Leptospirosis

WRAIR- GEIS 'Operational Clinical Infectious Disease' Course
Acknowledgments

• Thanks to:
  – COL Arthur Lyons
  – COL Scott Miller
  – LTC James Moon
  – MAJ Kris Paolino
  – Capt (Ret) Gregory Martin
  – COL (Ret) Duane Hospenthal
Disclaimer

The views expressed in this presentation are those of the speaker and do not reflect the official policy of the Department of Army, Department of Defense, or U.S. Government
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

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

*Directly responsible for animal that later perished*
## Labs

<table>
<thead>
<tr>
<th>Patient</th>
<th>Labs (CBC, CMP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 y.o. M</td>
<td>Not Done</td>
</tr>
<tr>
<td>32 y.o. M</td>
<td>WNL</td>
</tr>
<tr>
<td>20 y.o. M</td>
<td>Not Done</td>
</tr>
<tr>
<td>23 y.o. F*</td>
<td>Increased Alkaline Phosphastase</td>
</tr>
<tr>
<td>20 y.o. M</td>
<td>WNL</td>
</tr>
<tr>
<td>21 y.o. F</td>
<td>Not Done</td>
</tr>
<tr>
<td>27 y.o. M*</td>
<td>Increased LFT</td>
</tr>
<tr>
<td>24 y.o. F</td>
<td>WNL</td>
</tr>
<tr>
<td>23 y.o. M</td>
<td>WNL</td>
</tr>
<tr>
<td>23 y.o. M</td>
<td>Increased LFTs</td>
</tr>
<tr>
<td>29 y.o. M*</td>
<td>WNL</td>
</tr>
</tbody>
</table>

*Directly responsible for animal that later perished*
Question

• What is going on, how do you prove it, and what can you do about it?
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.
History

• The severe form of the disease was first described by Adolf Weil in Heidelberg, Germany in 1886.

• The causative agent was identified independently by Japan and German researchers during World War I.
Leptospira

- Finely coiled, motile spirochetes
  - 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.
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
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

Leptospirosis on Oahu: an outbreak among military personnel associated with recreational exposure.
Katz AR¹, Sasaki DM, Mumm AH, Escamilla J, Middleton CR, Romero SE.
WARNING!
LEPTOSPIROSIS
HEALTH HAZARD

FRESH WATER STREAMS AND MUD POSSIBLY POLLUTED WITH BACTERIA

SWIM OR HIKE AT YOUR OWN RISK
FOR MORE INFORMATION CALL HAWAII DEPARTMENT OF HEALTH

EXPLORATIONHAWAII.COM
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:
  - 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
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/IRA1/ 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.
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 Fevers!!
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

<table>
<thead>
<tr>
<th>Approximate time scale:</th>
<th>Week 1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>months-years</th>
<th>years</th>
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<tbody>
<tr>
<td><strong>Incubation period</strong></td>
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<td><strong>Inoculation</strong></td>
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<td>2 - 20 days</td>
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<td><strong>Leptospires present in:</strong></td>
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<tr>
<td>blood</td>
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<td>CSF</td>
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<td><strong>Antibody Titers</strong></td>
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<td>high</td>
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<td>“negative”</td>
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<td><strong>Laboratory Investigations</strong></td>
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<td>Culture</td>
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<td>Serology</td>
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<tr>
<td>Phases</td>
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</tr>
</tbody>
</table>

- **Acute stage**: fever
- **Convalescent stage**: ? interstitial nephritis
- **Convalescent shedder**: reservoir host
- **Leptospiremia**: 1
- **Leptospiruria and immunity**: 2
- **Serology**: 3, 4, 5
- **Normal response**: delayed
- **Titers decline at varying rates**:
<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.
Co-infection is Possible

<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>Total</td>
<td>34</td>
</tr>
</tbody>
</table>

AJT MH 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 <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.
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
  – Attributed to severe vasculitis w/ endothelial damage

<-May look like Viral Hemorrhagic Fevers!
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
“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.”

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 diasylate (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
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

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
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</th>
<th>Placebo</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
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<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Sehgal 2000</td>
<td>112</td>
<td>386</td>
<td>101</td>
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<tr>
<td>Takafuli 1984</td>
<td>1</td>
<td>469</td>
<td>20</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>855</td>
<td>867</td>
</tr>
<tr>
<td>Total events</td>
<td></td>
<td>113</td>
<td>121</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)

Prevention - Efficacy

Cochrane Review 2009
Prevention - Toxicity

Figure 5. Forest plot of comparison: 1 Pre-Exposure Prophylaxis with Doxycycline, outcome: 1.2 Adverse Events, Minor.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>200 mg weekly doxycycline</th>
<th>Placebo</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Sehgal 2000</td>
<td>3</td>
<td>386</td>
<td>0</td>
<td>396</td>
</tr>
<tr>
<td>Takafuji 1984</td>
<td>13</td>
<td>469</td>
<td>1</td>
<td>471</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>16</strong></td>
<td><strong>855</strong></td>
<td><strong>867</strong></td>
<td>100.0%</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td></td>
<td><strong>16</strong></td>
<td></td>
<td><strong>1</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.11$, df = 1 ($P = 0.74$); $I^2 = 0$

Test for overall effect: $Z = 2.84$ ($P = 0.004$)

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
Questions?

Leptospira interrogans