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
• Ehrlichiosi
• 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 tularense* 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 paleartic*,
  - 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 pltts (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:
• 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)
Heartland Virus

- Found in nymphal A. americanum ticks
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)
  - Human 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*
STARI vs Lyme Disease

**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 post bite - Abrupt fever, malaise, myalgias, vomiting
• 1-15 days post 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

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- 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

- 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

- 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 chaffensis*
• 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. phagocytophilus/equi, E. ewingii - granulocytes
EHRLICHIOSIS

- *Ammblyomma 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
  – Candiduria
  – Thrombocytopenia - multiple platelet transfusions
  – Non-Q wave MI
  – Line infection
EHRLICHIOSIS
Illustrative Case

• Lab
  – Sputum: bacteria, AFB
  – Tularemia titer
  – Exploratory lap

• 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
REFERENCES

• [https://www.cdc.gov/lyme/resources/TickborneDiseases.pdf](https://www.cdc.gov/lyme/resources/TickborneDiseases.pdf)

REFERENCES

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