization. A strict hemodynamic management protocol was used in which all patients were given fluid resuscitation (≥ 12 mL/kg) to maintain the pulmonary artery wedge pressure (PAWP) between 12-15 mm Hg. Hematocrit (Hct) was maintained at 30% with packed red blood cells. Dopamine was initiated at a dose of 5 mcg/kg/min followed by 5 mcg/kg/min increments up to a dose of 15 mcg/kg/min. Dobutamine was added at a dose of 5 mcg/kg/min with 5 mcg/kg/min increments if SvO_2 was less than 70% (provided SpO_2 > 95%, Hct > 30%). This vasoactive and inotropic support was titrated to keep MAP greater than 70 mm Hg, SvO_2 at 70% or greater, and urine output greater than 0.7 mL/kg/hr.

Hypotension persisted in all 97 patients despite this protocol. Patients were then nonrandomly assigned to one of two treatment protocols: 1) high dose dopamine (16-25 mcg/kg/min, n = 40) or 2) dopamine 15 mcg/kg/min and norepinephrine (started at 0.5 mcg/kg/min) with 0.3 mcg/kg/min increments, up to a maximal dose of 5.0 mcg/kg/min (n = 57). If the treatment failed to correct abnormalities in MAP, epinephrine was added to both protocols (n = 7 in high-dose dopamine protocol; n = 10 in norepinephrine protocol). When the hemodynamic status of patients was stable for at least 24 hours, progressive weaning of the drugs was begun.

The 97 patients included 29 women and 68 men with a mean age of 53 ± 12 years. The mean APACHE II score was 28 ± 4. Causes of septic shock were 50 pneumonia (52%), 33 peritonitis (34%), and 14 miscellaneous etiologies (11%). The hospital mortality was 73%. Patients treated with norepinephrine had lower mortality than patients treated with high dose dopamine on day 7 (28% vs 40%, $P < 0.005$), on day 28 (55% vs 8%, $P < 0.001$), and on hospital discharge (62% vs 84%, $P < 0.001$). Patients in both treatment protocols were analyzed and found to have similar characteristics.

Multivariate analysis revealed the use of norepinephrine was the only factor associated with a favorable outcome. Three factors were independently and significantly associated with an unfavorable outcome: pneumonia as the cause of septic shock ($P < 0.05$), high lactate concentrations (> 4 mmol/L) before treatment was started ($P < 0.001$), and organ system failure index of 3 or more ($P < 0.001$).

COMMENT BY KAREN JOHNSON, RN, PhD, CCRN

This study contributes to an increasing body of knowledge of factors that are associated with an increased mortality in septic shock of which two are known: a) high blood lactate concentration at the time of onset of shock, and b) dysfunction in three or more organ systems. The results of this study make us challenge our long held clinical assumptions that norepinephrine is a potent vasoconstrictor and potentiator of end organ hypoperfusion. We have to ask ourselves whether or not norepinephrine (Levophed) deserves its nickname, "leave 'em dead."

When multiple vasopressors are used in the management of shock, it is the last drug physicians typically order and the first drug nurses titrate down. Dopamine has typically been the vasopressor of choice in the management of patients with hypotension, despite adequate fluid resuscitation. However, this study revealed

the use of norepinephrine as part of a hemodynamic support protocol that was strongly related to a favorable outcome and was statistically considered a protective factor that markedly decreased hospital mortality.

A critical point must be made here. Martin et al paid special attention to achieving effective circulating volume before prescribing vasopressor therapy. Patients were subjected to strict fluid resuscitation protocols with specific resuscitation end points that included PAWP, Hct, MAP, urine output, SvO_2, and SpO_2. They carefully point out that the present study underscores some benefits of norepinephrine in patients who have received adequate fluid resuscitation. These results must be interpreted with extreme caution because the study's open label, nonrandomized design could have led to a potential bias. It is not clear how decisions were made as to what vasopressor agent patients received.

Large, prospective, randomized clinical trials are needed to answer additional questions this study raises: 1) Should dopamine or norepinephrine be used as the "first-line" vasopressor?; 2) Does the choice of one vasopressor over another truly affect survival?; 3) Should dopamine and norepinephrine be used as combination therapy? If so, when and how should these drugs be titrated? Perhaps this study will challenge us to pursue efforts to identify a standardized approach to resuscitation end points and vasopressor therapy in the management of septic shock. (*Karen Johnson works at the School of Nursing, University of Arizona, Tucson, Ariz.*) ❖

CME Questions

1. Prevention of leptospirosis during travel can be attempted by which one of the following?
- a. Weekly prophylaxis with doxycycline
- b. Weekly prophylaxis with mefloquine
- c. Receiving vaccination for hepatitis A and B simultaneously
- d. Not drinking untreated mountain water
- e. Not handling domestic animals

2. Which one of the following statements regarding vibrio infections is true?
- a. *Vibrio spp.* are generally isolated from fast moving fresh water streams in the tropics.
- b. Soft tissue infections are indolent and induce a granulomatous response to the causative bacteria.
- c. Iron overload states, such as cirrhosis, predispose to serious vibrio infections.
- d. The first generation cephalosporins remain the agents of choice for serious vibrio infections.
- e. Risk of vibrio infection is unrelated to seafood or shellfish ingestion.

3. All of the following factors are associated with an unfavorable outcome with septic shock *except*:
- a. administration of norepinephrine.
- b. pneumonia as the cause of septic shock.
- c. high serum lactate concentrations.
- d. failure of three or more organ systems.

4. In patients with septic shock, administration of norepinephrine:
- a. caused multisystem organ dysfunction syndrome.
- b. led to an increased incidence of renal failure.
- c. was associated with increased mortality.
- d. was associated with decreased mortality.

5. Which one of the following is correct?
- a. *Leptospira spp.* are halophilic Borrelia.
- b. *Leptospira spp.* are excreted in animal urine.
- c. Outbreaks of leptospirosis are associated with periods of lack of rainfall.
- d. *Leptospira spp.* are incapable of penetrating mucous membranes, cuts, or abrasions.

6. Which one of the following is correct?
- a. *Vibrio spp.* thrive in cold, brackish water.
- b. *Vibrio vulnificus* may cause cellulitis in the absence of exogenous inoculation of skin and soft tissue.
- c. *Vibrio spp.* are inhibited in the presence of iron.
- d. Among pathogenic *Vibrios*, none are halophilic.

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