Leptospirosis and Brucellosis

WRAIR- GEIS 'Operational Clinical Infectious Disease' Course

The opinions or assertions contained herein are the private views of the author, and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of Defense. Research was conducted in an AAALACi accredited facility in compliance with the Animal Welfare Act and other federal statutes and regulations relating to animals and experiments involving animals and adheres to principles stated in the Guide for the Care and Use of Laboratory Animals, NRC Publication, 2011 edition.
Question

• Which of the following infections cannot present with a primary clinical infection or relapse years after exposure?

A. Brucellosis
B. Tuberculosis
C. *Plasmodium falciparum* malaria
D. Meliodosis
E. All can present with delayed infection or relapse
Question

• Which of the following infections cannot present with a primary clinical infection or relapse years after exposure?

A. Brucellosis
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C. *Plasmodium falciparum* malaria
D. Meliodosis
E. All can present with delayed infection or relapse
Case

- 31 yo US infantryman reported fever for 5 weeks since return from Afghanistan
  - Poor compliance with malaria prophylaxis
  - Relapsing fevers to 103° F
  - Frequent headaches, nausea, malaise
  - Occasional cough and sore throat

- Exam unremarkable

- WBC 5.1   Hb 11.6   ALT/AST – 97/116

- HIV negative

- Chest X-ray, CT head, and lumbar puncture all normal
Case

• Evaluated at 4 separate clinics with diagnosis of “migraines” or “gastroenteritis”

• Has a “Fever of Unknown Origin” evaluation with ID
  – History of eating goat cheese on local economy
  – Empiric tx with malarone for malaria ineffective

• Blood culture grows small gram negative rods on day 4
Brucellosis

• This is the **MOST COMMON** zoonosis worldwide
  – Essentially places without effective animal and public health programs
  – Especially prevalent: Mediterranean, Arabian peninsula, Indian subcontinent, Central Asia, Africa, Mexico, Central/South America

• **Condition synonyms**: Undulant fever; Malta fever; Bangs disease, Mediterranean fever, Cyprus fever

• Organism first noted in the spleen of infected soldiers in 1886 by David Bruce
  – Small aerobic, gram negative coccobacillus
    • Closely related to *Bartonella*
  – Facultative intracellular bacteria
  – Grows slowly
  – Can aerosolize in the lab (need BSL-3)
Brucellosis

• Many species, all presenting in a similar manner
  – *B. abortus*: (cattle, bison, elk, caribou, camels, yaks)
  – *B. melitensis*: (goats, sheep, camels)
  – *B. suis*: (swine, wild pigs, hares, reindeer)
  – *B. canis*: (dogs, coyotes)
  – *B. pennipediae* (seals)
  – *B. ceti* (dolphins, porpoises)
  – *B. ovis* (sheep)
  – *B. neotomae* (rodents)

• Infective dose: 10-100 organisms (i.e. not many)
Brucellosis

- In animals
  - Blood stream infection in genitourinary tracts and reproductive systems
  - Causes abortion and sterility
  - Animal Transmission:
    - Shed in milk, urine, vaginal discharges, abortion products
      - Congenital transmission
      - Environmental contamination
        » 1 abortion contains $10^{10}$ bacteria/mL viable for up to 20 weeks
  - Economic Impact
    - Reproduction rate decreases
    - Milk production decreases
Brucellosis

• In humans
  – We are an accidental host
  – ~500,000 infections annually worldwide (underestimated)
    • Consider in differential diagnosis for every fever case in endemic areas
  – At risk:
    • Men (ages 20 – 40)
    • Rural shepherding communities
    • Slaughterhouse workers
    • Veterinarians
    • Family members of index cases
    • Consumption of unpasteurized milk products
      – Common cause in kids
Brucellosis

• In humans
  – Most U.S. cases are in immigrants from endemic areas
    • US-Mexico border
  – Only 12 DoD cases from 1998-2008
    • Many associated with unpasteurized milk products
  – Route of entry for infection:
    • Conjunctivae
    • Inhalation of aerosols (incl. potential biowarfare)
    • Ingestion (i.e., unpasteurized dairy products)
    • Contact with abraded skin
    • Sexual transmission
    • Laboratory exposure
Brucellosis

- Lab exposure
  - Need BSL-3 capabilities for a reason

Table 1. Ten most frequently reported laboratory-associated infections worldwide.

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of cases</th>
<th>No. of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brucellosis</td>
<td>426</td>
<td>5</td>
</tr>
<tr>
<td>Q fever</td>
<td>280</td>
<td>1</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>268</td>
<td>3</td>
</tr>
<tr>
<td>Typhoid fever</td>
<td>258</td>
<td>20</td>
</tr>
<tr>
<td>Tularemia</td>
<td>225</td>
<td>2</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>194</td>
<td>4</td>
</tr>
<tr>
<td>Dermatomycoses</td>
<td>162</td>
<td>0</td>
</tr>
<tr>
<td>Venezuelan encephalitis</td>
<td>146</td>
<td>1</td>
</tr>
<tr>
<td>Psittacosis</td>
<td>116</td>
<td>10</td>
</tr>
<tr>
<td>Coccidioidomycosis</td>
<td>93</td>
<td>2</td>
</tr>
</tbody>
</table>

NOTE. Data are for the years 1976 [3] and 1978 [4].

Table 2. Laboratory-associated infection and relative risk of infection, compared with the risk among the general population.

<table>
<thead>
<tr>
<th>Organism</th>
<th>No. of cases of infection</th>
<th>Relative risk of infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shigella species</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Brucella species</td>
<td>7</td>
<td>8012.5</td>
</tr>
<tr>
<td>Salmonella species</td>
<td>6</td>
<td>0.08</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>6</td>
<td>NA</td>
</tr>
<tr>
<td>MRSA</td>
<td>5</td>
<td>NA</td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>4</td>
<td>40.8</td>
</tr>
<tr>
<td>Escherichia coli O157:H7</td>
<td>2</td>
<td>8.6</td>
</tr>
<tr>
<td>Coccidioides species</td>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>1</td>
<td>0.03</td>
</tr>
</tbody>
</table>


Brucellosis

- Biowarfare
  - High attack rates possible if aerosolized
  - Resistant to drying
  - Has been produced previously in the U.S. and USSR
  - Works as an incapacitating agent
    - High morbidity, very low mortality
    - Could overwhelm medical staff
  - Soviets reportedly engineered a multidrug resistant strain
Brucellosis

• Accidental Exposures
  
  • **Accident:** vaccine manufacturing plant, Spain
    – *B. melitensis* strain Rev1 – 1 week production
    – Air from hood expelled out front of building
    – Attack rate of 17.1% (of 168) at the facility within 3 weeks
    – Workers who windows opened near exhaust vent: 39.5% attack rate

  • *B. abortus* S19 vaccine plant - Argentina
    – 70% developed active brucellosis after accident

Olle-Goig 1987 Am J Public Health; Wallach 2008 Clin Microbial Infect
Brucellosis

• Once infected….
  – Organism spreads to macrophages and placental trophoblasts
    • Avoids bactericidal action in phagosome
    • Spreads to lymph nodes, liver, spleen, bone marrow, and placenta
  – Treatments need to target this intracellular stage
Cell Membrane

BvrRS

Bruce/la
(Smooth)

LAM

P

Lysosome

EEA-1+

Rab5+

Lysosome

LAMP-1+

Rab?+

T4SS

Endoplasmic Reticulum
Sar1, Rab2 Rab pha

Omp22, Omp25

Cell Membrane
Brucellosis

• Clinical Presentations:
  – Many presentations
  – 2-4 week incubation period
  – Acute:
    • Fever (spiking)
    • Sweats
    • Malaise/Fatigue
    • Anorexia
    • Headache
    • Muscle/joint pain
  – Chronic:
    • Recurrent fevers (mild and relapsing)
    • Arthritis
    • Swelling of the testicles & scrotum

<table>
<thead>
<tr>
<th>Symptom or sign</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>94–100</td>
</tr>
<tr>
<td>Malaise</td>
<td>82–95</td>
</tr>
<tr>
<td>Chills</td>
<td>39–95</td>
</tr>
<tr>
<td>Sweating</td>
<td>39–93</td>
</tr>
<tr>
<td>Headache</td>
<td>29–77</td>
</tr>
<tr>
<td>Myalgia</td>
<td>39–68</td>
</tr>
<tr>
<td>Back pain</td>
<td>15–73</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>17–77</td>
</tr>
<tr>
<td>Anorexia</td>
<td>25–52</td>
</tr>
<tr>
<td>Weight loss</td>
<td>13–50</td>
</tr>
</tbody>
</table>

Hoover, Physicians Guide to Terrorist Attack, 2004
Brucellosis

Unilateral scrotal edema
Brucellosis

Carpus (caribou): The carpal bursa is markedly swollen and fluctuant. *Brucella suis*
Brucellosis

- Focal Disease (localized in ~30% of infections)

<table>
<thead>
<tr>
<th>System</th>
<th>Abnormality</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal</td>
<td>Any</td>
<td>5–37</td>
</tr>
<tr>
<td></td>
<td>Spondylitis</td>
<td>2–13</td>
</tr>
<tr>
<td></td>
<td>Sacroiliitis</td>
<td>7–19</td>
</tr>
<tr>
<td>Mononuclear phagocyte</td>
<td>Hepatomegaly</td>
<td>37–66</td>
</tr>
<tr>
<td></td>
<td>Splenomegaly</td>
<td>10–60</td>
</tr>
<tr>
<td></td>
<td>Lymphadenopathy</td>
<td>9–20</td>
</tr>
<tr>
<td></td>
<td>Liver enzymes</td>
<td>37–49</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Endocarditis</td>
<td>1–2</td>
</tr>
<tr>
<td>Nervous</td>
<td>Meningitis</td>
<td>0–1</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Epididymoorchitis</td>
<td>2–10</td>
</tr>
</tbody>
</table>

Hoover, Physicians Guide to Terrorist Attack, 2004
Brucellosis

- Musculoskeletal infection
- Up to a 1/3 of cases of focal disease

46yo man with brucellosis and right SI involvement.

Brucellar spondylitis

Osteoarticular Disease - Sacroiliitis
Osteoarticular Disease

Vertebral erosion
Spondylitis

Vertebral collapse
Paraspinal abscess
Brucellosis

• Neurobrucellosis (rare)
  – Subacute meningitis (usually) or meningoencephalitis
  – Myelitis, radiculitis, demyelinating disease
  – Psychiatric symptoms (depression, psychosis)
  – 1% of all patients with brucellosis

• Endocarditis (rare)
  – Most important cause of death
  – ~67% with underlying valvular disease
  – Treatment is antibiotics plus valve replacement
Brucellosis Complications

- GI tract: anorexia, nausea, vomiting, pain, diarrhea, constipation (70%), rare pancreatitis.
- Respiratory: flulike illness, bronchitis, pneumonia, lung nodules, abscess, hilar adenopathy, plural effusion/empyema
- GU: interstitial nephritis, pyelonephritis, glomerulonephritis, IgA nephropathy, epididymoorchitis (20%)
- Pregnancy: abortion
- Heme: pancytopenia, clotting disorders
- Ocular: uveitis, endophthalmitis
- Skin: rashes, papules, ulcers, abscess, erythema nodosum, petechiae, purpura, vasculitis
Brucellosis

• Diagnosis
  – High index of suspicion
    • Travel, occupational and dietary history important
  – Labs
    • Mild anemia
    • Leukopenia
    • Some moderate LFT elevations
  – X-rays of SI joint and spine, MRI, Bone scans
  – Culture (definitive diagnostic method)
  – Serology (need acute and convalescent titers; standard test does not detect B.canis)
  – PCR (not routinely available)
Brucellosis

• Diagnosis
  – Culture
    • Blood (positive 50-70% of the time)
      – Bone marrow better (92%)
      – Other samples cultured as clinically indicated

• Need to hold cultures for up to 6 weeks
  – BACTEC blood cx bottles typically 1-2 weeks

• Tell the lab you suspect *Brucella***!!!
Brucellosis

• Treatment
  – Shortens clinical duration of disease
  – Prevents complications (i.e. fatalities)
  – Typically requires long courses of antibiotics with combination
    • 15-30% will relapse if given single drug therapy
      – Doxycycline 100 mg PO bid + Rifampin 600 mg qd x 6 wks
      – Tetracycline x 6 weeks + streptomycin x 3 weeks
      – Doxycycline 200 mg PO qd + gentamycin x 7-14 days

• Alternatives
  – Quinolone + rifampin
  – TMP/SMX + rifampin (high failure rates)
  – Role of corticosteroids for meningitis unclear; not recommended.

Minimum 6-8 weeks of treatment
Brucellosis

• Non focal disease
  – [Doxy + gentamycin] OR [Doxy + rifampin] X 6 weeks

• Spondylitis, sacroilitis
  – [Doxy + gentamycin + rifampin] X 3 mos OR
  – [Cipro + rifampin] X 3 mos

• Neurobrucellosis
  – [Doxy + rifampin + ceftriaxone] until CSF normal
  – Role of corticosteroids unclear; not recommended

• Endocarditis
  – [Rifampin + doxy + TMP/SMX] X 6 months + gentamycin X 2-4 weeks

• Pregnancy
  – Not much data
  – Rifampin X 6 wks OR [Rifampin + TMP-SMX*] X 4 wks
  – *TMP-SMX in the last week of pregnancy can cause kernicterus
Brucellosis

• Treatment Relapses
  – Can occur even in cases treated with dual antibiotic therapy (<10-15%)
  – Typically not due to antibiotic resistance
  – Typically occurs within the first year after infection
    • One reported relapse occurred 28 years after the initial infection
  – Typically milder the second time around
  – Caused by persistent foci of infection in bone, spleen, liver
  – Lab: persistently high IgG
  – Repeat course of usual meds
Brucellosis

• Prevention
  – Control animal disease
    • Surveillance
    • Animal vaccinations
  – Pasteurization of milk
  – Avoid consuming dairy products while overseas
  – NO HUMAN VACCINE
  – Post-exposure prophylaxis
    • Doxycycline 100 mg bid + Rifampin 600 qd
      – Needlesticks = 6 weeks
      – Biowarfare = 3 weeks
LEPTOSPIROSIS
History

• Weil described a syndrome of severe multisystem disease, presenting with profound jaundice and renal impairment in Heidelberg in 1886.

• Leptospires were first visualized in autopsy specimens forming a patient thought to have had yellow fever, isolated several years later in Germany and Japan.

• Prominent researchers Stokes and Noguchi died while investigating early cases.
Leptospirosis

• General

• An acute systemic infection, characterized by extensive vasculitis
  – caused by spirochetes of the genus *Leptospira*
  – primarily a disease of wild & domestic mammals
  – humans infected occasionally
    • direct or indirect contact.
Leptospirosis

- General
  - Finely coiled, motile spirochetes
    - Greek *leptos* (thin) and Latin *spira* (coiled)

- 25 serotypes $\rightarrow$ 210 serovars
  - Distinct types are classified as servars
  - These classifications can help identify a common source epidemiologically

- Animal reservoirs (rodents-**Rats**, dogs)
  - Worldwide zoonosis (especially tropics)
  - Humans are dead end host
Source Animals

- Rodents
- Raccoons
- Opossums
- Cattle
- Swine
- Dogs
- Horses
- Buffaloes
- Sheep
- Goats
Leptospirosis

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

• General
  – 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%
Leptospirosis

• 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
Leptospirosis

• 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
Outbreaks of Leptospirosis among Triathletes
Illinois and Florida

- 834 of 876 triathletes contacted:
  - 98 (12%) reported being ill
  - Serum from 474 tested
    - 52 (11%) + lepto

- 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
Leptospirosis

• To summarize….DON’T
  – SWALLOW LAKE WATER
  – SWIM WITH ABRASIONS
  – TAKE YOUR TIME SWIMMING
Leptospirosis

• Clinical Disease
  – Bacteria penetrate intact mucous membranes, abraded skin, or inhalation of infectious aerosols
  – Develop bacteremia
  – Organs are seeded with probable concentration in liver
    • Aided by systemic vasculitis
  – Multiorgan failure
    • Liver cell injury (+/- necrosis) and Jaundice
    • Renal dysfunction
    • Pulmonary hemorrhage
Leptospirosis

• Clinical Disease
  – 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
# Co-infection

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria and leptospirosis</td>
<td>22</td>
</tr>
<tr>
<td>Malaria and rickettsiosis</td>
<td>2</td>
</tr>
<tr>
<td>Malaria and other (dengue, PTB)</td>
<td>2</td>
</tr>
<tr>
<td>Leptospirosis and rickettsiosis</td>
<td>4</td>
</tr>
<tr>
<td>Leptospirosis and other (dengue, PTB)</td>
<td>2</td>
</tr>
<tr>
<td>Rickettsiosis and other (typhoid, PTB)</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>34</strong></td>
</tr>
</tbody>
</table>
Leptospirosis

• Clinical Disease
  – Very broad spectrum of severity
  – Subclinical infection common
  – 90% with symptoms have milder icteric form
  – Incubation period: 7-12 days (range 2-26 days)
  – Initial bacteremic phase:
    • Lasts 5-7 days
    • Flu-like illness (next slide)
    • May be biphasic with a few days without fever
    • Spirochetes isolated from blood/CSF/urine
  – Second immune phase:
    • Lasts 4-30 days (may have severe complications)
    • No spirochetes in blood or CSF, but in all tissues/organs and urine
    • IgM appears
Leptospirosis

• Anicteric Leptospirosis
  – Abrupt fever (38 to 40°C)
  – Severe frontal headaches, chills, rigors
  – Severe muscle aches (*calf*, back/neck, abdomen)
  – **Abdominal pain**/nausea/vomiting (95%)
  – Defervescence for a few days followed by 2nd phase
    • Splenomegaly
    • Rash (infrequent)
    • Pharyngitis (infrequent)
    • Lymphadenopathy (infrequent)
    • Pulmonary involvement
    • Ocular findings
    • Meningitis

May see a low WBC
Leptospirosi

• Pulmonary involvement
  – Cough
  – Blood streaked sputum (hemorrhagic pneumonitis)
  – Chest pain
  – Infiltrates on chest x-ray
  – 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
Ocular Findings

Conjunctival Suffusion (Early):
- Most frequently found sign but variable (~95%)
  - some outbreaks seen in <½ 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.
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
Leptospirosis

• Icteric Leptospirosis (Weil’s Disease)
  – Can be seen with any serotype
  – Severe disease
    • Renal and hepatic dysfunction
    • Hemorrhage (pulmonary)
    • Vascular collapse, arrhythmias
    • Death 5-40% cases
      – Altered mental status best predictor

  Can look a LOT like viral hemorrhagic fevers

  – Labs:
    • Total bilirubin very high (mostly direct; <20 mg/dL)
    • AST/ALT 100-200
    • Elevated CPK (differentiates from viral hepatitis)
    • High WBC
Leptospirosis

• Icteric Leptospirosis (Weil’s Disease)
  – Renal disease
    • Protein, RBC, casts in initial phase
    • Renal failure in 25% of cases during 2\textsuperscript{nd} 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
Leptospirosis

• Icteric Leptospirosis (Weil’s Disease)
  – Pulmonary disease
    • May range from mild respiratory symptoms to full ARDS
    • Degree of symptoms may not correlate with findings on chest x-ray
  – Hemorrhage
    • Attributed to severe vasculitis w/ endothelial damage
      – Depletion of clotting factors and low platelets may make things worse, but are not a cause of bleeding
<table>
<thead>
<tr>
<th></th>
<th>Icteric (Weil’s Disease)</th>
<th>Anicteric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Renal failure</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Death</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Aseptic meningitis</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Disturbances of consciousness†</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*(−) = rare or absent; (+) = can occur; (+++) = characteristic.
†Due primarily to uremia in severe disease and to encephalitis in anicteric cases.
Leptospirosis Diagnosis

• Direct Detection Methods
  – Direct visualization (blood or urine): S/S 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)
Leptospirosis 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
Leptospirosis

• 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 if delayed in severe cases
    • Many antibiotics likely have activity against the organism
  – Supportive therapy essential for hospitalized
    • Volume, potassium repletion, hemodialysis, intubation
Treatment

- 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
Leptospirosis

• Prognosis
  – Depends on patient’s overall health
  – In U.S., case fatality rates are 2-10%
    • 5% if less than 30 yo
    • 33% if greater than 60 yo

– Death is rare in anicteric disease
  • If jaundiced, CFR increases to 15-40%
Leptospirosis

• Prevention
  – Avoiding contaminated water and mud is difficult for deployed personnel
  – Rodent control
  – Doxycycline appears effective in prevention
    • Given 200 mg PO once **weekly** as prophylaxis
      – Study of 940 deployed soldiers
        » 20 placebo group cases
        » 1 doxycycline group case

• Have to weigh the potential side effects of doxy
  – No human vaccine approved in the U.S.
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
Prevention- Efficacy

Figure 4. Forest plot of comparison: 1 Pre-Exposure Prophylaxis with Doxycycline, outcome: 1.1 Laboratory Identified Infection.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>200 mg weekly doxycycline Events</th>
<th>Placebo Events</th>
<th>Total Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sehgal 2000</td>
<td>112</td>
<td>386</td>
<td>101</td>
<td>396</td>
<td>54.5%</td>
<td>1.19 [0.87, 1.64]</td>
</tr>
<tr>
<td>Takafulji 1984</td>
<td>1</td>
<td>469</td>
<td>20</td>
<td>471</td>
<td>45.5%</td>
<td>0.05 [0.01, 0.36]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>855</td>
<td>867</td>
<td>100.0%</td>
<td>121</td>
<td></td>
<td>0.28 [0.01, 7.48]</td>
</tr>
<tr>
<td>Total events</td>
<td>113</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 5.16; Chi² = 10.55, df = 1 (P = 0.001); I² = 91%
Test for overall effect: Z = 0.76 (P = 0.45)

Cochrane Review 2009
Prevention- Toxicity

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

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>200 mg weekly doxycycline</th>
<th>Placebo</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Sehgal 2000</td>
<td>3</td>
<td>386</td>
<td>0</td>
</tr>
<tr>
<td>Takafuji 1984</td>
<td>13</td>
<td>469</td>
<td>1</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>855</td>
<td>867</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Total events 16

Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 2.84 (P = 0.004)
QUESTIONS?