

Leptospirosis, Water Sports, and Chemoprophylaxis

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Recreational activities, such as water sports and adventure travel, are emerging as an important risk factor for leptospirosis, a potentially fatal zoonosis. We report the clinical course of 2 patients who acquired leptospirosis through participation in water sports. Physicians caring for patients who participate in adventure travel involving water sports should be familiar with the risk factors for and diagnosis, prevention, and treatment of leptospirosis.

Recreational activities, such as water sports and adventure travel, are emerging as an important risk factor for leptospirosis [1]. There is the potential for large outbreaks of leptospirosis when these recreational activities are part of organized competitions. Leptospirosis, a common zoonosis throughout the world, has a higher prevalence in tropical regions, especially following periods of heavy rainfall [2]. Because of the increased participation of individuals in adventure travel and in recreational activities in tropical locations, it is imperative that travel physicians assess risk factors for leptospirosis and consider measures for the prevention of this potentially fatal disease.

The 2 patients with leptospirosis who we describe in this report were competitors in the Eco-Challenge Sabah 2000 competition, which took place in Malaysian Borneo from 21 August to 1 September 2000. The event attracted 76 four-person teams from 26 countries. Contestants took part in jungle trekking, caving, outrigger sailing, canoeing, scuba diving, mountain biking, and a 12-km swim in jungle rivers. Both patients reported

that they had developed skin excoriations due to contact with foliage and leech bites. Patients 1 and 2 presented to their physicians at 6 and 8 days, respectively, after completion of the Eco-Challenge competition.

Patient 1. A 32-year-old man presented with a 2-day history of fever (temperature, up to 40°C), headache, diffuse body aches, and generalized weakness. He had taken 1 oral dose of doxycycline, 100 mg, a few hours after the onset of fever. The patient appeared to be ill and mildly dehydrated, but he was afebrile at the time of presentation. No conjunctival suffusion was noted. Numerous excoriations attributed to leech bites were observed on the distal lower extremities and appeared to be healing. Laboratory tests revealed slightly elevated transaminase levels (alanine aminotransferase [ALT], 53 U/L; aspartate aminotransferase [AST], 49 U/L). The WBC count was 9200 cells/ μ L, with a differential count of 92.4% neutrophils, 5% lymphocytes, 2.4% monocytes, and 0.2% basophils. The patient's blood urea nitrogen and creatinine levels, as well as the results of urinalysis, were also within normal values. The results of malarial blood smears, blood cultures, and serologic testing for hepatitis viruses were negative. The patient received hydration with intravenously administered fluids and was treated with doxycycline, 100 mg by mouth (p.o.) b.i.d., which resulted in resolution of symptoms. Doxycycline treatment was continued for a total of 10 days. The leptospiral antibody titer was initially found to be <1:50 by indirect hemagglutination (Focus Technologies), but it increased to 1:400 fourteen days later.

Patient 2. A 46-year-old woman presented with a 5–7-day history of intense myalgias, fever, anorexia, nausea, vomiting, and a steadily worsening headache without photophobia. She appeared to be ill and had a temperature of 40°C. No conjunctival suffusion was noted. Tenderness in the right costal margin was noted in association with deep inspiration. Skin excoriations that appeared to be healing were noted on the arms and legs. The findings of initial laboratory studies were as follows: alkaline phosphatase, 224 U/L; ALT, 86 U/L; AST, 84 U/L; total bilirubin, 2.3 mg/dL; conjugated bilirubin, 1.4 mg/dL; amylase, 193 U/L; and lipase, 127 U/L. The WBC count was 8250 cells/ μ L, with a differential count of 88.1% neutrophils, 7.5% lymphocytes, 3.3% monocytes, and 1.1% eosinophils. The patient's blood urea nitrogen and creatinine levels were within normal values, and the results of urinalysis were also normal, with the exception of findings of 1+ bilirubin and trace protein. The results of malarial blood smears, blood cultures, and serologic testing for hepatitis were negative, with the

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exception of positive results for antibody to hepatitis B surface antigen, which resulted from previous immunization.

The patient was initially treated with ampicillin, 2 g iv q4h, and, doxycycline, 100 mg b.i.d. Treatment with doxycycline was continued for 3 weeks, until the amylase and lipase abnormalities resolved. The patient remained weak during this recuperative period and gradually resumed normal activities 6 weeks after her initial presentation. Results of serologic testing for leptospiral antibodies, by use of both Dip-S-Ticks and PanBio ELISA (PanBio), were initially negative, but positive results were obtained on the 10th day of hospitalization. Leptospire were isolated from blood samples that were obtained before the start of antibiotic therapy, cultured in PLM-5 medium (InterGen), and incubated for 2 weeks [3]. On the basis of its *rrs* and *secY* gene sequences (GenBank accession numbers AY034037 and AY034036, respectively), the isolate was determined to be most closely related to *Leptospira weilii*, a species that is found exclusively in Southeast Asia. The isolate was serologically analyzed using both monoclonal antibodies and the cross-agglutination absorption test [4, 5]. These serologic studies revealed that the isolate most likely represents a new serovar of the Hebdomadis group.

Risk factors for leptospirosis. Leptospirosis that occurs in association with recreational exposure to contaminated water is well documented. From 1939 through 1965, a total of 309 cases of leptospirosis associated with swimming in contaminated water in the United States were documented by national surveillance [6]. Increased interest in participation in water sports has led to an increase in the frequency that leptospirosis has been reported in association with a variety of recreational sport activities. Outbreaks of leptospirosis have been associated with caving [7], canoeing [8], kayaking [9, 10], and rafting in Thailand [11, 12] and Costa Rica [13]. The emerging popularity of competitive water-sport events has led to the recent occurrence of several large outbreaks of leptospirosis associated with triathlons held in Wisconsin, Illinois [14], and The Philippines [15]. At least 68 cases of leptospirosis occurred in association with the multisport Eco-Challenge event in Borneo [16] in which the 2 patients who we describe participated.

Outbreaks of leptospirosis that have occurred in association with water sports have demonstrated the ability of pathogenic *Leptospira* species to survive in an aqueous environment for extended periods after they have been shed from the renal tubules of animal reservoirs [17]. Transmission frequently occurs via skin abrasions or exposed mucous membranes. In our patients, leech bites, skin abrasions, and maceration may have served as risk factors for infection. The time and degree of immersion in contaminated water is probably important with regard to transmission of infection, especially if immersion results in skin maceration and exposure of the conjunctivae. In a study of US military personnel who were negotiating an un-

derwater obstacle course, the risk of leptospirosis was found to be 18 times higher for those who swallowed water during immersion [18]. Leptospirosis can be acquired from contaminated drinking water [19]. Additional evidence of the importance of oropharyngeal mucous membranes as a portal of entry for infection came from a cross-sectional study that found that smoking and drinking beverages while working with infected swine resulted in a 14-fold higher risk of acquisition of leptospirosis [20].

Outbreaks of leptospirosis are typically associated with heavy rainfall and periods of flooding [2, 13, 14, 21–23]. In settings in which flooding has occurred, humans have a higher risk of exposure to leptospire in surface waters, and multiple serovars may be involved [6, 17]. The Eco-Challenge Sabah 2000 participants encountered rainfall and the flooded Segama River during the race; when considered in combination with prolonged immersion in water and the abundance of cutaneous portals of entry for infection, these factors provide an explanation for the observed attack rate of 44% [16], which was much higher than the rates reported in association with other recent outbreaks. Leptospirosis has also been associated with drought conditions or subnormal rainfall, which may serve to concentrate organisms in bodies of stagnant water [18, 24].

Diagnosis. Clinicians should have a high index of suspicion for leptospirosis in patients who experience acute febrile illness after recreational exposure to natural bodies of fresh water. The incubation period of the disease is usually 5–14 days, but it may last up to 1 month [17]. A serologic survey has indicated that most patients are asymptomatic [25]. Symptomatic patients typically develop high fever, headache, chills, rigors, and myalgias (especially in the calf and lumbar areas). Conjunctival suffusion, which consists of engorged conjunctival vessels without purulent discharge, is frequently seen. The acute illness may resolve spontaneously, or it may be followed by an immune phase of illness, which is characterized by recurrent fever, aseptic meningitis, hemorrhagic pneumonitis, cardiac arrhythmia, liver failure, acute renal failure, and/or circulatory collapse. Mortality rates associated with severe leptospirosis range from 5% to 40% [17].

Leptospire are slender ($0.1 \times 6\text{--}12 \mu\text{m}$), tightly coiled, flexible, gram-negative bacteria that can be best visualized by use of dark-field or phase microscopy. Their morphology and corkscrew motility contribute to their ability to invade tissue barriers. A recent DNA-DNA hybridization study confirmed significant heterogeneity within the genus *Leptospira*, with 16 genomospecies defined [26]. The organism can be isolated from blood, CSF, and urine samples if the appropriate culture medium is available [27]. The yield of the organism is increased if cultures are obtained before initiation of antibiotic therapy. Cultures usually yield organisms within 1–2 weeks, although 4–6 months of incubation may be required for lep-

to spores to become detectable [27]. The outer envelope that surrounds the cell walls has high lipopolysaccharide levels. Antigenic variation of the lipopolysaccharide carbohydrate side chains determines the grouping of serologic variants (serovars); 25 serogroups and 268 named serovars have been recognized. There is evidence that the variability in virulence may be related to the infecting serovar.

Patients with leptospirosis develop a serogroup-specific antibody response, which is the basis of detection for the microscopic agglutination test, the "gold-standard" serodiagnostic test. The disadvantages of the microscopic agglutination test are (1) that it is available only at reference centers with expertise in performing the test, and (2) that it is time consuming. Simpler and faster serologic tests include indirect hemagglutination, IgM and IgG ELISAs, and various rapid IgM assays [28]. The results of serodiagnostic studies typically are negative at the time of clinical presentation, and testing should be repeated ~14 days after presentation to document seroconversion.

Prevention and treatment. Travelers should be taught how to minimize exposure to potentially contaminated soil and water. Protective clothing, especially footwear, should be worn, and other measures to prevent dermal cuts and abrasions should be followed. Travelers to the tropics should avoid submersion in and drinking of surface water.

Several studies have suggested that chemoprophylaxis with doxycycline may be an effective treatment for leptospirosis [29–31]. In a study of US army soldiers who participated in a 3-week training exercise in the jungles of Panama, doxycycline, 200 mg once weekly, was found to reduce the attack rate of clinical leptospirosis from 4.2% to 0.2%, for a preventive efficacy of 95% [29]. In residents of a rural area of the Andaman Islands, an area of high endemicity with annual outbreaks of leptospirosis associated with flooding, administration of doxycycline, 200 mg once weekly, was found to reduce the rate of symptomatic leptospirosis from 6.8% to 3.1%, for a preventive efficacy of 54%; however, such therapy did not reduce the rate of infection [30]. A pilot study conducted in São Paulo, Brazil, suggested that the use of postexposure chemoprophylaxis may be useful for rural residents of an area of high endemicity with flood-associated outbreaks of leptospirosis [31]. The patients studied and the nature of exposure to leptospirosis both varied in these different studies.

Further work is needed to improve chemoprophylaxis for leptospirosis. Administration of doxycycline at 1-week intervals may not be optimal, given the drug's relatively short 18-h half-life. In travelers at risk for malaria, an alternative strategy may be to use doxycycline, 100 mg p.o. daily, as prophylaxis against both malaria and leptospirosis. Although this regimen has not been studied as a chemoprophylaxis strategy for leptospirosis, it would be a reasonable approach for patients who anticipate having a relatively high level of exposure. The benefits of doxy-

cycline prophylaxis must be weighed against the potential adverse side effects of prophylaxis, which include gastric upset and photosensitivity. Taking doxycycline with food can minimize gastrointestinal toxicity; however, milk products interfere with the absorption of doxycycline and should be avoided. Photosensitivity caused by doxycycline can be minimized by the use of sunscreen. One limitation of doxycycline is that it is contraindicated in pregnant women and in children <8 years of age. Antibiotics which have longer serum half-lives, such as azithromycin, may be expected to be reasonable alternatives to doxycycline; however, clinical trials are needed to validate this approach. In patients whose anticipated exposure to water is insufficient to recommend prophylaxis, it may be appropriate to provide a 7-day course of doxycycline, 100 mg b.i.d., with instructions to initiate therapy in the event of a febrile illness consistent with leptospirosis [32]. A placebo-controlled, double-blind study has shown that intravenously administered penicillin G, 1.5 million U q6h, is effective for patients who require hospitalization [33]. Intravenous ampicillin is an appropriate alternative to intravenous penicillin G [17]. Patients who become ill after recreational exposure to water should also be counseled to seek medical attention as soon as possible, because the differential diagnosis of febrile illness in a traveler can be quite broad [34]. Travelers who return from the tropics with leptospirosis may initially be thought to have malaria, hepatitis, enteric fever, or dengue fever. The emergence of adventure travel makes it imperative that physicians consider whether their patients will be at risk for leptospirosis, a potentially life-threatening disease.

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