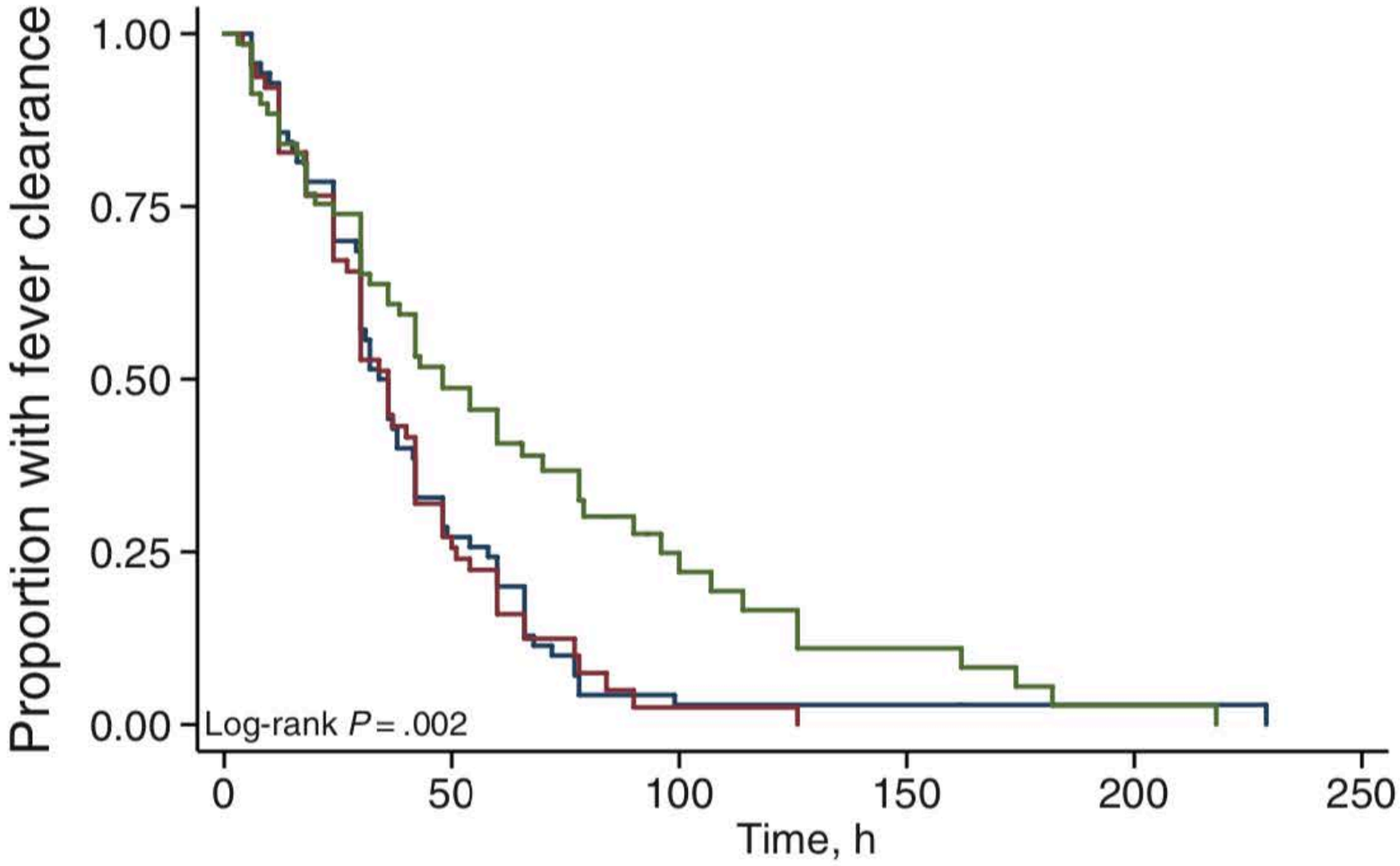
Clinical Infectious Diseases

MAJOR ARTICLE

A Prospective, Open-label, Randomized Trial of Doxycycline Versus Azithromycin for the Treatment of Uncomplicated Murine Typhus

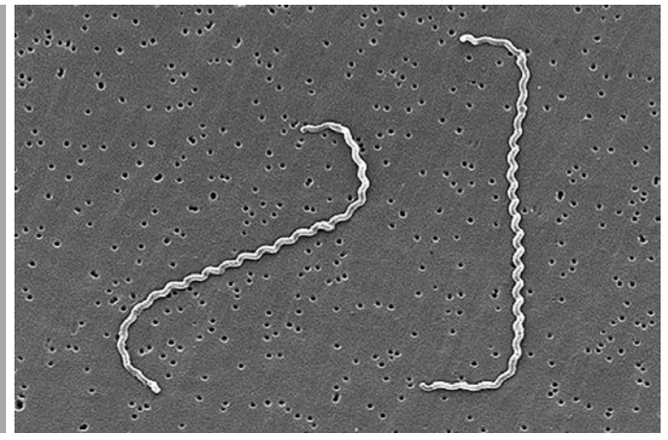


No. at risk

Doxycycline (7 d) (blue color)	70	19	2	2	1	0
Doxycycline (3 d) (red color)	64	17	1	0	0	0
Azithromycin (3 d) (green color)	69	31	9	4	1	0

Kaplan-Meier plot of fever clearance for all patients who presented with or developed fever (n = 203).

Leptospirosis



- The causative agents belong to the genus *Leptospira*, fine spiral bacteria

- The species *L. interrogans* is divided into serogroups and then into many serovars.

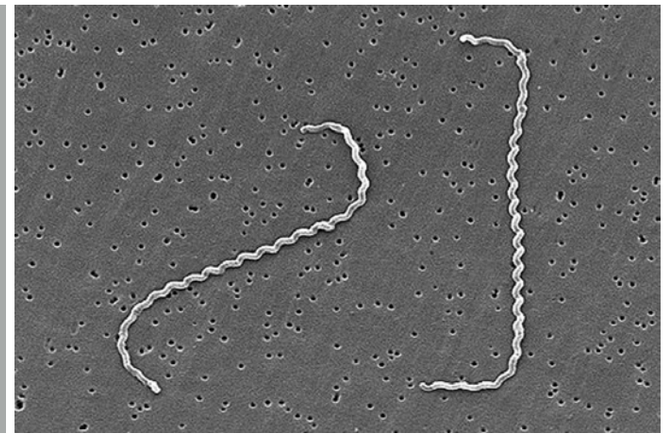
- Rodents, particularly species of rat, are the most important maintenance hosts of leptospires that may infect humans.

- Humans acquire infection by direct or indirect contact with the urine of maintenance hosts

- Leptospires are naturally aquatic bacteria, and their prolonged survival in urine contaminated water is an extremely important factor with regard to transmission of infection.

- The organism generally gains entry through fresh cuts or grazes on the skin and possibly through intact mucous membranes.

Leptospirosis



- The survival of leptospires in the environment is favoured by warm, moist conditions and neutral or slightly alkaline pH.

- They survive in fresh water at neutral pH for up to 4 weeks but at pH5, survival is reduced to about 2 days.

Clinical Manifestation

- Early non-specific bacteraemic phase

  - The incubation period is usually 7–12 (median 11) days

  - Acute febrile, influenza-like illness with chills, sore throat, headache, myalgia, back pain, anorexia, nausea and vomiting

  - Sometimes the acute phase is severe; prostrate and has a persistently high fever (39–40°C) with exquisitely tender muscles, some cough and perhaps even hemoptysis, with dyspnea

Clinical Manifestation

- Early non-specific bacteraemic phase

  - Transient skin rash; a pretibial rash with raised erythematous patches (2–5 cm in diameter) with some induration but much less tenderness than EN

  - Myalgia and tender musculature

  - Conjunctival suffusion

  - There may be moderate hepatomegaly but splenomegaly is less common.

- Leptospires may be cultured from blood, CSF and other tissues, but not from urine.

- Serological tests are negative until at least 5 days after the onset of symptoms.

- The platelet count may fall and thrombocytopenic purpura and frank bleeding ensue.

- Urinalysis shows proteinuria but creatinine clearance usually remains normal until tubular necrosis or glomerulonephritis occurs.

Clinical Manifestation

- Second (immune) phase

  - The antibody response is predominantly in the IgM class

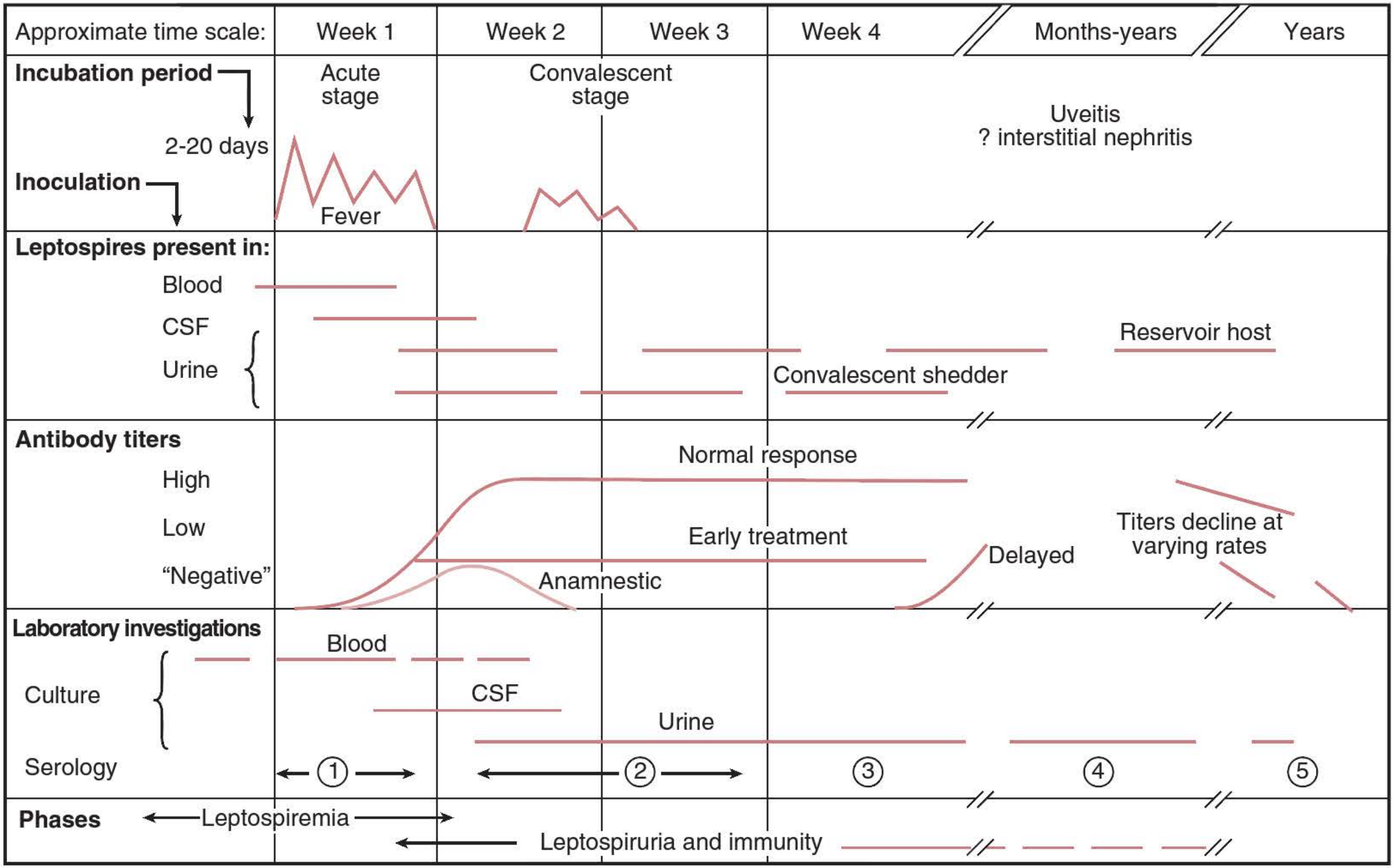
  - In mild cases, the second phase may be associated with minimal symptoms and signs

  - In the severe form of the disease, the first and second phases merge imperceptibly; with persistent high fever the patient deteriorates, becoming jaundiced and starting to bleed into the skin, mucous membranes and lungs.

Clinical Manifestation

- The liver enlargement
- The sclerae become icteric, the suffused vessels glow orange
- Purpura and ecchymoses are seen
- Oliguric renal failure, shock and myocarditis
- Pulmonary edema and sub-pleural pulmonary hemorrhages with hemoptysis, ARDS
- Gastrointestinal hemorrhage

Biphasic nature of Leptospirosis



Diagnosis

- Serological detection of antibodies to leptospires is the investigation of choice after symptoms have been present for 5–6 days

- Enzyme-linked immunosorbent assay (ELISA) techniques or microscopic agglutination against live or formalized organisms (MAT) - serogroups and serovars

Treatment

- Penicillin and other related β-lactam antibiotics are active against experimental leptospirosis in animals

- Penicillin (1.2 G benzyl penicillin intravenously or intramuscularly every 4–6 h) is the drug of choice

- Ceftriaxone was not better than penicillin in a small open-label study

Treatment

Indication	Regimen
Treatment	
Mild leptospirosis	Doxycycline[b] (100 mg PO bid) *or* Amoxicillin (500 mg PO tid) *or* Ampicillin (500 mg PO tid)
Moderate/severe leptospirosis	Penicillin (1.5 million units IV or IM q6h) *or* Ceftriaxone (2 g/d IV) *or* Cefotaxime (1 g IV q6h) *or* Doxycycline (loading dose of 200 mg IV, then 100 mg IV q12h)

Treatment

- There were no differences in outcome in patients with possible leptospirosis empirically treated with either penicillin, cefotaxime or doxycycline in an open-label study of 264 patients (confirmed) in northern Thailand, although the tetracycline was usefully active against rickettsial infection which affected 132 additional patients

- Organs supportive

Suputtamongkol Y, Niwattayakul K, Suttinont C, et al. An open, randomised controlled trial of penicillin, doxycycline, and cefotaxime for patients with severe leptospirosis. Clin Infect Dis 2004; 39:1417–1424

Any Question?