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# Leptospirosis

This article forms part of our travel medicine series for 2010, providing a summary of prevention strategies and vaccination for infections that may be acquired by travellers. The series aims to provide practical strategies to assist general practitioners in giving travel advice, as a synthesis of multiple information sources which must otherwise be consulted.

## Background

Leptospirosis is one of the many diseases responsible for undifferentiated febrile illness, especially in the tropical regions or in the returned traveller. It is a disease of global importance, and knowledge in the disease is continually developing.

## Objective

The aim of this article is to provide clinicians with a concise review of the epidemiology, pathophysiology, clinical features, diagnosis, management and prevention of leptospirosis.

## Discussion

Leptospirosis should be included in the broad differential diagnosis of febrile illness. The clinical manifestations of the disease vary from mild, nonspecific illness through to severe illness resulting in acute renal failure, hepatic failure and pulmonary haemorrhage. Diagnosis is dependant on accurate prediction of the time of infection: culture, polymerase chain reaction and serology may be used to confirm the diagnosis. Management is centred on prompt antibiotic therapy using doxycycline or intravenous penicillin G or intravenous ceftriaxone/cefotaxime. Prevention of leptospirosis revolves around the 'cover-wash-clean up' strategy.

**Keywords:** communicable/infectious diseases; tropical medicine; preventive medicine; travel; leptospirosis



leptospirosis infections in Australia.<sup>2</sup> Two new serovars have emerged in Australia over the past decade: *L. borgpetersenii* sv. *Arborea* and *L. weilli* sv. *Topaz*.<sup>2,5,6</sup> Given the increasing scientific knowledge of leptospirosis, clinical awareness needs to be drawn to the diagnosis, management and prevention of the disease.

## Epidemiology

*Leptospira* has a worldwide distribution, occurring in a range of climates. It is particularly prevalent in tropical areas such as Southeast Asia, and locally in northern Queensland due to the high humidity, rainfall and temperatures, which promote the survival of the organism.<sup>2</sup> The average notification rate of leptospirosis is 0.85/100 000 population/year in Australia (1991–2009), with Queensland having the highest notification rate of 2.45/100 000 population and the Australian Capital Territory the lowest (0.06/100 000 population).<sup>7</sup>

Many animals have been reported as vectors for *Leptospira*, including animals (cows, pigs, and sheep) and rodents such as rats and mice (both native and introduced species) and bandicoots, possums, bats and kangaroos.<sup>2,6,8,9</sup>

## Risk factors

Risk factors for leptospirosis include:

- occupation – high risk industries include cattle/dairy cow production, and banana cultivation
- contact with animals – either direct contact with animals or carcasses, or indirect contact through contaminated urine/soil
- recreational exposure – bushwalking, hunting, swimming, camping or adventure sports (eg. white water rafting). These activities result in prolonged exposure to contaminated soil and water
- travel to regions with high rainfall/temperatures – in Australia, the highest incidence of leptospirosis occurs in the areas surrounding Cairns in northern Queensland.<sup>2</sup>

Leptospirosis is the infection caused by the spirochaete genus *Leptospira*. It was first identified in Germany in 1886 by Weil.<sup>1</sup> Leptospirosis was first identified in Australia in 1933 after an outbreak in the northern Queensland town of Ingham.<sup>2</sup> Leptospirosis is considered an emerging infectious disease given its worldwide distribution and profound effect on developing world medicine.<sup>3</sup>

The *Leptospira* genus is divided into 20 species of which nine are pathogenic.<sup>4</sup> Serologically, *Leptospira* are divided into over 200 serovars, of which eight serovars cause the majority of

## Pathophysiology

*Leptospira* enter the body via contact of the organism with abrasions or mucous membranes; often as a result of contact with *Leptospira* contaminated urine or soil. There is an incubation period of 2–20 days. This is followed by a biphasic disease, with an acute spiraemic phase of approximately 7 days followed by an immunogenic phase characterised by the production of IgM and later IgG antibodies (Figure 1). The systemic illness is a consequence of *Leptospira* invading target organs such as the kidneys, lungs and liver, resulting in a systemic vasculitic reaction with endothelial damage.<sup>1</sup>

## Clinical features and complications

Clinical symptoms vary from a nonspecific flu-like illness through to febrile illness. Typical symptoms reported in the acute spiraemic phase include: fever, headaches, myalgias, rigors, arthralgia, nausea, vomiting and jaundice. Less common signs include hepato-splenomegaly and lymphadenopathy.<sup>2</sup> The most serious sequelae occurs during the immune phase of the disease, including acute renal failure, hepatic failure, aseptic meningitis and severe pulmonary hemorrhage syndrome.<sup>1</sup> Fulminant leptospirosis is uncommon in Australia due to the availability and quality of critical care units.

## Differential diagnosis

Given the nonspecific symptoms of leptospirosis and tropical geography of infections, one must entertain a large number of differential diagnoses including: malaria, dengue, cytomegalovirus, Epstein-Barr virus, typhoid, typhus, hepatitis, influenza, Q-fever, brucella, Ross River virus, Barmah Forest virus, Murray Valley encephalitis virus and Japanese encephalitis virus.

If the patient is a returning traveller from overseas with a febrile illness, the list of differential diagnosis widens. For a review on this subject refer to the article 'Assessment of febrile illness in the returned traveller' by PA Leggat.<sup>10</sup>

## Diagnosis

### Culture

During the spiraemic phase of the disease, it is possible to culture the organism using

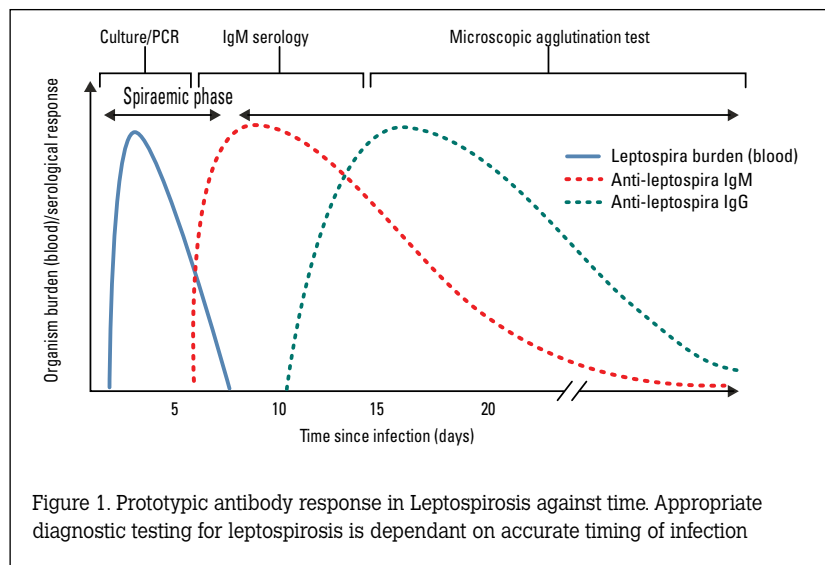


Figure 1. Prototypic antibody response in Leptospirosis against time. Appropriate diagnostic testing for leptospirosis is dependant on accurate timing of infection

specialised media. Typically several drops of aseptically collected blood are placed into Ellinghausen McCullough Johnson Harris (EMJH) media containing 0.5% agar. This is incubated for up to 1 month. It usually takes 1–2 weeks incubation for sufficient organisms to be present for visualisation under dark field microscopy. Further identification to a serovar level requires complex serological testing which may take months to be completed. Due to the 1–2 week delay in definitive diagnosis, culture is not an optimal tool to determine the initiation of management, but remains useful in studying the epidemiology of the disease.

### Polymerase chain reaction

A polymerase chain reaction (PCR) test for leptospirosis is available at the WHO/FAO/OIE Collaborating Centre for Reference and Research on Leptospirosis, Forensic and Scientific Services, Coopers Plains, Queensland. Requests for *Leptospira* PCR testing can be referred to the laboratory by private pathology companies. This test has been evaluated alongside the *Leptospira* IgM ELISA and culture for the early detection of leptospirosis and has a sensitivity of 96.4% and a specificity of 99.5% when compared to culture (IgM ELISA has a sensitivity of 4.2% and a specificity of 87.0% when compared to culture).<sup>11</sup> Compared to ELISA, the caveat of PCR testing is that it must be performed on samples likely to contain organisms – blood from patients in the acute phase. Consultation with an infectious disease physician or a clinical

microbiologist may be prudent before initiating PCR testing.

### Serology

The majority of leptospirosis diagnoses in Australia are made by serology. IgM antibodies are detectable in sera within 5–10 days after infection (Figure 1). These can be detected by a commercially available ELISA kit. The ability of these assays to diagnose leptospirosis is dependant on when the sera was taken, past exposure to *Leptospira* (residual levels of IgM), and the potential of IgM cross reactivity with other diseases. There is no *Leptospira* specific IgG ELISA method available, however confirmation of infection can be performed using the microscopic agglutination test (MAT). The MAT involves the reaction of antigens in the form of live *Leptospira* organisms with the antibodies found with the patient sera. A positive reaction will cause the *Leptospira* to agglutinate or clump and this can be viewed under dark ground microscopy. Dilutions of sera can be used to determine the titre of infection. The MAT is typically serovar specific, and can be used to approximate the epidemiology of this disease. The Public Health Laboratory Network has developed a standard case definition for the diagnosis of leptospirosis (Table 1).<sup>12</sup>

### Additional pathology testing

Additional testing should involve either serology or PCR testing (in the acute infection setting) to exclude other pathogens, especially malaria.

**Table 1. Case criteria for the diagnosis of leptospirosis<sup>12</sup>****Definitive criteria**

- Isolation of pathogenic *Leptospira sp.*, or
- Fourfold or greater increase in *Leptospira* MAT titre, or
- A single high *Leptospira* MAT titre greater than or equal to 400 against a pathogenic species

**Suggestive criteria**

- Detection of pathogenic *Leptospira sp.* by nucleic acid test (NAT), or
- A positive *Leptospira* (EIA) IgM result

**Table 2. Current recommended antibiotics for the treatment of leptospirosis<sup>14</sup>**

Antibiotic	Dose
Doxycycline	100 mg oral twice daily
Ceftriaxone	1 g IV once daily
Cefotaxime	1 g IV q6hr
Benzylpenicillin	1.2 g IV q6hr

Furthermore, it would be practical to order a baseline full blood examination, electrolyte urea and creatinine and liver function tests given the possibility of hepatic and renal involvement in the disease.

## Management

The current mainstay of leptospirosis management is prompt antibiotic therapy and patient support. Those with mild disease should be encouraged to maintain oral fluid intake, undertake bed rest and symptomatic relief with antipyretics. Admission to hospital should be considered in patients with severe disease, especially those with renal and hepatic impairment. Management may necessitate the involvement of an infectious disease physician where the diagnosis remains unclear or the patient fails to respond to treatment.

**Table 3. Interventions for reducing the incidence of leptospirosis<sup>15</sup>**

Cover	Wear fully covered shoes, gloves, long sleeved shirt, and face mask/goggles when handling animals and when in contact with animal fluids/secretions or contaminated soil, feed Cover all cuts and grazes with waterproof dressings
Wash	Wash hands and shower after contact with potentially contaminated soils, fluids, animals/carcasses
Clean up	Pest control (baiting/traps) and cleaning of workplaces/homes to minimise the infestation of potential vectors. Minimise build up of vegetation (wood piles) that may harbour rodents

Current recommendations for antibiotic choices are limited by the lack of randomised controlled trials and the presence of conflicting evidence. Currently recommended antibiotic therapy includes oral doxycycline for mild infections (in the absence of hepatic/renal disease or contraindications), or intravenous penicillin G or intravenous ceftriaxone/cefotaxime, which have been shown to be equally effective for severe disease (*Table 2*). There is currently no evidence for the use of oral amoxicillin as a substitute for doxycycline.<sup>13</sup> Treatment should begin early if there is clinical suspicion of leptospirosis, and the length of treatment is currently recommended as 7 days.<sup>14</sup>

## Public health prevention

- Prevention – general practitioners can promote the ‘cover-wash-clean up’ strategy to those engaging in high risk occupations or activities (*Table 3*)<sup>15</sup>
- Immunity – prior leptospirosis exposure does not confer complete immunisation to the organism. Future re-infections with other serovars is possible
- Chemoprophylaxis – a meta-analysis of prophylaxis treatment trials using doxycycline

for reducing leptospirosis in high risk environments has concluded that there was an unclear benefit shown (with an increase in nausea and vomiting amongst participants).<sup>16</sup> However if a patient is considering travel to a high risk environment, the threat of malaria could be equal or greater to leptospirosis, and doxycycline should therefore be considered

- Animal vaccination – currently animal vaccinations are available for *L. interrogans sv. Pomona* and *L. sv. Hardjo*. These vaccinations are used primarily to reduce the burden of disease in animals but can also reduce the potential for human exposure.

## Summary of important points

- Leptospirosis is acquired through direct contact with infected animals or via indirect contact through contaminated soil.
- It is most prevalent in tropical areas and consequently should be considered in the differential diagnoses of the returned traveller or those participating in high risk activities such as animal husbandry, banana cultivation or white water rafting.
- Leptospirosis has a spectrum of clinical presentations, with a biphasic natural history. Major systemic complications occur during the immune phase of the disease, which is usually 5–10 days after infection.
- Choice of diagnostic testing relies on accurate prediction of the infection. Acute disease is best detected by culture or PCR, and immune phase disease by serology.
- Mild uncomplicated disease may be treated in an outpatient setting using oral antibiotics, whilst complicated disease requires urgent hospital referral and multidisciplinary management.
- General practitioners have an important health promotion role in reducing the incidence of leptospirosis. This can be achieved by promoting the ‘cover-wash-clean up’ strategies to at risk individuals to reduce contact with infected animals or materials.

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