

Leptospirosis

WRAIR- GEIS 'Operational Clinical Infectious Disease' Course

WRAIR

Walter Reed Army
Institute of Research

Soldier Health • World Health



Sometime in Early September

- You are contacted by a military working dog training program in Texas regarding an outbreak of illness among their current human and non-human trainees
- Approximately one month prior, 11 students and 3 dogs participated in field training involving road marches, traversing streams, and other maneuvers
- Over the next 2 weeks, all three dogs became acutely ill and died (or were euthanized due to organ failure) and 8 of 11 human students also developed symptoms

Interview Data

Patient	Symptoms	Duration
18 y.o. M	None	N/A
32 y.o. M	Myalgias, Fatigue	1 week
20 y.o. M	None	N/A
23 y.o. F*	Headache, Chills, LBP	2 weeks
20 y.o. M	Mild fatigue	4 weeks
21 y.o. F	Mild fatigue	Unknown
27 y.o. M*	Myalgias, Fatigue	1 week
24 y.o. F	Myalgias, Headache	2.5 weeks
23 y.o. M	LBP	3-4 weeks
23 y.o. M	None	N/A
29 y.o. M*	Conjunctival suffusion	Unknown

Labs

Patient	Labs (CBC, CMP)
18 y.o. M	Not Done
32 y.o. M	WNL
20 y.o. M	Not Done
23 y.o. F*	Increased Alkaline Phosphatase
20 y.o. M	WNL
21 y.o. F	Not Done
27 y.o. M*	Increased LFT
24 y.o. F	WNL
23 y.o. M	WNL
23 y.o. M	Increased LFTs
29 y.o. M*	WNL

*Directly responsible for animal that later perished

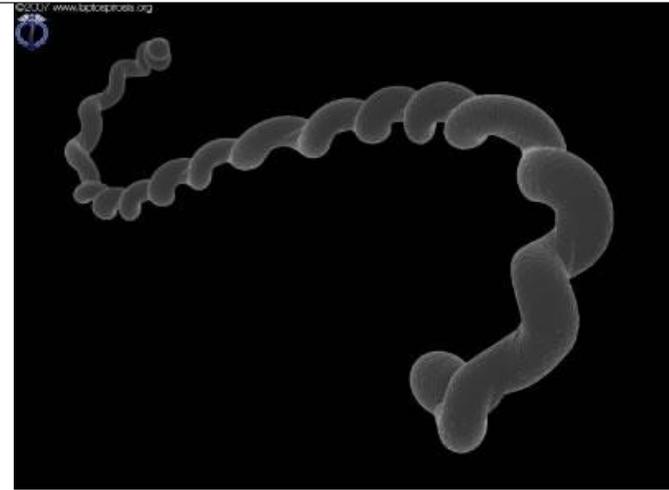
Question

- What is going on, how do you prove it, and what can you do about it?



www.jbmf.us

Leptospirosis



- The world's most common zoonosis
- Infection with spirochetal bacteria (spirochetes) from the genus *Leptospira*
- Potentially fatal in humans (though, generally not)
- 350,000-500,000 cases/year (likely underestimate)
 - Annual Incidence in tropical climates of approximately 10/100,000, with spikes up to 100/100,000 during epidemics.

Leptospira

- Finely coiled, motile spirochetes

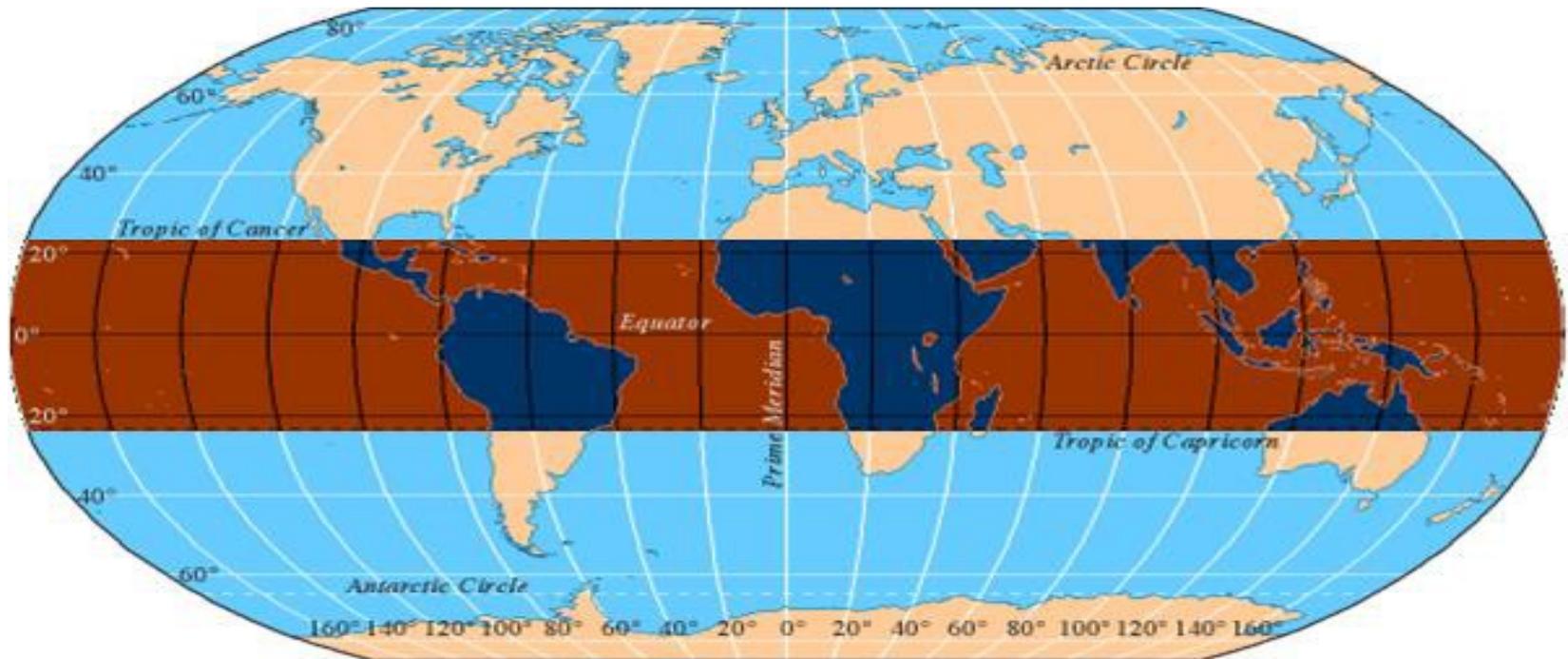


microbewiki.kenyon.edu

- Greek *leptos* (thin) and Latin *spira* (coiled)
- 25 serotypes □ 210 serovars
 - Distinct types are classified as serovars
 - These classifications can help identify a common source epidemiologically

Epidemiology

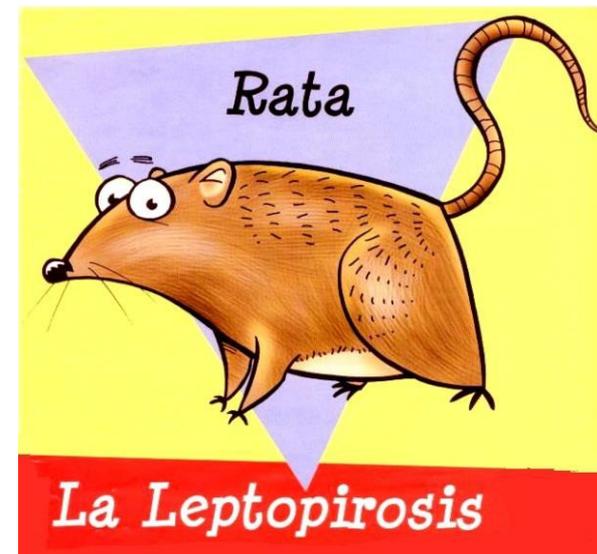
- Occurs Worldwide
 - Predominance of infections occurring in tropical climates
 - Summer-fall predominance for infections in temperate climates



Epidemiology

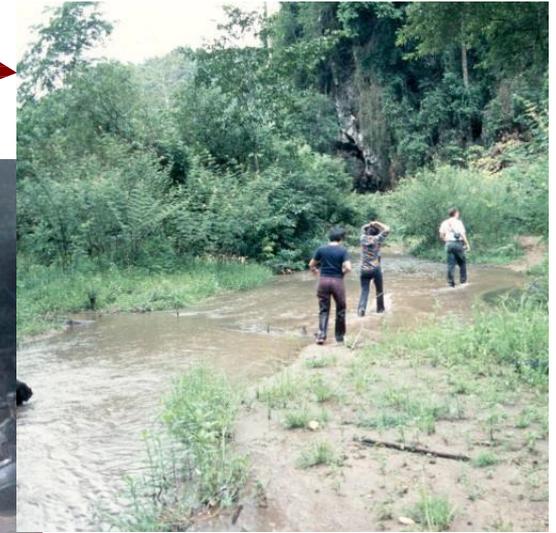
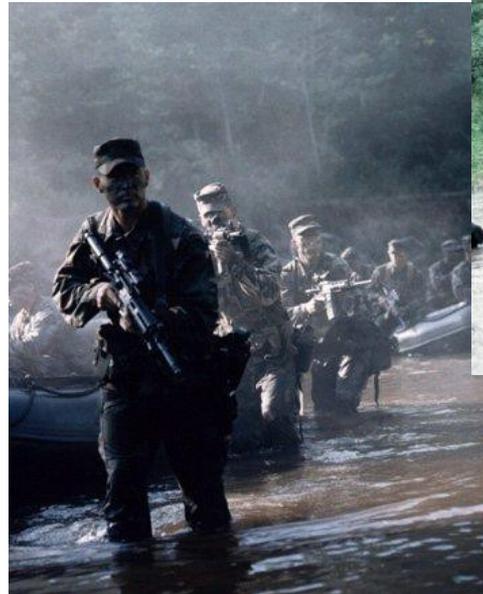
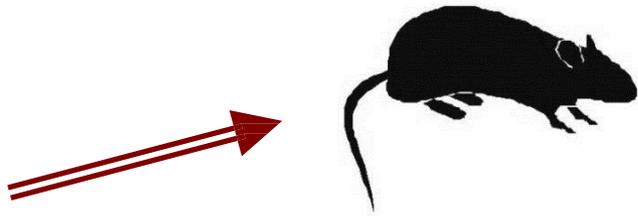
- Infection occurs after direct or indirect contact with the urine of an infected amphibian, reptile, or mammal.
 - Over 200 mammalian species have been shown to be reservoirs.
 - The brown rat (*Rattus norvegicus*) is the most common reservoir.
 - Humans are incidental (dead end) hosts, and generally incapable of transmitting the infection.

<http://www.telpin.com.ar/interneteducativa/Proyectos/2002/Enfermedadespobreza/leptospirosis.htm>



Transmission

- Zoonoses – spread to man from animals, typically rodents via urine/urine contaminated water



Environmental Persistence

- Environmental exposures
 - Infectivity in “urine spots” is retained for ~6-48 hours
 - May survive for weeks in the right conditions
 - Moist, non-polluted environment
 - Low salinity
 - Above 72° F
 - If urine is not acidic



www.myohun.com

Risk Factors

- Most cases in young adult men
- Transmitted by:
 - **Contaminated water or soil (infected urine)**
 - Direct animal contact
- Occupational and recreational exposure
 - Farmers, veterinarians, abattoir workers
 - Campers, swimmers
- Tropics – high seroprevalence
 - Thailand 27%
 - Vietnam 23%
 - Belize 37%



Risk Factors

- Occupations

- Farmers
- Mine Workers
- Sewer Workers
- Slaughterhouse Workers
- Veterinarians/Animal Caretakers
- Fishermen and people who work with fish
- Dairy Farmers
- Military Personnel

- Activities

- Swimming
- Rafting
- Kayaking

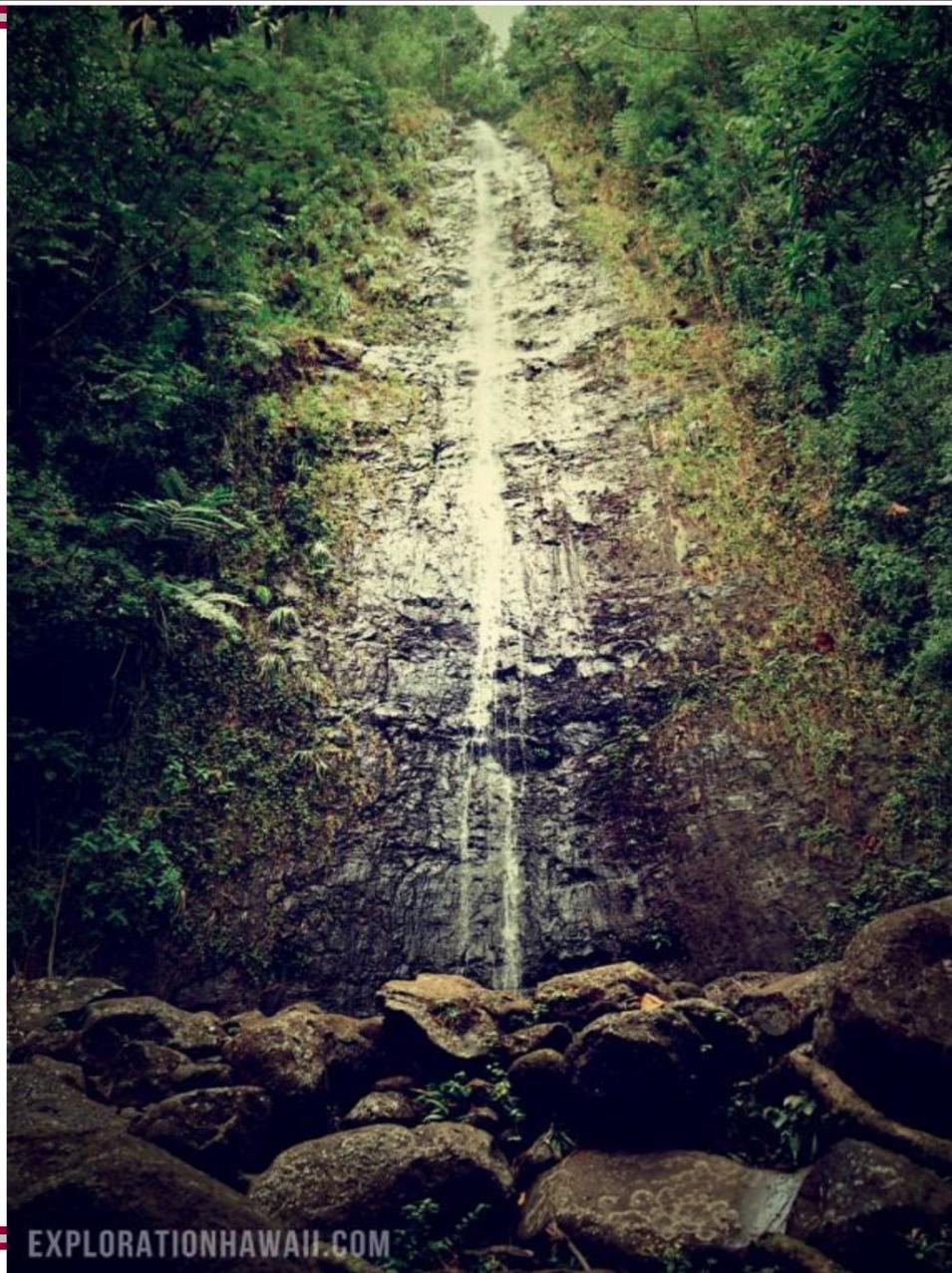


Risk Factors

- To summarize....DON'T
 - SWALLOW LAKE WATER
 - SWIM WITH ABRASIONS
 - IGNORE POSTED WARNINGS TO NOT SWIM IN A WATERFALL LAKE

[Mil Med.](#) 1997 Feb;162(2):101-4.
Leptospirosis on Oahu: an outbreak among military personnel associated with recreational exposure.

[Katz AR](#)¹, [Sasaki DM](#), [Mumm AH](#),
[Escamilla J](#), [Middleton CR](#), [Romero SE](#).

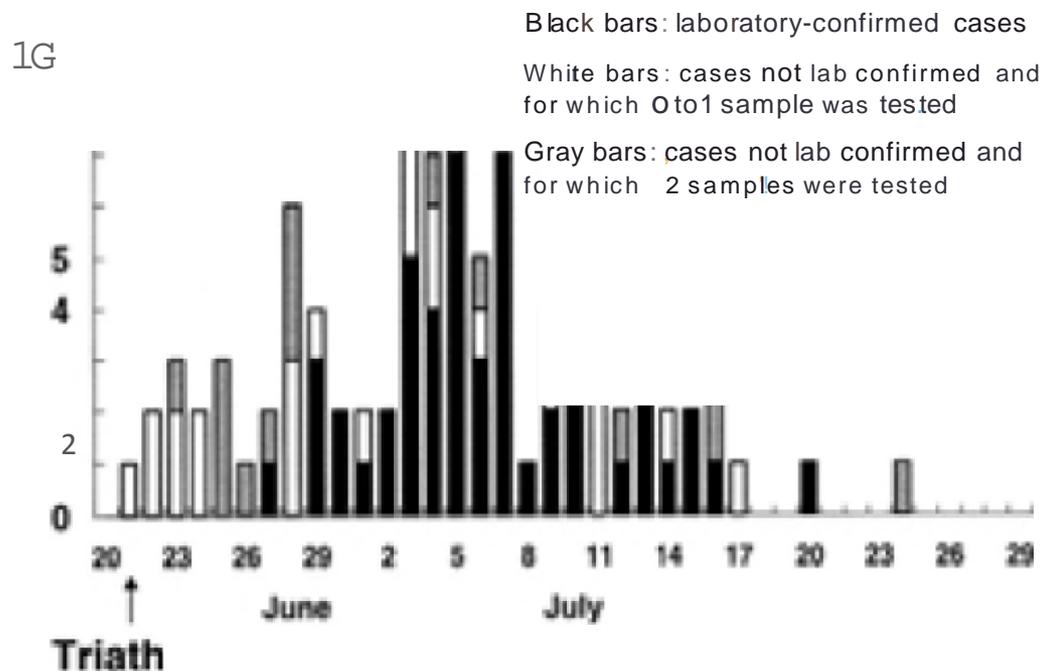


Leptospirosis in the US

- Hawaii
 - More cases than any other state (128/100,000)
 - 30 risk factors evaluated, and found association with:
 - Household water catchment systems
 - Skin cuts
 - Contact with cattle or urine of cattle
 - Handling of any tissues
 - 345 cases from 1999-2008
 - Associated with occupational exposures

Outbreaks of Leptospirosis among Triathletes Illinois and Florida

- 834 of 876 triathletes contacted:
 - 95 (12%) reported being ill
 - Serum from 474 tested
 - 52 (11%) + leptospirosis
- 14 (6%) of 248 symptomatic community residents + for leptospirosis.
- Swallow of lake water greatest relative risk (3.2)
 - Abrasions (2.1) and long swim 'times (2.4) also relative risk



Clin Infect Dis. 2002;34:1593-1599

Clin Infect Dis. 2010 15;50(6):843-9 *Outbreak of Leptospirosis among Adventure Race Participants in Florida*

Clinical Presentation

- “Leptospirosis is a zoonosis of protean manifestations” (various)
 - Ranges from completely asymptomatic to a severe illness with multi-organ involvement and a high mortality.
 - Most infections are subclinical and generally go undetected.
- Following an average incubation of 7-12 days (2-26), symptomatic infections will manifest as an acute biphasic febrile illness.

Septicemic Phase

- In the first (septicemic) phase, there is fever (38 to 40°C), often associated with other symptoms including:
 - headaches (severe, retro-orbital, possibly with photophobia)
 - myalgias (classically involving **calves** and lumbar region)
 - conjunctival suffusion
 - GI symptoms (95%): **abdominal pain**, nausea, vomiting, diarrhea
 - maculopapular rash (<10%)

“Flu-Like Illness”

- After 3-7 days, the patient will defervesce and experience a partial or complete remission of symptoms for several days, then enter the second phase of the illness.

Conjunctival Suffusion



homepages.irk.ru/IRAI/atlas_rus/leptospirosis.htm

Anicteric Leptospirosis

- For 90% of symptomatic patients, the second phase (**Immune Phase**) is marked by return of some or all of the original symptoms along with the development of antibodies.
 - New symptoms such as aseptic meningitis and renal dysfunction are also possible.
 - Full recovery generally occurs within 14 days, but may take upwards of a month.

Icteric Leptospirosis // Weil's Disease

- For the remaining 10%, the immune phase is severe, rapidly progressive, and marked by multi-organ involvement, most notably hepatic (jaundice) and renal failure.
 - Weil's Disease
 - Can include nearly any organ system
 - 10%+ mortality
 - Recovery may take many months, and permanent injury may result.

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Weil's Disease Continued

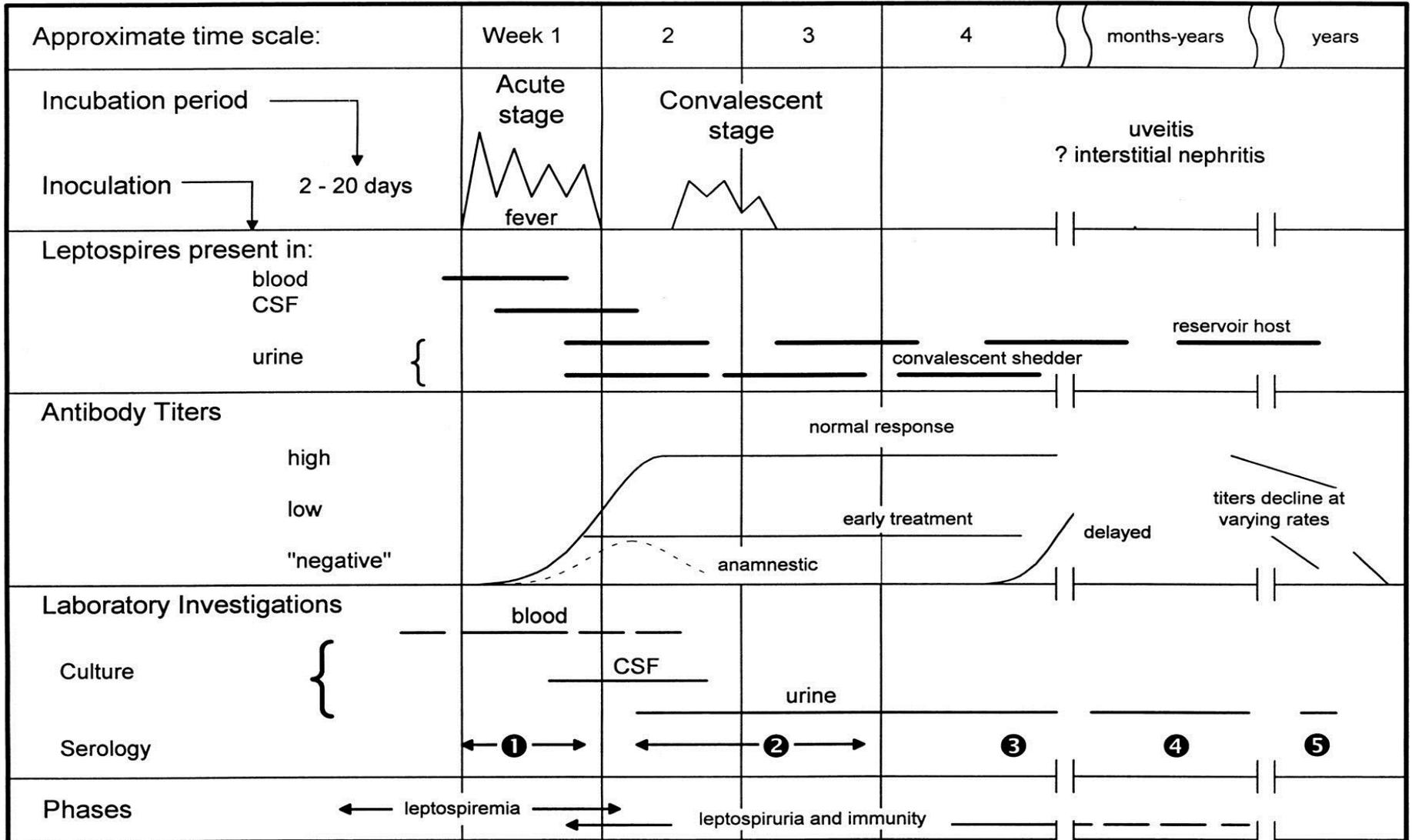
- Can be seen with any serotype
- Severe disease
 - Renal and hepatic dysfunction
 - Hemorrhage (pulmonary)
 - Vascular collapse, arrhythmias
 - Death 5-40% cases (Average ~10%)
 - Altered mental status best predictor
- Labs:
 - Total bilirubin very high (mostly direct; <20 mg/dL)
 - AST/ALT 100-200
 - Elevated CPK (differentiates from viral hepatitis)
 - High WBC

**Can Look a Lot like
Viral Hemorrhagic
Fever!!**

Weil's Disease Continued

- Renal disease
 - Protein, RBC, casts in initial phase
 - Renal failure in 25% of cases during 2nd week
 - Often requires dialysis to support the patient
- Low platelets (<30k) in 50% of cases
 - Associated with renal failure
- EKG changes possible
 - 50% of autopsies noted hemorrhagic myocarditis

Phases of Leptospirosis



Icteric
(Weil's) **Anicteric**

Jaundice	+++	
Leukocytosis	++	
Hemorrhage		-
Renal failure		-
Death	+	
Aseptic meningitis		
Disturbances of consciousness†	+	

*(-) = rare or absent; (+) = common; (++) = rare - - -.

†Due primarily to uremia in the acute and localized meningitis in icteric cases.

Co-infection is Possible

Diagnoses	Number
Malaria and leptospirosis	22
Malaria and rickettsiosis	2
Malaria and other (dengue, PTB)	2
Leptospirosis and rickettsiosis	4
Leptospirosis and other (dengue, PTB)	2
Rickettsiosis and other (typhoid, PTB)	2
Total	34

AJTMH 2006

Confusion is Possible

- Involvement of a single organ system may predominate leading to a misdiagnosis:
 - Hepatitis
 - Atypical pneumonia
 - Influenza
 - Viral Gastroenteritis
 - Meningitis or encephalitis
 - Surgical Abdomen
 - Acute nephritis

A Little More on the Ocular Findings

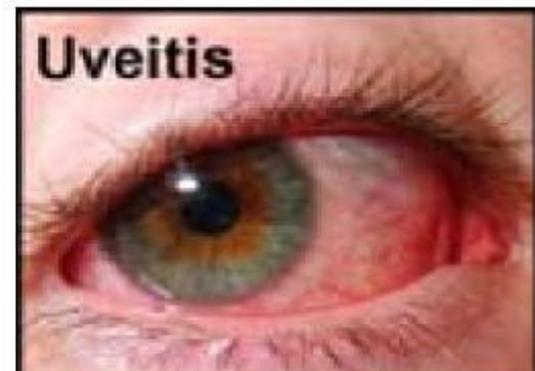
Conjunctival Suffusion (Early):

- Most frequently found sign but variable (~95%)
 - some outbreaks seen in <math>< \frac{1}{2}</math> cases
- Usually appears on day 3 or 4
- Differential:
 - Dengue, RMSF, relapsing fever
- Serous or purulent eye secretions unusual.
- Bulbar conjunctival suffusion & hemorrhage, (retro)orbital pain, photophobia - relatively common, may suggest Dx.



Uveitis (Late):

- Occurs late in the course of the disease.
- Usually at 4 - 8 months (up to 1 year).
- Sx: pain, photophobia, blurred vision.
- May be bilateral.
- Prognosis is usually good.



Meningeal Leptospirosis

- Aseptic Meningitis
 - Most important syndrome in immune stage
 - 90% of anicteric patients with WBC in CSF at 2 weeks
 - 50% have clinical signs of meningitis
 - A CDC study showed 10% of unexplained meningitis cases were seropositive for leptospirosis
 - Syndrome typically lasts only a few days
 - Lumbar puncture may help with headache although opening pressure is typically not elevated
 - Protein (slightly elevated) and glucose (normal)
 - Lymphocytic pleocytosis

Pulmonary Leptospirosis

- Seen more in Asian and Pacific serovars
 - 25% with pneumonia in Korea
- Doesn't appear to be a direct infection as organism not found in the lung tissue
- May range from mild respiratory symptoms to full ARDS
 - Degree of symptoms may not correlate with findings on chest x-ray
- Hemorrhage possible **<-May look like Viral Hemorrhagic Fevers!**
 - Attributed to severe vasculitis w/ endothelial damage

Rash in Leptospirosis-Ft. Bragg Fever

- July-August 1942 an outbreak of an unusual febrile illness was noted in soldiers at Ft. Bragg, NC, eventually* identified as a form of leptospirosis.
- In 40 hospitalized patients classic anicteric leptospirosis symptoms were observed, except for the extensive presentation of rash in 35/40 (88%) patients
 - 60% (24) Bilaterally symmetric, pretibial areas only
 - 20% (8) Pretibial and other scattered sites
 - 8% (3) Less defined or single lesions
- All patients had full recovery without complications.

*1951

Ft. Bragg Fever/Pre-Tibial Fever

- “Individual lesions consisted of an erythematous localized blush of irregular outline with ill-defined borders fading into the surrounding skin. These were often from 2 to 5 cm. in their largest diameter, gradually coalescing with adjacent lesions. The lesions were raised, warmer than the surrounding skin, and sometimes slightly tender to touch. In some patients, the lesions vaguely resembled erythema nodosum. In two patients, the rash became diffusely distributed over the entire body, and in a few it appeared urticarial. Following the generalized type of rash there was a residual pigmentation which persisted for about 2 weeks. None of the lesions were purpuric. In most instances, the cutaneous manifestations lasted 2 days, but they persisted longer in a few patients.”

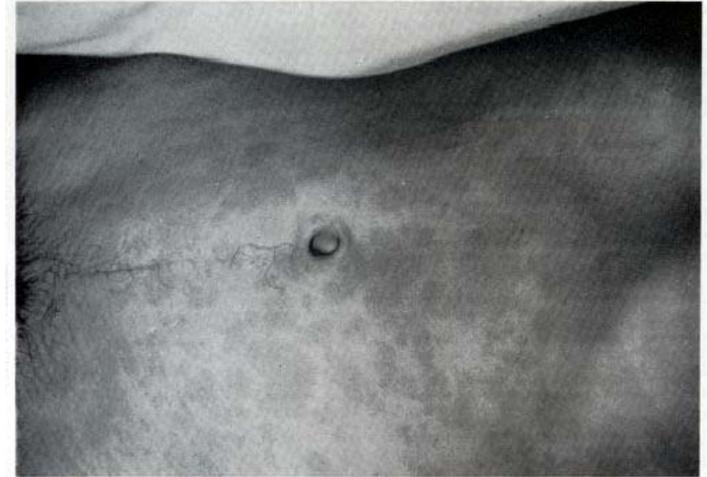


FIGURE 58.—Generalized form of skin eruption.



FIGURE 57.—Erythematous skin lesions over the pretibial regions.

Daniels WB. Fort Bragg Fever. <http://history.amedd.army.mil/booksdocs/wwii/infectiousdisvolii/chapter13.htm>. Accessed 24 June 2015.

Diagnosis

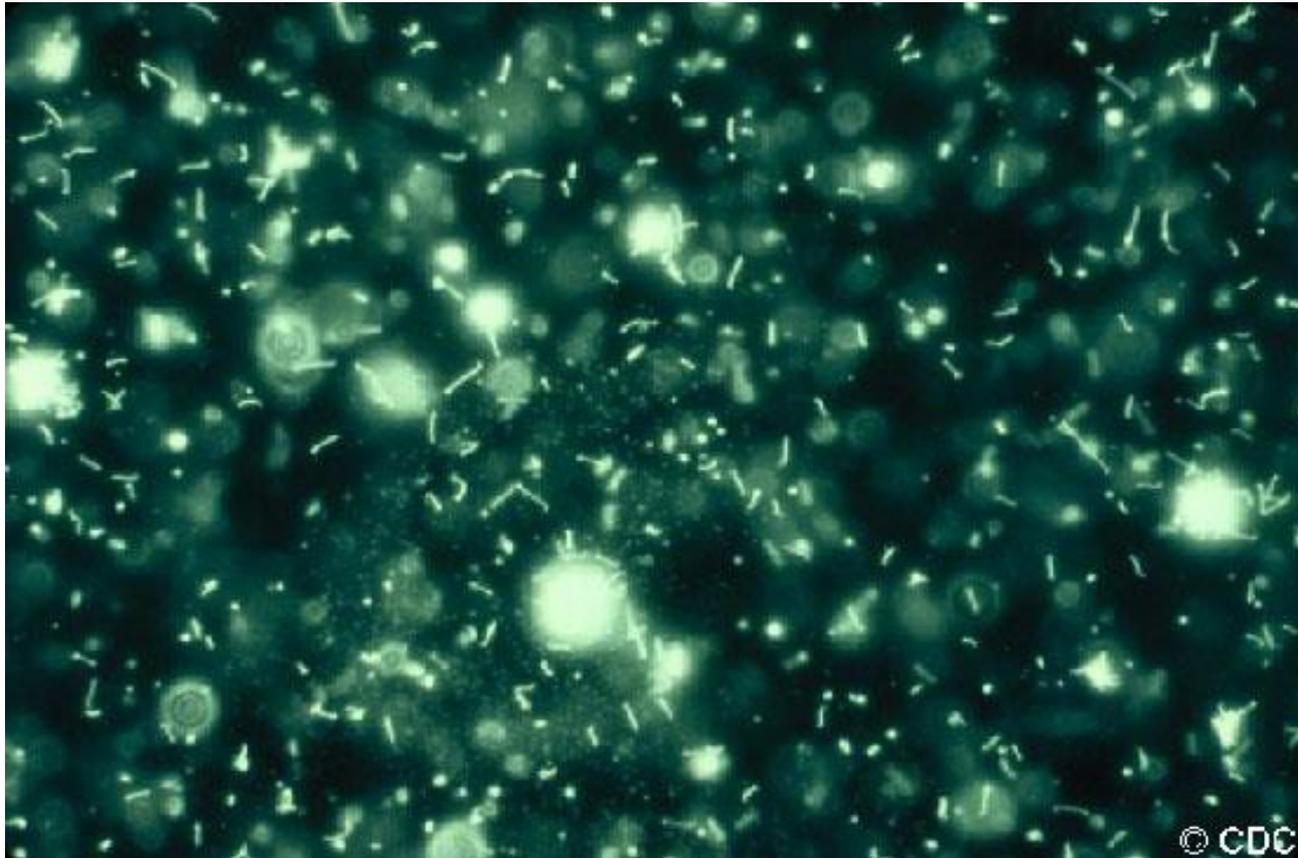
- In most environments, diagnosis is clinical
 - Chemistries and radiographs are nonspecific
 - Most organism-specific assays are either generally unavailable or entail delays that limit their practical usefulness.
 - Treatment should never be withheld waiting for laboratory confirmation.

Diagnosis

- Direct Detection Methods

- Direct visualization (blood or urine): Sensitivity/Specificity 40%/62%
- Leptospiral antigen detection: no real success
- PCR:
 - Serum, urine, aqueous humor, PM tissues
 - Confirm diagnosis during leptospiremic phase: treatment of benefit
 - Fulminating cases
- Isolate organism (may take up to 16 weeks)
 - Blood, CSF, peritoneal dialysate (first 10 days of illness); urine (after 7 days of illness)

Darkfield Microscopy



Diagnosis

- Indirect Detection Methods
- Seroconversion
 - Reference standard: Microscopic Agglutination Assay (MAT)
 - Serology useful after the first 6-12 days of illness
 - Antibiotics may suppress production of antibodies
 - Single titer >1:800 with compatible symptoms
 - Suggestive: >1:200 with symptoms
 - >4 x rise in titer with compatible clinical illness
 - Positive slide agglutination test with compatible illness
 - Delayed seroconversion common (up to 10% by 30 days)
 - Cross reaction (syphilis, relapsing fever, Lyme, viral hepatitis, HIV, legionella, autoimmune)

Most labs have little to no experience. Send samples to San Antonio Military Medical Center for testing.

Treatment

- Treatment
 - Usually a nonfatal disease (unless icteric disease)
 - Antibiotics
 - Start as early as suspicion allows!
 - Penicillins or tetracyclines may shorten illness and reduce complications if started by 4th day of illness
 - May have value in severe cases even if delayed
 - Many antibiotics likely have activity against the organism, but clinical research is limited!
 - Supportive therapy essential for hospitalized
 - Volume, potassium repletion, hemodialysis, intubation



World Health Organization

Treatment

ILS
International Leptospirosis Society

- WHO/ILS recommendations
 - Treatment, if begun in first 5 days of illness
 - High-dose IV penicillin for severe disease
 - Oral amoxicillin, ampicillin, doxycycline, or erythromycin for less severe disease
 - Ceftriaxone, cefotaxime, and ciprofloxacin appear effective

WHO 2003

Possible Regimens

- For Severe/Late Disease
 - Penicillin 1.5MU IV every 6hrs x 7 days
 - Ampicillin 0.5-1g IV every 6hrs x 7 days
 - Ceftriaxone 1-2g IV/IM every 24hrs x 7 days
 - Cefotaxime 1g IV every 6hrs x 7 days

- For Mild/Early Disease
 - Doxycycline 100mg orally twice daily x 7 days
 - Amoxicillin 500mg orally three times daily x 7 days
 - Azithromycin 500mg orally once daily x 7 days

Prognosis

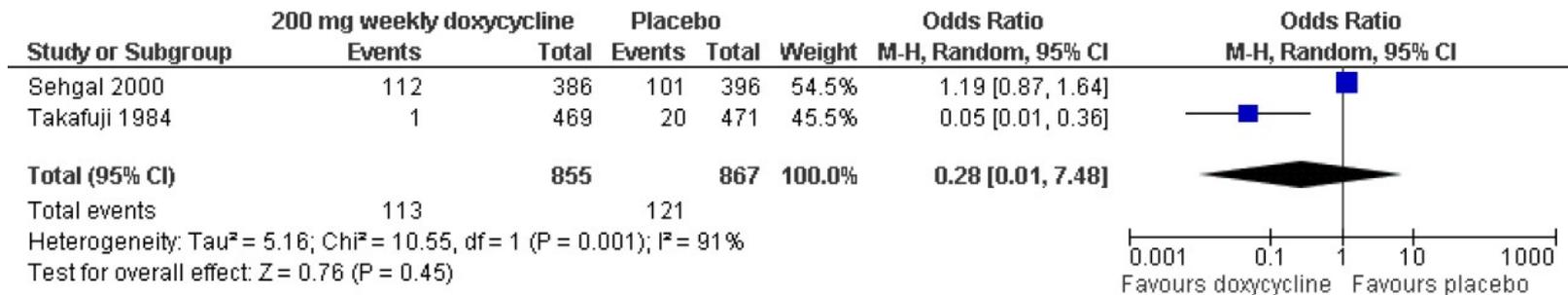
- Prognosis
 - Depends on patient's overall health
 - In U.S., case fatality rates are 2-10%
 - 5% if less than 30 years-old
 - 33% if greater than 60 years-old
 - Death is rare in anicteric disease
 - If Jaundiced, CFR increases to 15-40%

Prevention

- Limiting exposure to infected animals and contaminated environments (difficult during deployment)
- Military studies have shown that a single weekly dose of doxycycline (200mg) is 95% effective in preventing infection
 - Have to weigh the potential side effects of doxy
- No approved human vaccine in US

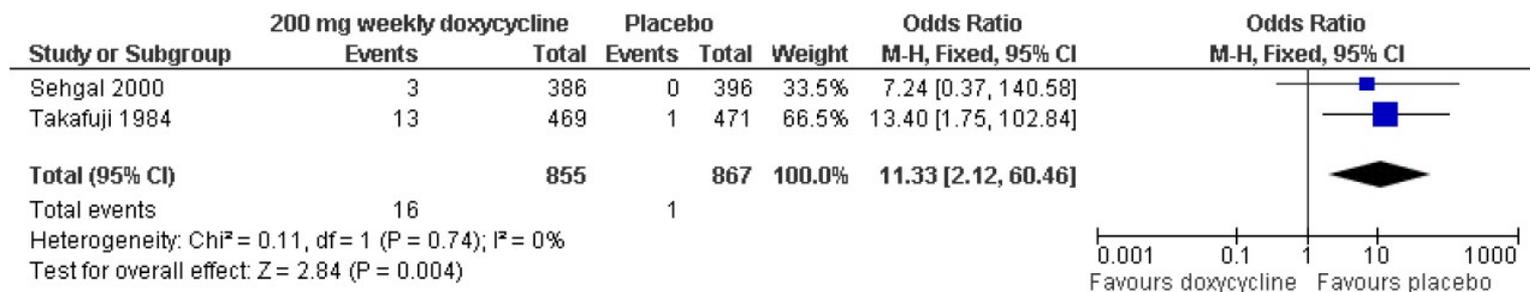
Prevention- Efficacy

Figure 4. Forest plot of comparison: I Pre-Exposure Prophylaxis with Doxycycline, outcome: I.I Laboratory Identified Infection.



Prevention- Toxicity

Figure 5. Forest plot of comparison: I Pre-Exposure Prophylaxis with Doxycycline, outcome: I.2 Adverse Events, Minor.



Cochrane Review 2009

Prevention

- THERE ARE SEVERAL STEPS YOU CAN TAKE TO HELP PREVENT GETTING LEPTOSPIROSIS. THESE INCLUDE:
 - See a veterinarian to get vaccines for your pets that can protect against this disease
 - Avoid contact with animal urine or body fluids, especially if there are any cuts or abrasion of the skin
 - Do not swim in, walk in, or swallow water that may contain animal urine
 - Wear protective clothing or footwear near soil or water that may be contaminated with animal urine