Leptospirosis: The Microscopic Danger in Paradise

William A. Londeree MD

Abstract

Leptospirosis is a zoonotic infection endemic in Hawai'i. This review discusses the incidence of documented human cases in Hawai'i and current recommendations for diagnosis, prevention, and treatment of leptospirosis.

Introduction

While vacationing or living in paradise, the last thought to pass through a person's mind is the possibility of contracting a serious or life-threatening bacterial illness like leptospirosis after a quick dip at a beautiful waterfall or a hike near a picturesque stream. *Leptospira interrogans* is a freshwater-borne zoonotic spirochete capable of infecting a variety of mammalian hosts to include cattle, swine, goats, and rodents, but rodents and feral swine mainly serve as carriers in Hawai'i. Once the infection has occurred in these carrier animals the spirochete will be shed intermittently in the urine where it will remain viable for days to months in soil or water with a neutral pH.[1,2]

The infection in humans can range from a subclinical infection to severe multi-organ failure. Leptospirosis has an incubation period of 2 to 26 days and classically presents with fevers, rigors, myalgias, and headaches in 75 to 100 percent of patients.[1,2] Given its variability in clinical presentation, leptospirosis can be a difficult disease to diagnose, so it is usually treated empirically when suspected. Medications and preventive stategies can decrease the likelihood of acquiring the systemic infection.

Relevance to Hawai'i

Leptospirosis is endemic worldwide, but the majority of infections occur in the tropical regions with Hawai'i reporting the highest incidence of human cases in the United States. The Hawai'i Department of Health reported 345 cases to the CDC in Hawai'i with 198 cases confirmed from 1999-2008.[2] Most of the 91% confirmed cases occurred in men, and 71% of these cases occurred in the age range of 20-49 years. Nearly 80% of these cases were due to freshwater exposure from outdoor recreational activities or taro farming. The remaining 11% percent of exposures were from home gardens.[2] Since the incidence of infection in Hawai'i is higher than the rest of the United States, and the main risk factor for leptospirosis is exposure to freshwater and moist soil, infection rates may decrease if people are educated on use of appropriate personal protection equipment, avoidance of freshwater exposure, and pharmacologic prophylaxis.

The most common infecting serovars are from serogroups Icterohemorrhagiae (40%) and Australis (44%), which have been shown to have predominantly rodent and swine carriers, respectively. In the past, serogroup Icterohemorrhagic was responsible for the majority of infections, but the increasing rate of Australis infections is most likely related to the increasing population and interactions between feral swine and humans.[2]

Example Case

A 21-year-old man with no prior significant medical history presented to the emergency department with progressive nausea and headache over the past week. Onset occurred one week after swimming at Maunawili Falls. He started having periumbilical pain and became intolerant of oral intake due to persistent nausea. Non-bloody, non-bilious emesis was followed by brown, watery diarrhea and a subjective fever. Initial vital signs demonstrated a temperature of 103.3°F, blood pressure of 110/66 mm Hg, heart rate of 95 beats per minute, respiratory rate of 18 per minute, and oxygen saturation of 100% on room air. Physical exam was only remarkable for mild diffuse abdominal tenderness without hepatosplenomegaly or peritoneal signs. Diagnostic laboratory studies demonstrated elevated C-reactive protein, erythrocyte sedimentation rate, and aspartate aminotransferase. A normochromic normocytic anemia, thrombocytopenia, and leukocytosis were also present. He was admitted to a telemetry ward and treated with ciprofloxacin for a suspected bacterial diarrheal illness and intravenous doxycycline for a possible leptospirosis infection. Four hours after the administration of antibiotics he developed respiratory distress and had to be intubated for hypoxic respiratory failure. A chest X-ray demonstrated pulmonary edema, and shortly after intubation he developed bloody sputum which was suctioned through his endotracheal tube. Diffuse alveolar opacities were seen on CT scan, and bronchoscopy with a bronchoalveolar lavage demonstrated only gross red blood cells consistent with diffuse alveolar hemorrhage. He was extubated after three days of mechanical ventilation and discharged three days later. Microscopic agglutination testing demonstrated a positive, 1:800 IgM antibody titer for *Leptospira interrogans* serovar Icterohemorrhagiae. At follow-up, he had made a complete recovery.

Presentation and Diagnosis

Cases of leptospirosis can range from a mild or subclinical infection to a very severe and potentially fatal one. Most mild cases usually present with fevers, myalgias, and headache similar to an acute viral febrile illness, but severe cases can present with jaundice, renal failure, hemorrhagic diathesis, anemia, hyponatremia, hypokalemia, and thrombocytopenia.[2,3]

Diagnosis of leptospirosis relies on a detailed history and clinical suspicion, because the current testing modalities have a long turnaround time and are not clinically useful in an acutely ill patient. The gold standard test is the microscopic agglutina-

tion test (MAT), which uses antigens from live spirochetes from multiple serogroups and mixes them with a patient's serum to detect concentrations of agglutinating antibodies. One downfall of this test is its prolonged turnaround time. Another downfall of the MAT is the requirement for maintenance of live cultures of *Leptospira* which are endemic to the local area. Also, a single MAT test cannot differentiate between a current or recent prior infection, and there is cross reactivity with other previous spirochete infections.[4] Titer range for test positivity is open to debate, but is typically set at a value >1:200. Enzyme-linked immunosorbent assay (ELISA) is another test showing promise because it is able to detect an earlier rise in IgM antibodies. The test has variable specificity and sensitivity due to operator expertise, so it is currently not recommended.[2,5,6] Polymerase chain reaction (PCR) is another test undergoing development but it is best when it is utilized in conjunction with ELISA. Combining ELISA for IgM detection, followed by PCR to detect the antigen in the blood or in the urine to confirm an active infection, is currently being evaluated.[7,8]

Prevention

Prevention starts with avoiding high risk exposures to infected water sources. There are roles for chemoprophylaxis and vaccination of animals; however, there is no currently approved human vaccine for use in the United States.

Vaccination faces many challenges because leptospirosis has more than 200 pathogenic serovars. China and France are the only countries that have a vaccine available for human use. A difficulty with developing an efficacious vaccine is matching the local serovars to the vaccine. Limited safety data are available on human use.[9,10] Even though there is no vaccination available for residents of Hawai'i, pharmacological prophylaxis strategies are available.

The United States Army assessed 940 US soldiers during deployed jungle training in Panama with doxycycline prophylaxis 200 mg a week orally versus a placebo. The soldiers receiving doxycycline had an infection rate of 0.2% compared to a 4.2% infection rate experienced by the placebo group, yielding an efficacy of 95%.[11] Since the soldiers were likely a naïve population, studies have also been conducted on indigenous populations to assess prophylaxis efficacy. Two studies assessed indigenous populations from Brazil and North Andaman with doxycycline prophylaxis (200mg weekly) versus placebo. The Brazilian study found a protective association with doxycycline and seroconversion, but it was a small pilot study and did not demonstrate statistical significance.[12] The study from North Andaman included 782 persons and it revealed an infection rate of leptospirosis was not statistically different from the placebo group, however, there was a significant protective effect in reducing morbidity and mortality in the doxycycline group.[13] In contrast to these studies, a systematic review conducted in 2000 did not demonstrate certainty for leptospirosis prevention with doxycycline, but it could not make an argument against prophylaxis.[11,14] The World Health Organization recommends physicians consider using prophylactic doxycycline in highly endemic areas and in areas after natural disaster where flooding or contaminated bodies of water are present.[15]

Exposure to freshwater or moist soil which has been contaminated with spirochetes from infected mammalian urine is a major risk factor for contracting leptospirosis. Humans can help prevent infection by avoiding exposure to stagnant water, properly draining farm water runoff, and keeping food away from animal waste contamination. Vaccination of domestic animals has been extremely effective; however, some immunized animals still acquire the infection and shed spirochetes in their urine because the infection resides in the renal tubules. These carriers must be treated with antibiotic therapy in order to clear their infection but this is not practical due to the animals continued exposure to leptospirosis.[16]

Several control measures are available for humans. Prevention education in high risk areas is important. Controlling the disease in domestic animals by vaccination is useful. Additional measures include limiting exposure to feral swine, rodent control, and protection of food from animal contamination (either domestic or feral). Doxycycline is available as chemoprophylaxis for people at increased risk of exposure.[15]

Treatment

The clinical efficacy of antimicrobials in a mild leptospirosis infection is not well established and remains a topic of controversy. A meta-analysis demonstrated that there may be decreased duration for the clinical illness by 2-4 days, but the results were not statistically significant.[17] Given the risks associated with the severe form of infection, a patient should be treated with appropriate antibiotic therapy as soon as possible, preferably within five days of symptom onset.[15]

Penicillin is recommended for a severe leptospirosis infection by the World Health Organization (WHO), but usually stronger antibiotics are given in the hospital in order to broaden coverage. Worldwide, leptospirosis has not demonstrated a pattern of resistance, and it is susceptible to a large variety of antibiotics. Antimicrobial activity against leptospirosis has been observed during in vitro studies with penicillins, cephalosporins, tetracyclines, chloramphenicol, fluoroquinolones, macrolides, telithromycin, carbapenems, and aztreonam. In 2008, Ressner, et al, published a comprehensive review of antimicrobial susceptibilities in different geographic regions. Overall, the study analyzed 13 *Leptospira* isolates from Egypt, Thailand, Nicaragua, and Hawai'i. Among thirteen antimicrobial agents tested, ampicillin, cefepime, azithromycin, and clarithromycin had the lowest MICs (<0.016mcg/ml), with slightly higher MICs recorded for cefotaxime, ceftriaxone, imipenem-cilastatin, penicillin G, moxifloxacin, ciprofloxacin, and levofloxacin (0.030- 0.125 mcg/ml). Overall, the highest MICs were for doxycycline and tetracycline at 2.0 and 4.0, respectively, for strains obtained in Egypt. Icterohemorrhagiae was the Hawaiian serovar analyzed in this study and its MICs to doxycycline and tetracycline were the highest when compared to the other antibiotics at 0.50 and 1.00, respectively.[18]

Most cases of leptospirosis are subclinical and will never

undergo antibiotic treatment. However, for adult patients with mild disease who are candidates for outpatient therapy, doxycycline or azithromycin are accepted treatments. Children and pregnant women can be treated with amoxicillin or azithromycin (for those with beta-lactam allergy) in order to avoid use of doxycycline.

When a patient has a more severe presentation of leptospirosis requiring hospitalization, intravenous antibiotics such as penicillin, doxycycline, ceftriaxone, or cefotaxime should be administered.[15] Upon initiation of antibiotic therapy there is a risk a severely infected patient could develop a Jarisch-Herxheimer reaction (JHR). The JHR is hypothesized to be secondary to an acute inflammatory response caused by a large amount of cytokines released during clearance of spirochetes from the circulation. This reaction typically occurs within 1-4 hours after initial antibiotic administration and is commonly manifested by hypotension, rigors, fevers, and tachycardia, but may also include respiratory distress and renal failure. No one antibiotic has been shown to have a higher association with JHR. Patients should be closely monitored for the JHR after initiation of antibiotic therapy.[19]

Conclusions

The best way to avoid a leptospirosis infection is through avoidance of areas of water and moisture which are exposed to feral animals, especially swine and rodents. Patients should be educated by their primary care provider about contact avoidance. Prophylaxis with weekly oral doxycycline should be considered for individuals when exposure is unavoidable. Individuals who elect to forego prophylactic antibiotics should be counselled to seek immediate medical attention if they start feeling ill after an exposure to freshwater. Initiation of antibiotic therapy should be based on history, physical exam findings, and laboratory results that are consistent with possible leptospirosis infection. Patients with moderate to severe infections should be hospitalized for antibiotic therapy in a setting where they can be closely monitored for the development of serious systemic disease or a Jarisch-Herxheimer reaction.

Disclosure

The author reported no conflicts of interest.

Disclaimer

The views expressed in this abstract/manuscript are those of the author and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the US Government.

Acknowledgments

Dr. Marta Guerra and Dr. Sean Shadomy for their guidance on this paper.

Author's Affiliation:
Department of Medicine, Tripler Army Medical Center, Honolulu, HI 96859

Correspondence to:
William A. Londeree MD; Tripler Army Medical Center, Honolulu, HI 96859;
Email: william.a.londeree.mil@mail.mil

References

1. Kaufmann, AF, Weyant, RS. Leptospiraceae. In: *Manual of Clinical Microbiology*, 6th ed, ASM Press, Washington, DC, 1995, p. 621.
2. Katz AR, Buchholz AE, Hinson K, Park SY, Effler PV. Leptospirosis in Hawaii, USA, 1999–2008. *Emerging Infectious Diseases*. 2011Feb;17(2):221-226
3. Katz AR, Ansdell VE, Effler PV, Middleton CR, Sasaki DM. Assessment of the clinical presentation and treatment of 353 cases of laboratory-confirmed leptospirosis in Hawaii, 1974-1998. *Clin Infect Dis*. 2001;33(11):1834.
4. Guerra MA. Leptospirosis: Public health perspectives. *Biologicals*. 2013 Sep;41(5):295-7.
5. Tanganuchitcharnchai A, Smythe L, Dohnt M, Hartskeerl R, Vongsouvath M, Davong V, Lattana O, Newton PN, Blacksell . Evaluation of the Standard Diagnostics Leptospira IgM ELISA for diagnosis of acute leptospirosis in Lao PDR. *Trans R Soc Trop Med Hyg*. 2012 Sep;106(9):563-6.
6. Desakorn V, Wuthiekanun V, Thanachartwet V, Sahassananda D, Chierakul W, Apiwattanaporn A, Day NP, Limmathurotsakul D, Peacock SJ. Accuracy of a commercial IgM ELISA for the diagnosis of human leptospirosis in Thailand. *Am J Trop Med Hyg*. 2012 Mar;86(3):524-7.
7. Picardeau M, Bertherat E, Jancloes M, Skouloudis AN, Durski K, Hartskeerl RA. Rapid tests for diagnosis of leptospirosis: current tools and emerging technologies. *Diagn Microbiol Infect Dis*. 2014 Jan;78(1):1-8.
8. Budihal SV, Perwez K. Leptospirosis diagnosis: competancy of various laboratory tests. *J Clin Diagn Res*. 2014 Jan;8(1):199-202.
9. Guerra MA. Leptospirosis: Public health perspectives. *Biologicals*. 2013 Sep;41(5):295-7.
10. Wang Z, Jin L, Wegrzyn A. Leptospirosis vaccines. *Microb Cell Fact*. 2007 Dec 11;6:39.
11. Takafuji ET, Kirkpatrick JW, Miller RN, Karwacki JJ, Kelley PW, Gray MR, McNeill KM, Timboe HL, Kane RE, Sanchez JL. An efficacy trial of doxycycline chemoprophylaxis against leptospirosis. *N Engl J Med*. 1984;310(8):497.
12. Gonsalez CR, et al. Use of doxycycline for leptospirosis after high-risk exposure in Sao Paulo, Brazil. *Revista do Instituto de Medicina Tropical de Sao Paulo* 1998;40:59–61.
13. Sehgal SC, et al. Randomized controlled trial of doxycycline prophylaxis against leptospirosis in an endemic area. *International Journal of Antimicrobial Agents*. 2000;13:249–255.
14. Guidugli F, Castro AA, Atallah AN. Antibiotics for preventing leptospirosis. *Cochrane Database Syst Rev*. 2000;(4):CD001305.
15. Human leptospirosis: guidance for diagnosis, surveillance and control. Geneva, World Health Organization/ International Leptospirosis Society, 2003.
16. Martins G, Lilenbaum W. Leptospirosis in sheep and goats under tropical conditions. *Trop Anim Health Prod*. 2014 Jan;46(1):11-7.
17. Brett-Major DM, Coldren R. Antibiotics for leptospirosis. *Cochrane Database Syst Rev*. 2012;2:CD008264.
18. Ressner RA, Griffith ME, Beckius ML, Pimentel G, Miller RS, Mende K, Fraser SL, Galloway RL, Hospenthal DR, Murray CK. Antimicrobial susceptibilities of geographically diverse clinical human isolates of Leptospira. *Antimicrob Agents Chemother*. 2008 Aug;52(8):2750-4.
19. Guerrier G, D'Ortenzio E. The Jarisch-Herxheimer reaction in leptospirosis: a systematic review. *PLoS One*. 2013;8(3):e59266.

Lower Waikeakua Falls (Photo: William Harner MD)