

TICK-BORNE DISEASES

- US - Ticks transmit the most vector-borne diseases
 - Bacteria, Rickettsia, Viruses, Protozoa
- Rural population increasing
- Deer population increasing
- Outdoor activity increasing

TICK-BORNE DISEASES IN MISSOURI

- Tularemia
- Rocky Mountain spotted fever
- Ehrlichiosis
- Q Fever
- Babesiosis (3 cases)
- “Missouri Lyme”
- Heartland Virus (7 cases + 1 in TN)

TULAREMIA
History

- 1837 - first described in Japan
- Early 1900's *Bacterium tularensis* after Tulare County
- 1928 - Dr. Edward Francis - 800 cases
- Weaponized by the US in the 1950s - other countries suspected also

TULAREMIA Microbiology

- *Francisella tularensis* - facultative, intracellular, gram-negative bacterium
- Characterized on growth characteristics, biochemical reactions, and virulence
- *Francisella tularensis* biogroup *tularensis*
 - Type A
 - North America
 - Most virulent species

TULAREMIA Microbiology

- *Francisella tularensis* biogroup *paleartica*,
 - Type B, Asia and Europe but also North America, less virulent in humans and of low virulence in rabbits
- Cysteine or cystine for growth
 - Glucose cysteine blood agar, modified Thayer-Martin medium, and buffered charcoal-yeast agar
- Beta-lactamase positive

TULAREMIA Epidemiology

- Very common in the US prior to WW II
 - Incidence has steadily decreased
- MO, AR ,OK - 55% of the total US cases
- June thru August and in December.
 - Summer peak - tick-acquired
 - Late winter - hunting-associated cases
- Lab worker, farmer, veterinarian, hunter or trapper, and cook or meat handler

TULAREMIA
Epidemiology

- Lagomorphs and rodents and beavers
- Bite of an insect or contact with contaminated animal products
- Other routes - aerosol droplets, contact with contaminated water or mud, and animal bites
- Human-to-human spread does not occur

TULAREMIA
Clinical

- Incubation 1-21 days (average 3-5 days)
 - Acute onset
- Ulceroglandular, glandular, typhoidal, oculoglandular, pharyngeal, and pneumonic
- 10 to 50 organisms - disease if inhaled or infected intradermally; 10 to the 8th required with oral challenge

TULAREMIA
Clinical

- Ulceroglandular (75-85 % of cases)
 - Inoculation with blood or tissue fluids
- Fever, chills, HA, malaise, an ulcerated skin lesion, painful regional adenopathy.
- Skin lesion usually located on the fingers or hands
- Glandular (5-10 %) fever, tender lymphadenopathy but no skin ulcer

TULAREMIA
Clinical

- Typhoidal (5-15%) - inhalation of infectious aerosols, intradermal or gastrointestinal challenge
- Fever, prostration, weight loss; no lymphadenopathy
- Pneumonia most common in typhoidal
- Diagnosis difficult - Respiratory c/o, substernal discomfort, dry cough

TULAREMIA
Clinical

- Oculoglandular (1-2%) inoculation of conjunctivae with infectious material
- Unilateral, painful, purulent conjunctivitis with preauricular or cervical adenopathy
- Chemosis, periorbital edema, and small nodular lesions or ulcerations of the palpebral conjunctiva are noted in some patients

TULAREMIA
Clinical

- Oropharyngeal tularemia - primary ulceroglandular disease confined to the throat
- Acute exudative or membranous pharyngotonsillitis with cervical adenopathy

TULAREMIA
Clinical

- Pneumonic tularemia - 30-80 percent of typhoidal cases and in 10-15 percent of ulceroglandular cases
- Case fatality rate without treatment is ~5% for ulceroglandular form and 35% for typhoidal form
- All ages are susceptible, and recovery is followed by permanent immunity

TULAREMIA
Diagnosis

- Staining ulcer fluids or sputum - generally not helpful
- Routine culture is difficult
- Isolation represents a clear hazard to lab personnel and should only be attempted in a BL-3 lab

TULAREMIA
Therapy

- Streptomycin 1gm q 12 hours IM 10-14d
- Gentamicin 3-5 mg/kg/day IV 10-14 days
- Tetracycline and chloramphenicol - ? associated with significant relapse rates
- Cipro > 10 days
- Lab related infections with Tularemia very common; person-to-person spread unusual and respiratory isolation is not required

TULAREMIA
Prophylaxis

- Vaccine: live, attenuated given by scarification
 - Proven effectiveness in preventing laboratory acquired tularemia as well as in experimentally exposed human volunteers.
- Antibiotics: Tetracycline 500mg po QID for 2 weeks is effective as prophylaxis when given after exposure

TULAREMIA
Illustrative Case

- 7/15/96 - 23 y/o WM - Owensville, MO
- Sx: left groin pain, f/c, HA, malaise, anorexia
- PE: Faget sign, left shin ulcer, left groin node
- WBC-11K, plts-96K, Na-133, LFTs-wnl
- Therapy: Doxycycline, node aspiration
- Serology 4x rise in 2 weeks, PCR + on pus
- Risk: Tick bite 5 days prior to onset

COXIELLA BURNETTI
History

- 1935 - 20 of 800 Australian meatpackers ill. Derrick coins term 'Query' or 'Q' fever
- 1937 - Burnett and Freeman - transmissible agent is a rickettsia
- 1939 - Davis and Cox - Montana - isolate organisms from ticks

Coxiella burnetii

- Gram-negative pleomorphic coccobacillus
- Enters host cells thru passive mechanism
 - Survives in phagolysosomes
- Worldwide zoonosis
- Cattle, sheep, goats, parturient cats
 - Urine, feces, milk, birth products of infected animals
- Spore stage - Inhalation of aerosols, raw milk, goat cheese

Spectrum of Acute Q Fever

- Clinical - Flu-like syndrome, isolated fever, atypical pneumonia, hepatitis, pericarditis, myocarditis, meningoencephalitis, infection during pregnancy
- Lab – Normal WBC (90%), low plts (25%)
 - Increased transaminase levels (70%)
 - Smooth muscle autoantibodies (65%)
 - Anti-phospholipase antibodies (50%)

Spectrum of Chronic Q Fever

- Clinical - Endocarditis, aneurysm infection, bone infection, infection during pregnancy, pseudotumor of the lung, hepatitis
- Lab - Increased transaminases (50%), low plts (50%), increased creatinine (65%), circulating immune complexes (90%), rheumatoid factor (60%)

Q FEVER
Pathology

- Lung - Histiocytes, vascular injury
- Liver - Granulomas
- Heart Valve - Perforations, vegetations
- Enters cell passively, multiplies in cytoplasmic vacuoles, destroys cell

Q FEVER

- Diagnosis - Serology, PCR
- Therapy
 - Acute: Doxycycline 100mg BID 15-21 days
 - Chronic: Combo therapy - doxycycline and hydroxychloroquine, valve replacement
- Prevention
 - Educate at-risk workers
 - Check your research animals
 - Vaccine (not available in US)

Q FEVER
Illustrative Case

- 6/10/90 - 61 y/o WM - Hallsville, MO
- Sx: fever, HA, anorexia, nausea, sweats, photophobia, abdominal pain
- PE: diaphoretic, tachycardic, mild epigastric tenderness
- WBC-3.5K, plts-116K, ALT-43, AST-60

Q FEVER
Illustrative Case

- CSF Glucose-82, Protein 45, no WBCs
- CXR: old scarring of LLL
- Therapy: Doxycycline
- Serology:
 - 6/11/90 - <1:16 6/27/90 - 1:256
- Risk: Birthing calves

?

- 73 y/o WM SE MO, splenectomy 1979, MI
- 7/1/92 - fever, rigors, dry cough, HA, sore throat, joint pain for 4 days
- 38.9C, Small knee effusion, plts-70K
- Intra-erythrocytic ring forms on bld smear
- Started on Quinine and Clindamycin
- Died 7/20/92

HUMAN BABESIOSIS

- Unknown in US until 1966
- 2011 - 1,124 cases nation wide
- 97% - CT, MA, MN, NJ, NY, RI, WI
- Nantucket, Martha's Vineyard, Cape Cod, Block Island, Long Island, Shelter Island
- 82% - symptom onset June-August
- Vertical transmission: asymptomatic mom

BABESIOSIS

- Frequently asymptomatic
- 1-4 wks after tick bite - gradual onset malaise, anorexia, fatigue then fever, drenching sweats, myalgia
- Up to 40.3 C - N/V/C, hemoglobinuria, hyperesthesia, emotional lability, depression
- Parasitemias
- Hemolytic anemia, nl wbc, low plts

BABESIOSIS

- Splenectomy, AIDS - severe cases
- Co-infection with Lyme
- Ixodes scapularis - 36-48 hrs of attachment
- June and July
- Transfusion of platelets, rbcs from asymptomatic donors

BABESIOSIS Diagnosis

- Giemsa-stained thin blood smears
- Tetrad forms - Maltese-cross
- Predominant forms closely resemble rings of Plasmodium spp
- IFA - 1:64
- PCR
- Hamster inoculation method

BABESIOSIS

Treatment

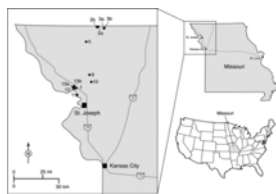
- Quinine and Clindamycin
- Atovaquone and Azithromycin
- Erythrocyte exchange transfusion in seriously ill patients who do not respond to pharmacologic intervention

Heartland Virus

- Phlebovirus genus of Bunyaviridae family
- 2 original patients from Missouri
- Fever, fatigue, anorexia, diarrhea
 - Leukopenia w/ neutro- and lymphopenia
 - Thrombocytopenia, elevated LFTs
- McMullan, L. K., et al. (2012)
 - "A new phlebovirus associated with severe febrile illness in Missouri." N Engl J Med **367**(9): 834-841.

Heartland Virus

- Found in nymphal *A. americanum* ticks
 - Savage, H. M., et al. (2013). "First detection of heartland virus (Bunyaviridae: Phlebovirus) from field collected arthropods." Am J Trop Med Hyg **89**(3): 445-452.



Heartland Virus

- Initially misdx'ed as HGA
- Most closely related to Severe Fever w/ Thrombocytopenia Syndrome Virus
- SFTSV – disease in China and Japan
 - Potentially fatal (2-15% fatality rate)
 - Humman to human transmission possible

MISSOURI LYME

- *Borrelia burgdorferii* transmitted by *Ixodes scapularis*
- SE MO - many reports of Lyme Disease
- Patients with Erythema migrans lesions
- CDC investigated 45 Missouri cases from 1990-1993

MISSOURI LYME

- Case definition - EM lesion >5 cm, summer
- 45 patients
 - Fatigue - 24, HA - 19, stiff neck - 18
- 11/22 had + *B. burgdorferii* EIA
- 10 paired serums showed no antibody rise
- More specific EIA test - all samples negative

MISSOURI LYME

- Immunoblots against *B. burgdorferii* on 40 samples showed no IgG
- 25 punch biopsies - no growth of *B. burgdorferii*
- All 45 patients received antibiotics

MISSOURI LYME

- Expanding annular erythema often accompanied by mild symptoms, often preceded by a tick bite
- Theories
 - Allergic reaction to tick bites
 - Novel spirochete in *Amblyomma americanum*
 - ? Lone Star Virus (PLoS ONE 8(4): e62083)

STARI vs Lyme Disease

Wormser, G. P., et al. (2005). *Clin Infect Dis* 41(7):958-65

STARI

- *A. americanum*
- Recall tick bite – 86%
- Symptomatic – 20%
- Single EM – 95%
- Central clearing – 75%

Lyme Disease

- *I. scapularis*
- Recall tick bite – 20%
- Symptomatic – 75%
- Single EM – 75%
- Central clearing – 25%

Rocky Mountain Spotted Fever

- Most frequently reported rickettsial disease in the US
- 1st described in Bitterroot, Snake, Boise river valleys
- 1906-1909 Howard Ricketts

Rickettsia rickettsii

- Small, pleomorphic, obligate intracellular parasite
- Survives briefly outside a host
- 2 tick species: *Dermacentor variabilis* and *D. andersoni*
- Rickettsiae released from salivary glands of feeding adult ticks
- 6-10 hours attachment; 50% recall bite

RMSF

- Most cases in south Atlantic coastal, western, southcentral states - NC, SC, OK, TN
- April thru September
- 5-9 year olds high risk group
- Dog exposure, wooded area, male

RMSF

- Fever, rash, tick exposure - 60 to 70% of cases
- 2-14 days p bite - Abrupt fever, malaise, myalgias, vomiting
- 1-15 days p illness onset - Rash: macules on wrists, ankles
- Spreads to trunk, face, palms, soles - papular, petechial, purpuric

RMSF

- Low WBC, low plts, elevated AST/ALT, low Na. CSF normal
- Poor prognosis - old age and delay in therapy
- 25% mortality w/o therapy, 5% with
- Death due to fluid leakage (lung/brain) from widespread rickettsia-induced vasculitis

**RMSF
Diagnosis**

- Direct immunofluorescent exam of skin biopsy
- Serology - antibodies in 7 to 10 days
- Weil-Felix lacks sensitivity and specificity
- PCR

RMSF Diagnosis

Am Academy of Peds Committee on Infectious Diseases

- Serology, isolation of *R. rickettsii* from blood or tissues, and ID of the agent in skin or other tissues by immunofluorescence help confirm the diagnosis
- To be useful, serologic tests require 3 serum samples, taken during the 1st, 2nd, and 4th to 6th weeks of illness
- A 4-fold or greater change in titer between acute- and convalescent-phase serum specimens is diagnostic when determined by:
 - Indirect immunofluorescence antibody (IFA)
 - Enzyme immunoassay (EIA)
 - Complement fixation (CF)
 - Latex agglutination (LA)
 - Indirect hemagglutination (IHA)
 - Microagglutination (MA) tests
- The IFA, EIA, and IHA are the most sensitive and specific tests
- Antibodies are detected by IFA 7 to 10 days after onset of illness

RMSF Diagnosis

Am Academy of Peds Committee on Infectious Diseases

- The nonspecific and insensitive Weil-Felix serologic test (*Proteus vulgaris* OX-19 and OX-2 agglutinins) is not recommended
- Culture of *R. rickettsii* usually is not attempted because of the danger of transmission to lab personnel
- *R. rickettsii* have been identified by immunofluorescent staining of skin biopsy specimens obtained from the site of the rash - 70% sensitive and 100% specific, but it is not widely available
- PCR for detection of *R. rickettsii* in blood and biopsy specimens during the acute phase of the illness confirms the diagnosis, but this test is available only in reference labs
- PCR is specific but not sensitive for diagnosing RMSF

McQuiston al. (2014). "Inadequacy of IgM Antibody Tests for Diagnosis of RMSF." *Am J Trop Med Hyg* 91(4):767-70

- 13 suspected RMSF cases IDed thru an enhanced surveillance program in TN
- Abs to *R. rickettsii* detected in 10 (77%) pts w/ IFA
- IgM Abs observed in 6 of 13 pts (46%) w/o corresponding development of IgG
 - 3 of 10 pts (30%) at least 1 year post-onset

McQuiston al. (2014). "Inadequacy of IgM Antibody Tests for Diagnosis of RMSF." Am J Trop Med Hyg 91(4):767-70

- Recent infxn w/ spotted fever group rickettsiae not be confirmed for any pt
 - Lack of rising Ab titers in acute and convalescent serologic specimens
 - Negative findings by PCR
- Case definitions in national surveillance programs lack specificity
- Use of IgM antibodies should be reconsidered as a basis for diagnosis and public health reporting of RMSF

Rocky Mountain Spotted Fever Therapy

- Doxycycline - drug of choice
- Empiric therapy - initiated promptly in suggestive clinical presentation
- Should respond rapidly to doxycycline
 - Fever persisting for >48 hours after initiation of therapy – consider an alternative or additional diagnosis
- Delay in treatment - can lead to severe disease and death

Don't Use Bactrim!

- Before doxy- PABA, analogue of sulfonamide - successful Rx of guinea pigs w/ RMSF
- PABA - frequent dosing and bicarb to keep therapeutic blood levels and prevent urinary precipitation
 - May be associated w/ interference of bacterial utilization of para-hydroxybenzoic acid
- Sulfonamides -structural analogs and competitive inhibitors of PABA

Don't Use Bactrim!

- Sulfonamides bind to dihydropteroate synthetase (DHPS) - inhibit 1st step of dihydrofolic acid synthesis
 - *R. rickettsii* lacks folP gene that encodes DHPS, making it resistant to SMX
- TMP binds to dihydrofolate reductase (DHFR) and inhibits conversion of dihydrofolic acid to tetrahydrofolic acid
 - Rickettsial species also lack folA, which encodes DHFR

EHRlichiosis

- 1986 - First case USA
- 1990 - Isolation of agent from blood- DNA sequencing - *Ehrlichia chaffeensis*
- 1992 - Application of PCR to whole blood
- Asymptomatic to fulminating with death
- 1994 - 2nd human agent *Anaplasma phagocytophila/equi*
- 1999 - *E. ewingii*

EHRlichiosis

- Acute, nonspecific febrile illness
- Sudden onset f/c, HA, nausea, myalgia, arthralgia, malaise
- Indolent cases with prolonged fever, occasional fatalities
- CNS manifestations
- *E. chaffeensis* - monocytes
- *A. phagocytophila/equi*, *E. ewingii* - granulocytes

EHRlichiosis

- *Amblyomma americanum*
- *Dermacentor variabilis*
- March thru October
- Predominantly male
- Duffers

EHRlichiosis

- Thrombocytopenia
- Leukopenia
- Abnormal LFTs
- Lymphopenia in acute phase followed by lymphocytosis
- Prolonged PTT
- Morulae in WBCs

EHRlichiosis

- Diagnosis
 - PCR
 - Acute and convalescent serology
 - Culture
- Therapy
 - Doxycycline
 - Chloramphenicol (some controversy)
 - Rifampin (theoretical)

EHRlichiosis
Illustrative Case

- 80 y/o WM-6d hx flu-like illness - Tm-39.4
- PE:fever,tachycardia,diffuse abd tenderness
- Lab: WBC-4.6, Hgb-13.2, plt-108, AST-57, ALT-64
- CXR: Atelectasis
- Intermittent fevers despite ampicillin/sulbactam and erythromycin

EHRlichiosis
Illustrative Case

- 3rd hospital day: presumed aspiration, intubated
- Next 41 days
 - Tracheostomy Non-Q wave MI
 - Candiduria Line infection
 - Thrombocytopenia - multiple platelet transfusions

EHRlichiosis
Illustrative Case

- Lab
 - Sputum: bacteria, AFB ECHO
 - Tularemia titer Bone marrow
 - Exploratory lap LP
- All above unrevealing
- Therapy:beta-lactams, aminoglycosides, clindamycin, fluoroquinolones, INH

EHRlichiosis Illustrative Case

- No improvement - Hospital day 44 - Transfer to UMC
- Lab: WBC-6.0, Hgb-7.4, plts-81, AST-72, ALT-49, LDH-396, Alk phos-289
- Tick exposure history

EHRlichiosis Illustrative Case

- PCR for *E. chaffeensis* 16S rDNA positive
- Doxycycline - Day 3 afebrile - Day 7 normal platelet count
- Titers to *E. chaffeensis*

- Day 50	Day 58	Day 182
- 1:32	1:64	1:128

PREVENTION OF TICK-BORNE DISEASES

- Long sleeved shirts, long pants, closed-toed shoes, walk on cleared trails
- Repellents
 - N,N-diethyl-m-toluamide: skin, clothing
 - Permethrin: clothing
- Tick removal
 - Tweezers as close to the skin as possible, steady pressure pull



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