

# Leptospirosis and Brucellosis

## WRAIR- GEIS 'Operational Clinical Infectious Disease' Course

**WRAIR**

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Soldier Health • World Health



# 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?
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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

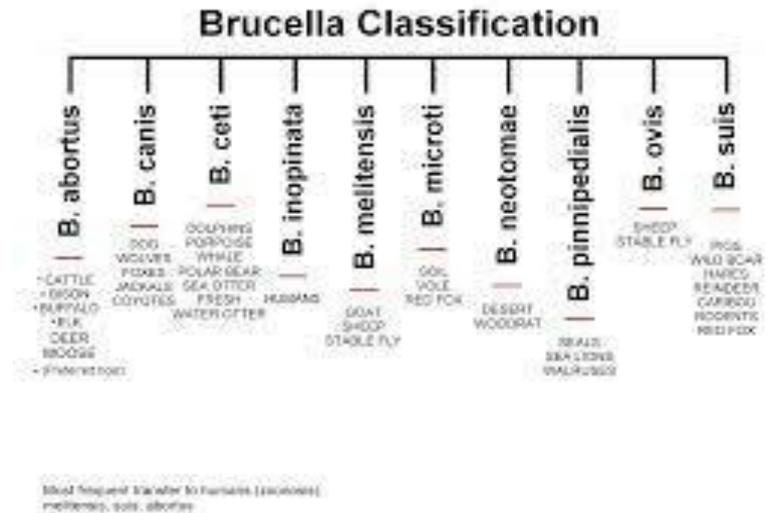
- Evaluated at 4 separate clinics with diagnosis of “migraines” or “gastroenteritis”
- Has a “Fever of Unknown Origin” evaluation with ID
  - History of eating goat cheese on local economy
  - Empiric tx with malarone for malaria ineffective
- Blood culture grows small gram negative rods on day 4

# 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**

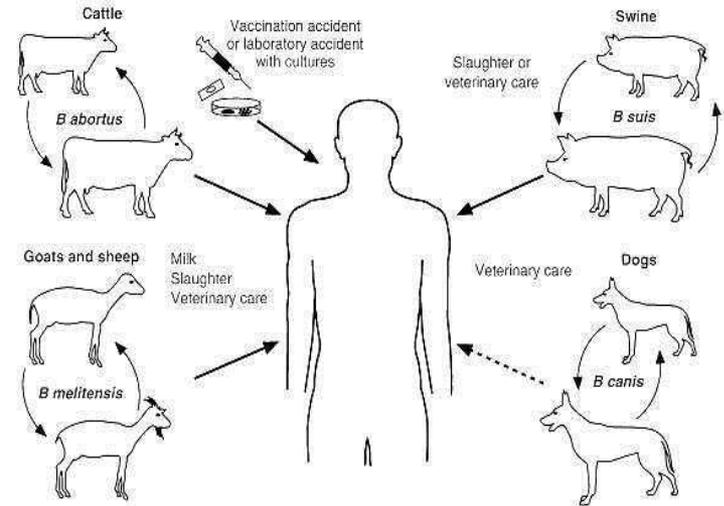
- Blood stream infection ☐ genitourinary tracts and reproductive systems
- Causes abortion and sterility
- Animal Transmission:
  - Shed in milk, urine, vaginal discharges, abortion products
    - Congenital transmission
    - Environmental contamination
      - » 1 abortion ☐  $10^{10}$  bacteria/mL ☐ 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.**

Disease	No. of cases	No. of deaths
Brucellosis	426	5
Q fever	280	1
Hepatitis	268	3
Typhoid fever	258	20
Tularemia	225	2
Tuberculosis	194	4
Dermatomycoses	162	0
Venezuelan equine encephalitis	146	1
Psittacosis	116	10
Coccidioidomycosis	93	2

**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.**

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

**NOTE.** Data are for the years 2002–2004 [11]. MRSA, methicillin-resistant *S. aureus*.

Singh, K. CID, 2009; 49: 142-7.

# 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

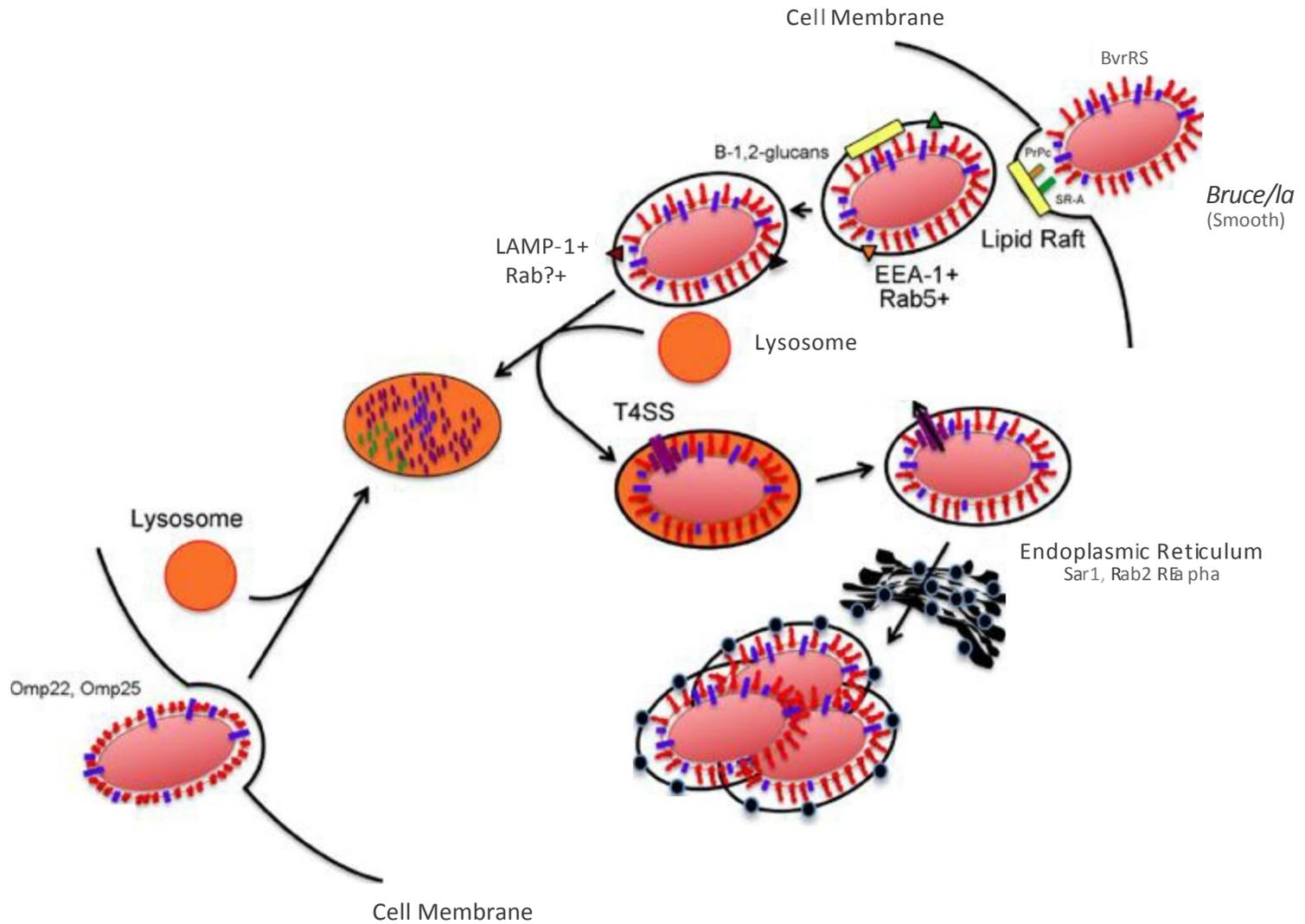
# Brucellosis

- 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



# 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

## General Signs and Symptoms of Brucellosis

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

Hoover, Physicians Guide to Terrorist Attack, 2004

# Brucellosis



**Unilateral scrotal edema**

# Brucellosis



Figure 1A

Ayaşlıoğlu, et al., Rheumatol. Int. 2005



Carpus (caribou): The carpal bursa is markedly swollen and fluctuant.

*Brucella suis*

# Brucellosis

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

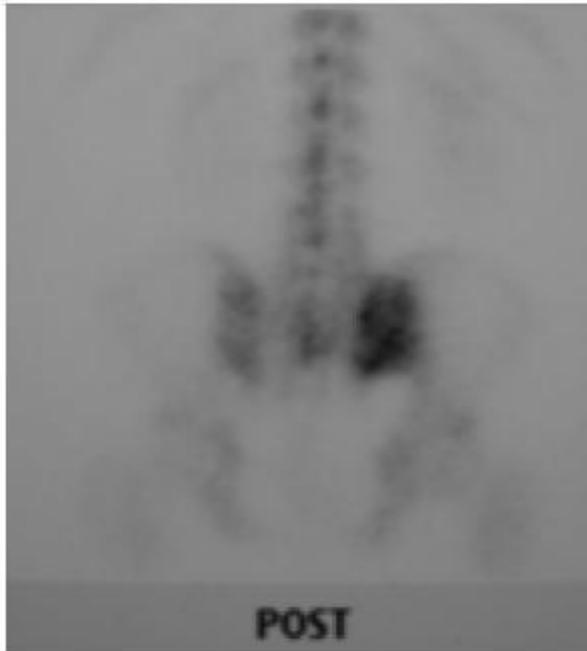
Focal Disease in Brucellosis

<i>System</i>	<i>Abnormality</i>	<i>Frequency (%)</i>
Musculoskeletal	Any	5–37
	Spondylitis	2–13
	Sacroiliitis	7–19
Mononuclear phagocyte	Hepatomegaly	37–66
	Splenomegaly	10–60
	Lymphadenopathy	9–20
	Liver enzymes	37–49
Cardiac	Endocarditis	1–2
Nervous	Meningitis	0–1
Genitourinary	Epididymo-orchitis	2–10

Hoover, Physicians Guide to Terrorist Attack, 2004

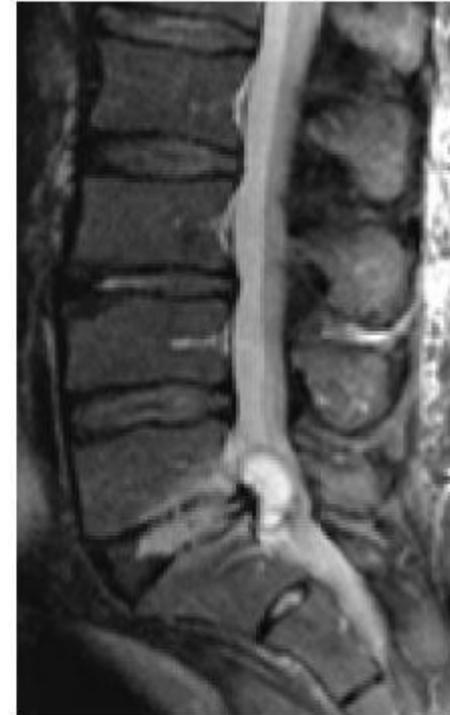
# Brucellosis

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



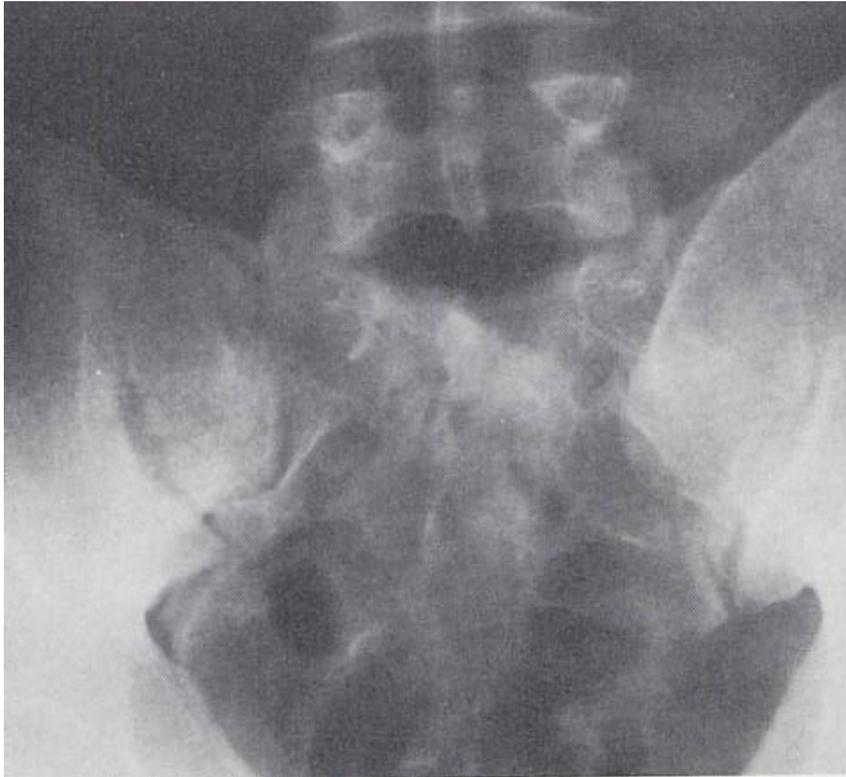
46yo man with brucellosis and right SI involvement.

Pourbagher 2006 AJR Am J Roentgenol. 187:873-80



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

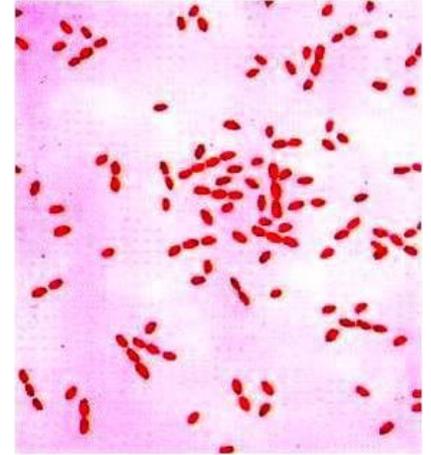
- GI tract: anorexia, nausea, vomiting, pain, diarrhea, constipation (70%), rare pancreatitis.
- Hepatobiliary system: Elevated AST/ALT, granulomatous disease, “viral hepatitis” like picture, abscesses.
- Respiratory: flulike illness, bronchitis, pneumonia, lung nodules, abscess, hilar adenopathy, plural effusion/empyema
- GU: interstitial nephritis, pyelonephritis, glomerulonephritis, IgA nephropathy, epididymo-orchitis (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

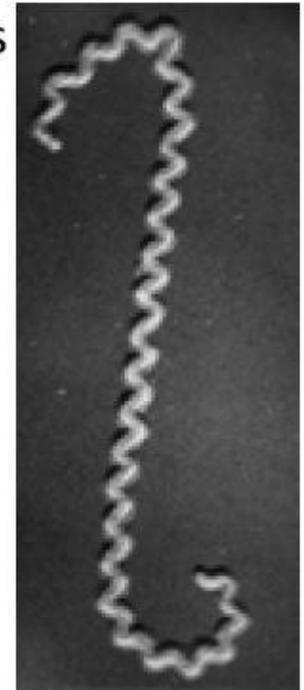
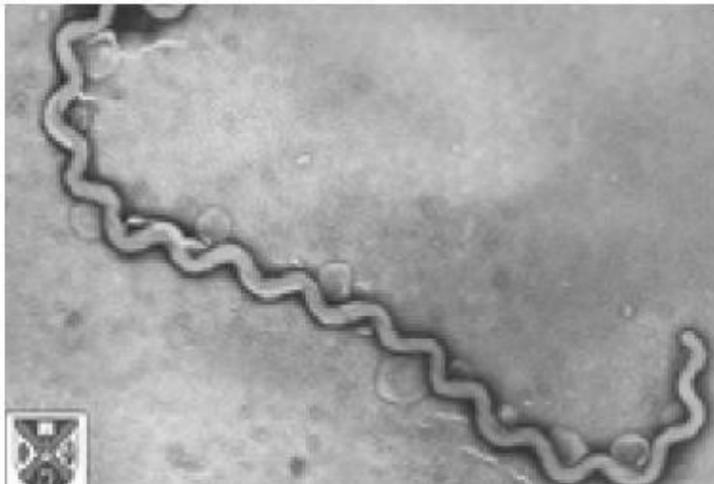
# History

- Weil described a syndrome of severe multisystem disease, presenting with profound jaundice and renal impairment in Heidelberg in 1886.
- Leptospire were first visualized in autopsy specimens from 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 → 210 serovars
    - Distinct types are classified as serovars
    - 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

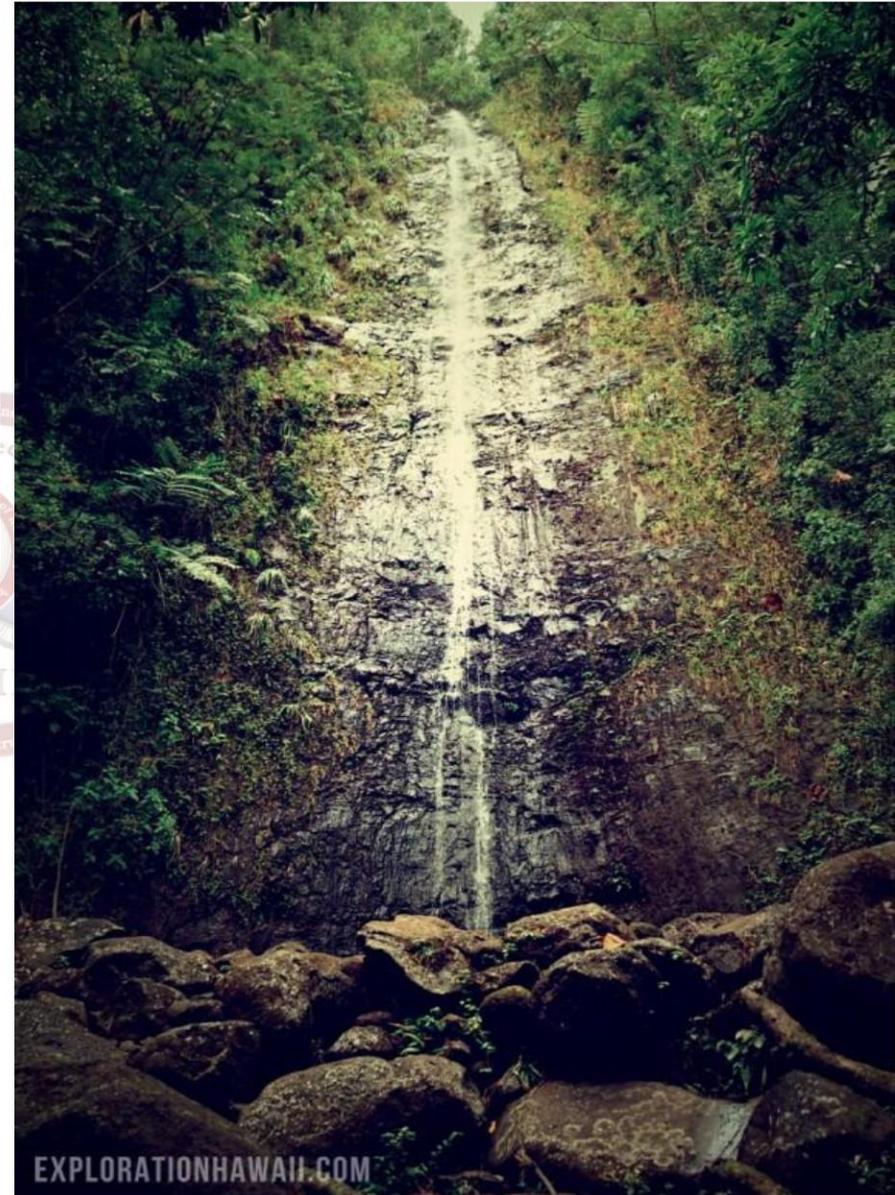


- Activities

- 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

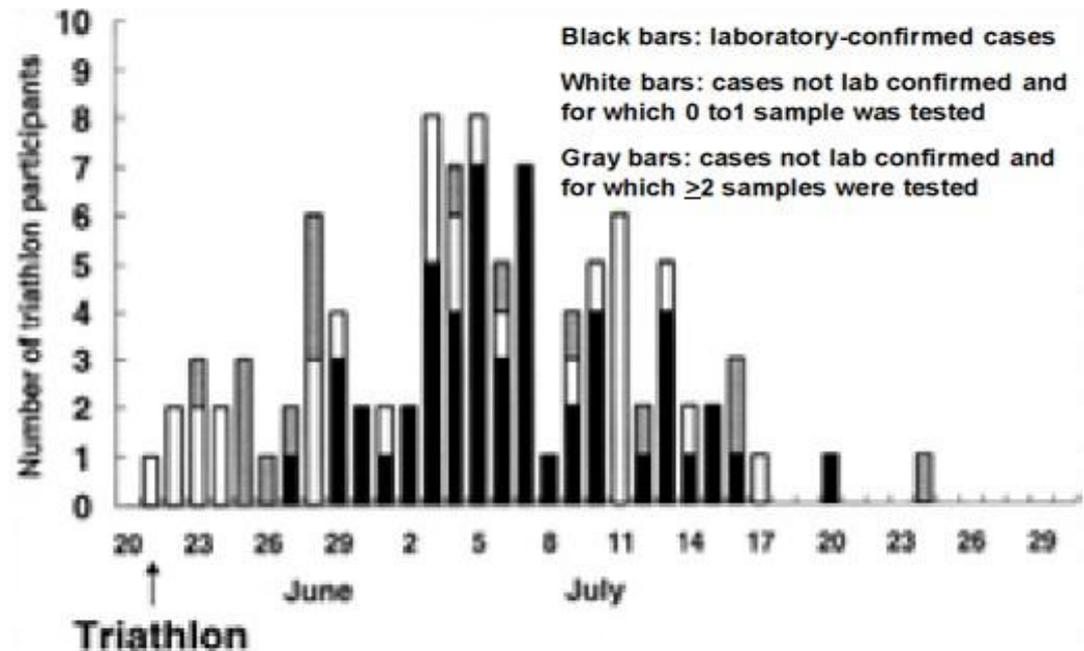
# Leptospirosis

- 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

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

# 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

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

# Leptospirosis

- Clinical Disease

- Very broad spectrum of severity
- Subclinical infection common
- 90% with symptoms have milder anicteric 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 2<sup>nd</sup> phase
    - Splenomegaly
    - Rash (infrequent)
    - Pharyngitis (infrequent)
    - Lymphadenopathy (infrequent)
    - Pulmonary involvement
    - Ocular findings
    - Meningitis

**May see a low WBC**

# Leptospirosis

- 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

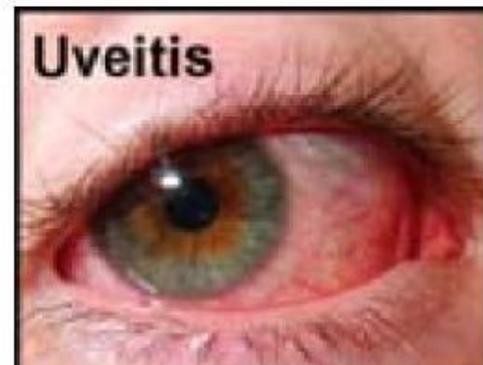
## Conjunctival Suffusion (Early):

- Most frequently found sign but variable (~95%)
  - some outbreaks seen in <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.



# 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
  - 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**

# Leptospirosis

- Icteric Leptospirosis (Weil's Disease)
  - Renal disease
    - Protein, RBC, casts in initial phase
    - Renal failure in 25% of cases during 2<sup>nd</sup> 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

	Icteric (Weil's Disease)	Anicteric
--	-----------------------------	-----------

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

\*(-) = 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 4<sup>th</sup> 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



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

# 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

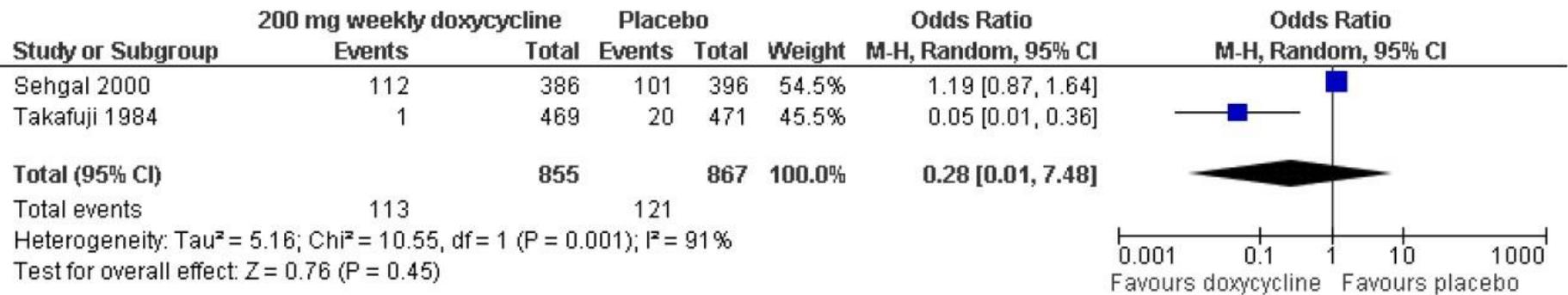
- Prevention
  - Avoiding contaminated water and mud is difficult for deployed personnel
  - Rodent control
  - Doxycycline appears effective in prevention
    - Given 200 mg PO once **weekly** as prophylaxis
      - Study of 940 deployed soldiers
        - » 20 placebo group cases
        - » 1 doxycycline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

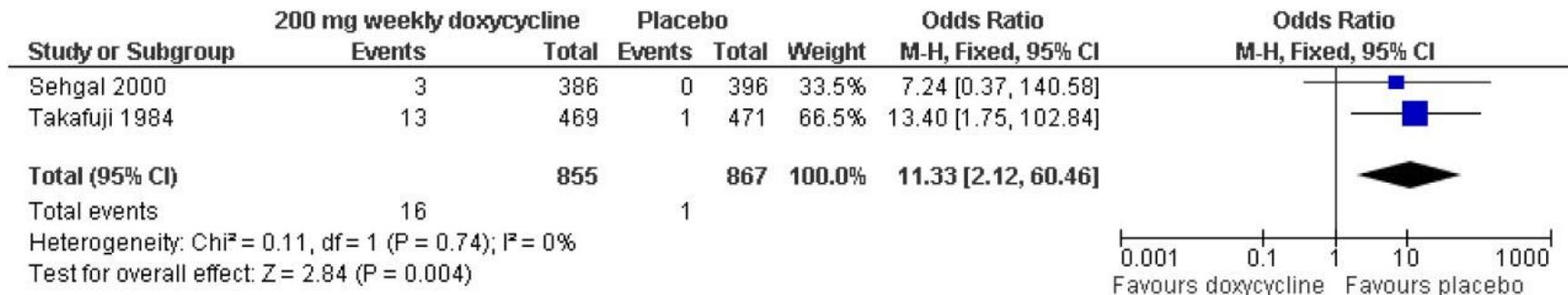
# Prevention- Efficacy

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



# Prevention- Toxicity

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



**QUESTIONS?**

