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Leptospirosis: a Global Health Burden in Review

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Abstract

Leptospirosis is a zoonotic disease transmitted by fresh water and mammalian vectors in predominantly tropical regions, with an incidence of 0.1-10 per 100,000 in temperate climates, 10 or more per 100,000 in tropical climates, and up to 100 or more per 100,000 during outbreaks. Its rate of transmission spikes in areas affected by natural disasters such as floods and heavy rainfall and, because it often presents with non-specific symptoms, it can be difficult to diagnose. The case fatality rate in severe leptospirosis from <5 - 30% makes it a pathogen of clinical importance. This review aims to summarize the most recent literature on the subject and provide recommendations to providers who may encounter afflicted patients.

Introduction

Leptospirosis is a zoonotic disease, caused by the pathogenic protozoa of genus *Leptospira*, and is transmitted by fresh water and mammalian vectors in predominantly tropical regions. Despite a once relatively limited geographic distribution, this disease and it's potentially life threatening complications are becoming more widespread [1]. Bolstered by progressively warming global temperatures, and capitalizing on bodies of stagnant water, leptospirosis is re-emerging as a global health burden1. With heavy implications on tourism, trade and continued regional development, improving the understanding, diagnosis and treatment of leptospirosis is vital in quelling this disease with epidemic potential.

Background

The icteric form of leptospirosis was first described by Adolf Weil in Heidelberg, Germany in 1886 [2]. However, the disease was recognized much earlier as an occupational hazard of rice harvesting in ancient China [3]. The organism was first visualized at time of autopsy in a patient who was thought to have Yellow Fever in the early 1900s, before the rat was identified as a prominent source of leptospirosis infection in 1917 [3].

Epidemiology

The incidence of leptospirosis has been increasing and is the most widespread zoonosis in the world. It is endemic to areas of the Caribbean, Central America, South America, Southeast Asia and Oceania [3]. Although leptospirosis is primarily considered a tropical disease, it has become most prevalent in temperate climates due to factors such as climate change and human migration. As a result of increasing awareness and high case incidence, leptospirosis has been listed as an emerging global public health disease.

The incidence of leptospirosis is estimated to be 0.1-10 per 100,000 in temperate climates, 10 or more per 100,000 in tropical climates, and up to 100 or more per 100,000 during outbreaks. According to the WHO, there are around 873,000 severe cases annually with 49,000 deaths. The case fatality rate for severe leptospirosis has been quoted as anywhere from <5- 30% [1].

Although typically thought of as a rodent-borne illness, there has been increasing evidence that domestic animals, such as cats and dogs, play a role in transmission, with a growing number of species of leptospirosis found in these domesticated animals [1]. Farmers and agricultural workers are at higher risk for infection, owing to their frequent contact with large mammals that are known to be carriers, such as cattle, sheep and pigs, and their frequent contact with fresh water, which can harbour the pathogenic *Leptospira*.

Other at risk populations include those affected by natural disasters such as floods and heavy rainfall, as evidenced by the increased incidence in the Phillipines after Tropical Storm Washi at the end of 2011. There have also been notable outbreaks associated with adventure tourism, such as during an Eco-Challenge competition in Malaysia in 2000, amongst a group of white-water rafters in Costa Rica in 1996, and in athletes competing in various triathlons in Wis-consin and Illinois in 1998 [1].

Pathophysiology

Leptospirosis is in the order spirochaetales, the family Leptospiraceae and the genus *Leptospira*. Prior to 1989 the genus *Leptospira* was divided into *Leptospira interrogans*, which included the pathogenic strains, and *Leptospira biflexa*, which included the saprophytic, or non-pathologic, strains. These two species were then divided into serovars, with similar serovars grouped into serogroups based on cross-reactivity of anti-lipopolysaccharide (LPS) antibodies. In total there have been over 250 serovars and 24 serogroups identified within the *Leptospira interrogans*, or pathogenic, species.

This older classification is useful when developing new testing, treatment and prevention strategies. However, an alternative classification system has been developed which utilizes genotype to divide the genus *Leptospira* into 20 species, of which nine are considered to be pathogenic, five considered being intermediate, and six considered to be non-pathogenic [5].

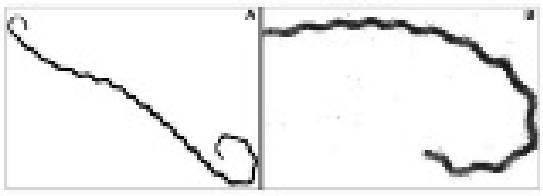

Figure 1: Transmission electron micrographs of *Leptospira interrogans* serovar Pomona [4].

Leptospires are obligate aerobes that grow at warm temperatures and can be identified by their coil shaped body, rotational movement, and relatively large size, boasting a width of 0.1-0.2 μm and a length of 6-20 μm^3 (Figure 1). They have two periplasmic flagella that enable translation and rotational movement along with two subterminally attached flagella that allow forward movement [6].

The outer membrane of the leptospire, which overlays the peptidoglycan cell wall, is made up of lipopolysaccharide as well as outer membrane proteins that are conserved at the genus level, and are therefore a focus of diagnostic testing [3].

Leptospira spp. invades and infects the proximal renal tubules of various mammals, and is excreted in the urine. These organisms can then survive for up to 16 days in fresh water, and up to 24 days in soil. It is typically spread to humans via either direct contact with the tissues or urine of infected animals, or via contact with organisms in contaminated soil and water. The organism enters the host through cuts or abrasions, mucous membranes or through wet skin [5]. There have been rare reports of spread through breast milk, trans-placental transmission, and sexual contact [7].

Once the organism enters the human host, ninety percent of those infected with the bacteria will be asymptomatic. Among those that do develop symptoms, there are two distinct phases of disease. The first consists of a flu-like illness that is associated with leptospiremia and local invasion. These symptoms last for up to one week and then dissipate. From there, most patients will develop the subclinical form; while some go on to develop more severe symptoms. Although not well understood, the second and potentially more serious phase is thought to be related in part to an autoimmune etiology. Amongst individuals with serious infections, depositions of IgM, IgG, IgA and C3 have been found along alveolar basement membranes, and are believe to contribute to the pulmonary complications of leptospirosis [7]. Potential virulence factors have also been identified that may contribute to the pathogensis of *Leptospira* infection, including LPS, hemolysins, outer membrane proteins and other surface proteins, and cell adhesion molecules [1].

Clinical Presentation

In tropical regions of the world, leptospirosis may be confused with other common maladies such as dengue, malaria and typhoid fever [8]. Symptoms of infection by *Leptospira* may range from flu-like illness, to fatal disease [4,5,8]. Following infection, the organism incubates for 1 to 2 weeks, after which a period of septicemia begins, causing symptoms such as chills, myalgia, abdominal pain, headache and conjunctivitis [3,4]. A period of defervescence follows for 1-3 days, with recurrence of fever, flu-like symptoms, and possibly aseptic meningitis during the immune phase [4]. It is during this phase that antibodies are produced, and the organism is excreted in the urine [4].

Serious complications of *Leptospira* infection include hepatic and renal dysfunction, with death typically resulting from kidney failure, pulmonary haemorrhage, or other end-organ dysfunction. The progression and severity of infection are impacted by *Leptospira* virulence factors and patient co-morbidities, which heavily influence overall prognosis [8]. Icteric leptospirosis, or Weil's disease, occurs in 5-10% of infected patients, and carries a mortality of 20-40% [9]. It is the prime example of severe *Leptospira* infection, which causes jaundice, as a result of cholestasis rather than hepatocellular death, haemorrhage, and renal failure [4,5,8,9].

Oliguric renal failure is a large predictor of death in afflicted patients [8]. Additionally, thrombocytopenia occurs in 50% of patients, and in severe cases may cause subcutaneous bleeding, subconjunctival hemorrhage, hemoptysis and gastrointestinal bleeds [8]. An extreme manifestation of *Leptospira* infection is Leptospirosis-associated pulmonary hemorrhage syndrome (LPHS). With a mortality rate of 30-70%, LPHS carries a worse prognosis than Weil's Disease, and is a notable cause of ARDS and prolonged ICU stay (Figure 2) [4,8]. These symptoms may occur rapidly between days 4-6 of symptom onset, and can lead to death within 72 hours [8].

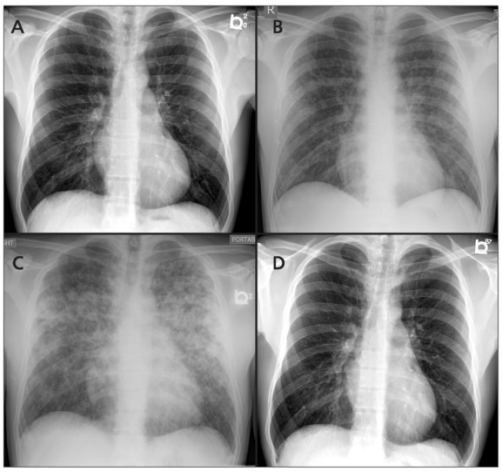

Figure 2: Chest radiographs of a male patient who presented with fever and hemoptysis, demonstrating: (A) a normal image on day 4, (B) patchy airspace opacities on day 7, (C) worsening diffuse airspace opacification on day 8, (D) a normal image at 3-month follow up [10].

Diagnosis

Leptospirosis should be considered in patients who live in, or are returning from travel to, tropical regions of the world and present with the above symptoms [4,8]. A study performed by LaRocque et al found that the presence of high fever for a long duration and subconjunctival hemorrhage was very suggestive of leptospirosis [8]. In assessing the patient, a thorough physical exam should be performed. While nonspecific, highly suggestive findings such as bruising and hepatosplenomegaly are suggestive of severe disease [8]. Lab analysis should include a complete blood count with differential, which may demonstrate leukocytosis with neutrophilia, thrombocytopenia and/or

anemia, a basic metabolic panel to evaluate renal function, and coagulation studies (Table 1) [5,8,9]. If obtained, urine analysis may demonstrate proteinuria, and inflammatory tests, such as ESR, are typically elevated [9]. Leptospirosis may cause severe jaundice, though LFTs are typically only slightly elevated, in the range of 100-200, which distinguishes this infection from viral hepatitis. A chest X-ray, at a minimum, should be used to assess for effusions, pulmonary hemorrhage, or ARDS [9].

Diagnostic Testing	Findings
Complete Blood Count (CBC)	Leukocytosis (>12,000 WBC/mm3) with neutrophilia and Thrombocytopenia (< 100,000 platelets/mm3)
Serum Creatinine	>3 mg/dL (or CrCl < 20 mL/min) and BUN > 23 mg/dL
Liver Function Tests	AST/ALT ratio > 4; Bilirubin > 190 µmol/L
Bleeding Parameters	Prothrombin Time (PT) prolonged
Potassium (Serum)	>4 mmol/L
Arterial Blood Gas (ABG)	Metabolic acidosis (pH < 7.2; HCO_3 < 10) and Hypoxemia (PaO_2 < 60 mm Hg; SaO_2 < 90%; PaO_2/FiO_2 < 250)
Chest Radiograph	Extensive alveolar infiltrates
Electrocardiogram	Heart Block, Myocarditis and/or Repolarization Abnormalities

Table 1: Compilation of diagnostic studies consistent with leptospirosis [9].

Since the symptoms of leptospirosis at first are nonspecific, its diagnosis and early detection is often problematic [5,11]. Growth of *Leptospira* in blood, CSF or urine is the most specific method of diagnosis, but these methods are hindered by the time needed to obtain results [11]. Serological assays, therefore, are the mainstay of diagnosis, with microagglutination (MAT) being the gold standard [5,11]. The test requires the maintenance of a battery of standard strains of *Leptospira*, which is then supplemented by locally prevalent strains and evaluated by trained expert microscopists [11]. While serologic assays have aided in the diagnosis of leptospirosis, the maintenance and interpretation of the study largely limits its use in the field, or certain areas of the developing world [11].

Serological IgM or IgM/IgG ELISA assays are considered to be effective for rapid diagnosis; however, they rely on host antibody development and have high false negative rates in the early stages of infection (Figure 3) [11]. An alternative testing method currently being investigated utilizes a dual path platform, which uses recombinant *Leptospira* immunoglobulin-like protein as the antigen, and both visual observation and direct detection of Leptospiral nucleic acids for diagnosis of infection [5,11].

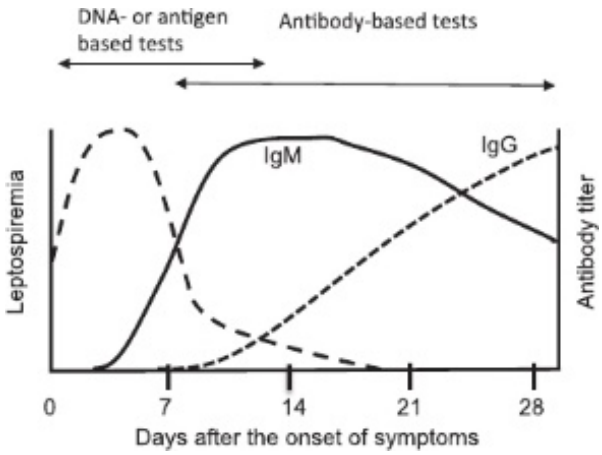

Figure 3: Immunologic blood markers of *leptospira* infection [2].

Treatment

The current recommendation is to treat mild to moderate cases of leptospirosis with doxycycline, and severe disease with penicillin, ampicillin or a cephalosporin [11]. Antibiotics should be initiated as soon as leptospirosis is suspected, and ideally before day 5 from the onset of symptoms [9]. In pregnant females, doxy/tetracycline should be avoided, and amoxicillin, ampicillin or azithromycin should be used instead [9].

However, a Cochrane review published in 2012 demonstrated insufficient evidence in favor of or against the use of antibiotics for the treatment of leptospirosis. Despite shortening the duration of fever by an average of two days, none of the trials which compared antibiotics to placebo demonstrated a decrease in mortality [12].

ICU admission is needed for patients who develop Weil's disease, and dialysis should be available for those who develop ARF [9]. Additionally, patients may require blood products, including whole blood and platelets [9].

Prevention

Most local outbreaks of leptospirosis have arisen from contaminated water sources [5]. The risk of leptospirosis transmission increases as the organism finds more suitable environments in which to thrive, which have been furthered by global climate change [5]. People can effectively lower their risk of exposure to *Leptospira* by avoiding the source: wading in contaminated waters [9]. Those who are at risk of coming into contact with the bodily fluids of infected animals should use personal protective equipment, including boots, goggles, and rubber gloves, and contaminated surfaces should be treated to eradicate the organism with desiccants, acids, phenols, disinfectants,

antiseptics, or heat. Rodent control, especially in urban areas and near communal water sources, is essential to limiting infection. Prophylactic antibiotics for residents of, or travelers to, endemic areas are not routinely recommending [9].

Water treatment is an especially important, yet globally neglected, process that can greatly decrease the incidence of disease [5]. Most infectious agents are eliminated from water in the developing world through chlorination, only to be recontaminated later as it sits stagnant in uncovered, shallow wells [5]. Poor regulation, lack of funds and equipment, and desperation contributes greatly to the rapid spread of this deadly disease [5].

Until recently, prevention has focused on the vaccination of domestic animals, which does not prevent the carrier state [9,13]. Human vaccines are available in China, Japan and Vietnam, but they are serovar-specific, and require annual boosters [9]. A vaccine against multiple serovars has been developed in Cuba, and shown to be 78.1% effective, but is currently in the early stages of clinic trials and safety testing [9].

Summary

Leptospirosis is a zoonotic infection once relegated to tropical regions, now with a continually expanding impact on global health in the setting of changing climate patterns. In spite of more than a century of research, this animal-borne protozoan continues to affect developing and established communities worldwide, often-times in epidemic patterns following floods, hurricanes and other natural disasters. With a broad spectrum of clinical manifestations, this potentially fatal infection, while largely responsive to antibiotic regimens, is difficult to diagnosis due to poorly standardized and expensive point-of-care testing. Despite the continuous development and improvement of diagnostic tools and strategies, leptospirosis represents a rapidly re-emerging global health burden, propagated by the expanse of climates which promote *Leptospira* colonization. Accordingly, it is imperative that practitioners and travelers alike be aware of the risks, signs and symptoms, and treatments for this potentially devastating disease. Without readily available, low cost diagnostic tools or clearly defined containment strategies during outbreaks, education and awareness are essential to curbing the global impact of leptospirosis, and accordingly, is the primary intent of this review article.

References

1. Wasinski B, Dutkiewicz J (2013) Leptospirosis--current risk factors connected with human activity and the environment. Ann Agric Environ Med 20: 239-244.
2. Picardeau M, Bertherat E, Jancloes M, Skouloudis A, Durski K, et al. (2014) Rapid tests for diagnosis of leptospirosis: Current tools and emerging technologies. Diagn Microbiol Infect Dis 78: 1-8.
3. Musso D, La Scola B (2013) Laboratory diagnosis of leptospirosis: a challenge. J Microbiol Immunol Infect 46: 245-252.
4. Fraga TR, Barbosa AS, Isaac L (2011) Leptospirosis: aspects of innate immunity, immunopathogenesis and immune evasion from the complement system. Scand J Immunol 73: 408-419.
5. Wynwood SJ, Graham GC, Weier SL, Collet TA, McKay DB, et al. (2014) Leptospirosis from water sources. Pathog Glob Health 108: 334-338.
6. Schreier S, Doungchawee G, Chadsuthi S, Triampo D, Triampo W (2013) Leptospirosis: current situation and trends of specific laboratory tests. Expert Rev Clin Immunol 9: 263-280.
7. Ko AI, Goarant C, Picardeau M (2009) Leptospira: the dawn of the molecular genetics era for an emerging zoonotic pathogen. Nat Rev Microbiol 7: 736-747.
8. Toyokawa T, Ohnishi M, Koizumi N (2011) Diagnosis of acute leptospirosis. Expert Rev Anti Infect Ther 9: 111-121.
9. Puliyath G, Singh S (2012) Leptospirosis in pregnancy. Eur J Clin Microbiol Infect Dis 31: 2491-2496.
10. Leung V, Luong M, Libman M (2011) Leptospirosis: pulmonary haemorrhage in a returned traveller. CMAJ 183: 423-427.
11. Ricaldi JN, Swancutt MA, Matthias MA (2013) Current trends in translational research in leptospirosis. Curr Opin Infect Dis 26: 399-403.
12. Brett-Major DM, Coldren R (2012) Antibiotics for leptospirosis. Cochrane Database Syst Rev : CD008264.
13. Dhama K, Verma AK, Kumar A, Deb R, Rahal A, et al. (2012) Leptospirosis-persistence of a dilemma: An overview with particular emphasis on trends and recent advances in vaccines and vaccination strategies. Pak J Biol Sci 15: 954-963.