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MINIREVIEWS

Leptospirosis: A clinical review of evidence based diagnosis, treatment and prevention

Alison B Lane, Michael M Dore

Alison B Lane, Walter Reed National Military Medical Center, Bethesda, MD 20899, United States

Michael M Dore, Department of Medicine, Naval Hospital Guam, Guam, CA 96910, United States

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Correspondence to: Michael M Dore, MD, Department of Medicine, Naval Hospital Guam, PSC 4555 Box 208, FPO AP 96540, Guam, CA 96910,
United States. michael.m.dore.mil@mail.mil
Telephone: +1-671-3449202
Fax: +1-671-3449010

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Abstract

Leptospirosis is a zoonotic disease with worldwide distribution and increasing prevalence. Infection is caused by the spirochete Leptospira, with common exposure being contaminated fresh water. Most infections are asymptomatic, but symptoms range from a mild, self-limiting, non-specific febrile illness to fulminant respiratory and renal failure with a high mortality rate. The combination of jaundice, renal failure, and hemorrhage is known as Weil's disease and is the most characteristic pattern associated with severe leptospirosis. Clinical suspicion alone may be enough to warrant empiric antibiotic treatment in many cases. Serological methods are the most commonly used means of confirming a diagnosis of leptospirosis. The "gold standard" is the microscopic agglutination test. Typical treatment for mild causes is oral doxycycline, though azithromycin and oral penicillins are reasonable alternatives. Intravenous penicillin G has long been the standard of care for severe cases though limited studies show no benefit compared to third generation cephalosporins. We review the clinical presentation, diagnosis, treatment and prevention of leptospirosis.

Key words: Leptospirosis; Tropical diseases; Infectious disease

Core tip: Leptospirosis is a zoonotic disease with worldwide distribution and increasing prevalence. Infection is caused by the spirochete Leptospira, with common exposure being contaminated fresh water. Most infections are asymptomatic, but symptoms range from a mild, self-limiting, non-specific febrile illness to fulminant respiratory and renal failure with a high mortality rate. Typical treatment for mild cases is oral doxycycline, though azithromycin and oral penicillins are reasonable alternatives. Intravenous penicillin G has long been the standard of care for severe cases though limited

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INTRODUCTION

Leptospirosis, caused by the spirochetal bacteria *Leptospira*, is a zoonotic disease with worldwide distribution and increasing prevalence. Clinical presentation is often nonspecific and can vary in severity from asymptomatic to fatal multi-system organ failure. The recent estimated worldwide incidence of leptospirosis is approximately 1.03 million cases with 58900 associated deaths[1]. Actual rates are likely higher: Many cases may go unrecognized due to their mild and nonspecific nature, definitive confirmation of diagnosis *via* laboratory testing is challenging, and in many countries (including the United States as well as many developing nations with high endemicity), leptospirosis is not a reportable disease[2,3]. The incidence in tropical areas is up to ten times higher, likely due to a combination of factors, including environmental (higher temperatures, humidity, and rainfall favoring organism survival) as well as socioeconomic (poor sanitation, closer human contact with both rodents and domestic animals)[4,5]. Occupations with exposure to animals or water (farmers/ranchers, vets, rice farmers, military personnel) have also been associated with higher risk of acquiring leptospirosis[6]. In developed countries, travel-related infections and recreational exposures have become increasingly recognized as a source of *Leptospira* infection. A 2009 review estimated that over half of leptospirosis cases in the United Kingdom were acquired abroad during travel to tropical regions[7]. Many cases have occurred in association with water-based activities such as swimming, triathlons, canoeing, and kayaking, including several outbreaks within the United States and abroad[6,8-10].

Leptospirosis is caused by bacterial spirochetes of the genus *Leptospira*. There are 21 identified *Leptospira* species (classified by genetic relatedness), 9 of which are known to be pathogenic[11]. Leptospires are also classified by serogroup, with over 26 pathogenic serogroups and 250 pathogenic serovars identified, as well as more than 60 nonpathogenic serovars[11,12]. The organisms are thin and corkscrew-shaped, with a characteristic end hook. Leptospires are motile, aerobic organisms that grow best between 28 ℃-30 ℃ and thus can remain viable for months in the environment (water or soil), where they are often widespread[2,12,13]. Additionally, animals are a natural reservoir for *Leptospira* species, as they live commensally in renal tubules of many species - most significantly rodents but also other mammals including livestock[12]. Shedding from kidneys and excretion in urine of colonized animals contributes to environmental perseverance of the organisms.

Transmission to humans is most commonly environmental *via* contact with water or damp soil contaminated with leptospires, but may also occur from direct contact with urine or blood from an infected or colonized animal[11]. The organisms typically enter the human body *via* cuts and abrasions or mucous membranes (oral mucosa, conjunctivae), and are likely unable to penetrate intact skin[13]. Water contaminated with pathogenic *Leptospira* may also rarely cause infection *via* the fecal-oral route (accidental ingestion) or respiratory route (inhalation of aerosolized organisms)[11,13]. Organisms then spread to the bloodstream and multiply, and hematogenous dissemination throughout the body occurs, with potential to affect nearly every organ system due to the ability of the spirochetes to easily cross tissue barriers before the host antibody response clears them from the blood[11,13,14].

CLINICAL PRESENTATION

The clinical features of leptospirosis are both highly variable and nonspecific, depending on both host and pathogen factors. A significant proportion of infections are likely asymptomatic or subclinical, and when symptoms do occur, onset is typically 2 to 30 d after exposure, with average incubation time of 7 to 12 d[13,14]. The majority of symptomatic cases (up to 90%) follow a biphasic pattern, consisting of an initial symptomatic leptospiremic phase lasting 5 to 7 d followed by an immune phase during which symptoms can gradually improve as the host mounts an antibody response, though clinically the two phases may be difficult to differentiate[11]. Symptoms typically begin with abrupt onset of fever, chills, myalgias, and headache, similar to many other febrile illnesses[2,11]. In leptospirosis, muscle pain is often focused in the calves and lower back, and headache is typically frontal and throbbing in character[13]. Conjunctival suffusion (erythema without exudate) is the most characteristic physical finding, but presence may be variable (seen in anywhere from 7% to 60% of patients based on review of several large case series)[11] Gastrointestinal symptoms (anorexia, nausea, vomiting, diarrhea) are common, and nonproductive cough occurs in approximately half of cases[13]. Aseptic meningitis is also relatively frequent (up to 80% of cases), and usually manifests approximately 7 d into the illness as the immune phase begins[11]. Less frequently, patients may have hepatosplenomegaly, lymphadenopathy, or pharyngitis. Of note, rash as a clinical manifestation of leptospirosis is very rare, and in fact is suggestive of other etiologies in a patient with febrile illness[13].

In a minority of cases, leptospirosis can progress to severe, fulminant disease with mortality rate from 5%-40%[11]. The combination of jaundice, renal failure, and hemorrhage is known as Weil's disease and is

the most characteristic pattern associated with severe leptospirosis, though any organ system in the body can be affected due to wide hematogenous dissemination during the leptospiremic phase. Kidney involvement is common because of the organism's predilection for renal tubules in their natural hosts, and renal failure occurs in 16%-40% of cases[15]. Renal dysfunction in leptospirosis is typically non-oliguric and associated with hypokalemia. Though renal function typically recovers with appropriate supportive care, its presence is associated with higher mortality[16]. Hepatic involvement typically occurs in a cholestatic pattern, with high conjugated bilirubin levels and more mild elevations in serum aminotransferases. Though improvement is slow, liver failure is generally reversible and not an independent contributor to increased mortality[13]. Coagulopathy and hemorrhagic complications can occur due to impaired synthetic function. Pulmonary manifestations of severe leptospirosis include alveolar hemorrhage (termed severe pulmonary hemorrhagic syndrome or SPHS) and pulmonary edema, both of which can result in acute respiratory distress syndrome (ARDS)[17]. Pulmonary involvement is associated with significantly higher mortality from leptospirosis, with case fatality rates estimated from 50%-70%[1,18]. *Leptospira* infection can also involve the heart, most commonly causing nonspecific echocardiogram abnormalities (even in mild disease). Myocarditis, pericarditis, heart block and arrhythmias may occur, and repolarization abnormalities are a poor prognostic sign[11,19]. Even after recovery, patients may have continued late sequelae including neuropsychiatric and ocular symptoms[14].

Laboratory findings commonly associated with leptospirosis are generally nonspecific, but may include mild leukocytosis often with left shift in up to 2/3 of patients, as well as thrombocytopenia[14]. Inflammatory markers (ESR, CRP) may be elevated. In cases with more severe renal manifestations, serum creatinine is often elevated, and both hypokalemia and hyponatremia may be present[13]. Even when clinical manifestations are mild, conjugated hyperbilirubinemia is often present, and can reach levels up to 40-80 mg/dL[2,13]. Mild elevations of serum transaminases are frequently seen[14]. Urinalysis may reveal proteinuria, pyuria, and occasional microscopic hematuria[2]. Creatine kinase and serum amylase may also be elevated. Examination of cerebrospinal fluid is typically consistent with aseptic meningitis, with a lymphocytic pleocytosis, moderately increased protein, and normal glucose levels[13].

DIAGNOSTIC TESTING

Because clinical manifestations of leptospirosis are very non-specific and have significant overlap with a variety of other febrile illnesses, a combination of exposure history and symptoms should prompt confirmatory testing. However, clinical suspicion alone may be enough to warrant empiric antibiotic treatment in many cases. In general, definitive diagnosis of leptospirosis can be made *via* either traditional microbiological methods (direct detection, culture) or serology. *Leptospira*, like other spirochetes, stains poorly with traditional staining methods and is best visualized with darkfield microscopy, however sensitivity and specificity are both poor when examining clinical samples[12,20]. Culture of *Leptospira* from patient samples is also challenging: The organisms typically take 1-2 wk to grow but may take over a month, and special growth media is required, often necessitating advance notice to the lab. Though specificity of culture is excellent, sensitivity is very poor (5%-50%)[11]. Blood and CSF cultures are most useful during the first 10 day of illness (leptospiremic phase), when organisms are spreading hematogenously[12,14]. However, as the immune phase begins, yield of blood cultures decreases significantly. After the second week of illness, urine cultures for *Leptospira* are more likely to be positive due to the organism's proclivity for renal tubules, and may remain positive for up to 30 d after resolution of symptoms.

Serological methods are the most commonly used means of confirming a diagnosis of leptospirosis. The "gold standard" is the microscopic agglutination test (MAT), in which acute and convalescent sera from a suspected case is mixed with a panel of live antigens from different serogroups of *Leptospira* organisms and examined for agglutination[11-13]. While there is some variability amongst labs/references, most commonly, a single titer of 1:100 (range is 1:100 to 1:800), or a four-fold rise in titer between acute and convalescent sera, serologically confirms the diagnosis of leptospirosis[12-14]. Though test characteristics are overall superior to culture and microscopy (90% sensitivity, > 90% specificity), this method has several limitations[11]. The test requires a panel of live organisms specific to the area the patient is suspected to have acquired the infection as well as specialized lab expertise, limiting use to reference laboratories[13]. Additionally, there is significant cross-reactivity both between different serogroups of *Leptospira*, as well as with other spirochetes (*Treponema* and *Borrelia* species)[11]. Because the antibody response required for MAT testing is often insufficient for detection until the second week of disease (when the immune phase begins), sensitivity when symptoms begin is limited. Several serologically-based methods to detect the early host response during the first week of disease have been developed; the most commonly used is enzyme-linked immunosorbent assay (ELISA). These assays use a general leptospiral antigen that will detect IgM to both pathogenic and non-pathogenic serogroups of *Leptospira*[14]. In addition to having greater sensitivity than the MAT during the first week of leptospiral infection, ELISA is more easily standardized, and several commercial products are available, so use is not restricted to reference laboratories.

As both culture and serological methods are limited in early detection (by leptospiral growth rate and host immune response development, respectively), newer molecular methods have been developed to facilitate

early detection. Both conventional and real-time PCR techniques are highly sensitive even early in disease, prior to development of antibody response[21]. Because this period correlates with the leptospiremic phase, blood is the best sample in which to detect leptospiral nucleic acid, though urine, CSF, or tissue may also have detectable levels later in disease[11]. Of note, because PCR detects nucleic acid and is not dependent on presence of live organisms, this technique can be used even after initiation of empiric antibiotics[21]. Other molecular techniques for early diagnosis of leptospirosis have been described, including *in-situ* hybridization and loop-mediated isothermal amplification, but though promising, the clinical applicability of these molecular methods has yet to be established[21]. Additionally, because specialized equipment is typically required, utility may be limited in resource-poor or field environments. In these situations, early IgM detection tests are likely to be the best balance of rapid results with suitable test characteristics, ease of use, and cost. In addition to ELISA as discussed above, several other rapid screening test methods have been developed including dipsticks, latex and slide agglutination tests, and immunochromatography[12-14]. Regardless of the method used, all positive tests require confirmatory testing, ideally with the MAT[14].

TREATMENT

Initial treatment depends on the severity of the illness at presentation. Most cases of leptospirosis are mild and self-limiting, and patients often do not present for care[22]. For milder cases, oral doxycycline, azithromycin, ampillicin or amoxicillin are all options based on *in vitro* testing though no randomized clinical trials comparing antibiotic regimens in mild cases have been performed[22,23]. In a small double blind randomized study by of 29 patients by McClain *et al*[24], antibiotic treatment has been shown to reduce symptoms including fever, malaise and headache by 2 d, and prevent leptospiruria, but there is insufficient evidence to conclude that treatment prevents progression to severe disease. Considerations for treatment should depend on cost, availability and differential diagnosis. Doxycycline should be avoided in pregnant women and children. In areas where rickettsial diseases are endemic, doxycycline or azithromycin are the drugs of choice[22]. Regardless of antibiotic choice, a Jarisch-Herxheimer reaction can develop, typically within the first few hours after antibiotic administration. For severe cases, intravenous penicillin G sodium has been the traditional recommended treatment based on a 1988 study by Watt *et al*[25], in which penicillin G treatment compared to placebo demonstrated significant reductions in fever duration, creatinine elevation and hospital duration in 42 patients and has been reinforced by expert opinion[14,23,25,26]. Due to emerging antibiotic resistance of bacterial pathogens, the narrow spectrum against other tropical infections, and several studies showing no clinical benefit including mortality with penicillin, there has been interest in evaluating other antibiotics[26-28]. In an open, randomized study by Suputtamingkot *et al*[26], 256 patients with confirmed leptospirosis were randomized to receive intravenous penicillin G, doxycycline or cefotaxime. There was no significant difference in mortality rate (1.2%, 1.2% and 0%), duration of fever (72, 72 and 60 h), and duration of hospitalization (6, 5 and 5.5 d)[26]. Similar findings were seen in an open-label, randomized study by Panaphut *et al*[29], which compared intravenous ceftriaxone to intravenous penicillin G in 173 patients with severe leptospirosis. There was no statistically significant difference in fever duration (3 d in each group), duration of renal impairment including failure (RR = 1.0; 95%CI: 0.7-1.4), or mortality (5 patients in each group, 5.8% overall case mortality rate)[29]. Interestingly, the role of any antibiotic in the treatment of leptospirosis has come into question. Both a 2012 Cochrane Review by Brett-Major and Coldren and in a 2013 meta-analysis by Charan *et al*[30] found insufficient evidence to recommend antibiotic treatment for both mild and severe cases of leptospirosis[29,30]. Specifically, Charan *et al*[30] demonstrated no statistically significant effect of penicillin G *vs* placebo on mortality or need for dialysis.

The reported mortality associated with severe pulmonary involvement is up to 50%-70%[1,18]. A proposed mechanism of pulmonary injury is immune-mediated inflammatory response, hence an interest in adjunctive treatment with steroids. Rodrigo *et al*[31] examined the role of steroids in patients with severe pulmonary infection in a 2013 meta-analysis. Of the five identified trials, four demonstrated benefits of early steroid administration; however, each was considered methodically flawed. The fifth trial was a double-blind, randomized control study, which demonstrated no mortality benefit and a potentially increased risk of infection[31]. Desmopressin has also been evaluated as adjunctive treatment, but a randomized study of 52 patients with confirmed leptospirosis by Niwattayaku *et al*[32] found no mortality benefit.

PREVENTION

There have been very few studies examining the efficacy of leptospirosis chemoprophylaxis. A 2000 Cochrane review article by Guidugli *et al*[33] identified two such studies, one of which was found to be flawed. The included study by Takafuji *et al*[34] was a double-blind, randomized study of 940 United States soldiers deployed to Panama. Subjects were randomized to either oral doxycycline 200 mg weekly or placebo. Twenty cases of leptospirosis occurred in the placebo group (incidence of 4.2%) *vs* 1 case in the doxycycline group (incidence of 0.2%), with an estimated protective efficacy of 95%[34]. The applicability of chemoprophylaxis in other situations is unclear[33].

CONCLUSION

Leptospirosis is a zoonotic disease with worldwide distribution and increasing prevalence. Infection is caused by the spirochete *Leptospira*, with common exposure

being contaminated fresh water. Incubation is typically 7-12 d but ranges from 2-30 d. Most infections are asymptomatic, but symptoms range from a mild, self-limiting, non-specific febrile illness to fulminant respiratory and renal failure with a high mortality rate. Laboratory confirmation of disease can be problematic, especially in resource poor areas. Serologic testing is most frequently performed, although newer diagnostic tests are becoming available. Oral doxycycline is the typical treatment for mild cases, though azithromycin and oral penicillins are reasonable alternatives. We favor doxycycline or azithromycin as confirmatory testing is often not available for mild cases and treatment will cover most rickettsial infections as well. Intravenous penicillin G has long been the standard of care for severe cases though limited studies show no benefit compared to third generation cephalosporins. While some controversy exists regarding the benefit of treatment of any cases of leptospirosis, we recommend treatment, particularly for severe cases until definitive studies are available, given the high mortality rates. Antibiotics should be chosen based on certainty of diagnosis, cost, availability and clinical support. Given the paucity of data, we cannot provide any evidenced based recommendations for chemoprophylaxis.

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