Lecture Objectives

- Distinguish the unique structural and morphologic characteristics of spirochetes, including those specific to *Treponema pallidum*, *Borrelia*, and *Leptospira*.
- Identify the primary mode of transmission of *Treponema pallidum*.
Treponema pallidum

- Structural characteristics
  - Thin, tightly coiled
  - Darkfield microscopy or immunofluorescence
  - Do not grow well in culture
  - Outer membrane does not contain lipopolysaccharide

Treponema pallidum

- Culture and growth
  - Can be cultured but only for a few generations on media with rabbit epithelial cells
  - Very sensitive to drying and heat
  - Microaerophilic (3-5% oxygen)
- Pathogenicity not well characterized
Treponema pallidum: epidemiology

- Found worldwide and 3rd most common sexually transmitted infection in U.S.
  - Steady increase in prevalence since 2005
  - In 2012, CDC reported > 50,000 new cases
  - Incidence particularly rising among men who have sex with men (MSM)
- Found only in humans

Treponema pallidum: epidemiology

- Transmission via direct sexual contact with an infective primary or secondary mucosal lesion
  - Genitals, anus, lip
  - Acquisition risk of 30% per sexual contact
- Congenital infection
- No sexual spread >4 years after acquiring infection
Lecture Objectives

• From a clinical description, recognize the different stages of Treponema pallidum infection, including congenital infection

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical hallmarks</th>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Painless ulcer (chancre) at site of inoculation</td>
<td>10-90 d after infection</td>
</tr>
<tr>
<td></td>
<td>Painless regional lymphadenopathy</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>Flu-like syndrome</td>
<td>2-10 weeks after chancre</td>
</tr>
<tr>
<td></td>
<td>Diffuse lymphadenopathy</td>
<td>(peaks 3-4 months after infection)</td>
</tr>
<tr>
<td></td>
<td>Generalized mucocutaneous rash</td>
<td></td>
</tr>
<tr>
<td>Latent</td>
<td>Asymptomatic</td>
<td>A few years to as many as 25 years</td>
</tr>
<tr>
<td>Tertiary</td>
<td>Granulomatous lesions (gummas)</td>
<td>Generally at least 5-10 years since infection</td>
</tr>
<tr>
<td></td>
<td>Neurosyphilis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiovascular syphilis</td>
<td></td>
</tr>
</tbody>
</table>

Treponema pallidum: clinical manifestations

• Primary syphilis
  – Chancre has smooth margins and crusted base
  – Darkfield positive
  – Firm local adenopathy
  – No systemic manifestations
  – Heals spontaneously

Murray, Pfaller, Rosenthal: Medical Microbiology, 8th edition, 2016
Treponema pallidum: clinical manifestations

• Secondary syphilis
  – Rash – including palms and soles
  – In moist areas: papules coalesce – condylomata lata
  – Other sites: hepatitis, aseptic meningitis, periostitis, nephritis
  – Fever and generalized lymphadenopathy
  – Heals spontaneously

• Tertiary syphilis
  – 1/3 of those untreated will develop tertiary
  – Gummas: granulomatous mass lesions in many different types of organs (bone, skin, liver, etc)
  – Neurosyphilis
  – Cardiovascular – aortic aneurysms, vasculitis
  – Not infectious at this stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Type</th>
<th>Pathology</th>
<th>Symptoms and signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early (secondary)</td>
<td>Asymptomatic</td>
<td>CSF pleocytosis and elevated protein</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Meningovascular</td>
<td>Meningitis, Vasculitis</td>
<td>Headache, neck stiffness, fever, cranial neuropathy, stroke</td>
</tr>
<tr>
<td>Late (tertiary)</td>
<td>General paresis</td>
<td>Chronic meningovascular</td>
<td>Dementia, Aphasia, Muscular weakness, Ataxia</td>
</tr>
<tr>
<td></td>
<td>Tabes dorsalis</td>
<td>Demyelination of spinal cord</td>
<td>Loss of pain and temperature sensation</td>
</tr>
</tbody>
</table>
**Treponema pallidum: clinical manifestations**

- Congenital syphilis
  - Most babies born asymptomatic but then develop:
    - Rhinitis (snuffles) and widespread rash, hepatomegaly
    - Long-term effects in those who survive:
      - Bone and teeth malformation – frontal ‘bossing’
      - Facial abnormalities – ‘saddle nose’
      - Blindness, deafness, cardiovascular disease
  - Prevent with routine screening and treatment during 1st trimester of pregnancy

**Lecture Objectives**

- Distinguish between non-specific non-treponemal and specific treponemal serologic tests for syphilis
- Identify the common patterns of non-treponemal and treponemal serologic reactivity for different stages of syphilis

**Treponema pallidum: diagnosis**

- Scrapings or tissue from primary or secondary lesions:
  1. Darkfield microscopy
  2. Direct fluorescent antibody
  3. PCR
- All are difficult to perform and not readily available
Treponema pallidum: diagnosis

• Serologic diagnosis with non-treponemal tests:
  - Reaginic antibodies
  - IgM and IgG against lipids (bovine cardiolipin)
  - NOT directed specifically against T. pallidum
  - VDRL (serum & CSF) – Venereal Disease Research Laboratory
  - RPR (serum) – Rapid Plasma Reagin
  - Quantitated into titers and used to follow treatment > revert to negative with treatment or enough time
  - False positive tests common

Treponema pallidum: diagnosis

• Serologic diagnosis with specific treponemal tests:
  1. Fluorescent treponemal antibody absorption (FTA-Abs)
  2. T. pallidum particle agglutination (TP-PA or TP-HA)
  3. T. pallidum enzyme immunoassay (EIA) or chemiluminescence immunoassay (CIA)

  - Tests remain positive for life, regardless of treatment

Serologic Reactivity in Syphilis
False positive non-treponemal (RPR) tests:
- Viral infection
- Drugs
- Autoimmune disease
- Leprosy, malaria
- Pregnancy
- Recent immunization

Treponema pallidum: treatment

- Benzathine penicillin G (long acting)
  - Single injection for primary and early secondary
  - Three injections weekly for congenital, latent, tertiary
- IV penicillin G for neurosyphilis
- Jarisch-Herxheimer reaction
  - Fever, chills, headache, hypotension
  - Release of toxic products from dying spirochetes
- Doxycycline is an alternative

Question 1

A 23 year old man presents to his primary care physician with complaints of a diffuse rash all over his body. On physical examination, a maculopapular red rash is noted, including the palms and soles. The patient confirms he is sexually active and does not regularly use condoms. He thinks he may have had a painless sore on his penis a few months ago but isn't sure. It went away on its own and he did not seek medical care at that time. His PCP suspects syphilis and sends serologic tests.

Which combination of serologic tests is most consistent with this patient’s current stage of infection?

A. RPR negative; TP-PA negative
B. RPR positive; TP-PA negative
C. RPR positive; TP-PA positive
D. RPR negative; TP-PA positive
Serologic Reactivity in Syphilis

Borrelia

Lecture Objectives:

• Distinguish the unique structural and morphologic characteristics of spirochetes, including those specific to Treponema pallidum, Borrelia, and Leptospira.
• Identify the Borrelia species responsible for Lyme disease in the U.S. and for epidemic relapsing fever.
• Describe how Borrelia escapes immune recognition during clinical relapsing fever.
**Borrelia**

- Larger spirochete that is spread from a mammalian reservoir to humans by tick or louse vectors resulting in **Relapsing fever** or **Lyme borreliosis (Lyme disease)**
  - *Borrelia burgdorferi* – Lyme in US and Europe
  - *Borrelia garinii* and *B. afzelii* – Lyme in Europe and Asia
  - *Borrelia recurrentis* – epidemic relapsing fever
  - Many species – endemic relapsing fever

**Borrelia: structure and culture**

- Neither gram-pos nor gram-neg
- Larger than other spirochetes
- Stain with Giemsa or Wright’s stain
  - *B. recurrentis* can be seen in blood smear with light microscopy
- Microaerophilic with complex nutritional needs = very difficult to culture

**Borrelia: pathogenesis**

- Little known due to difficulty with isolation and culture
- *B. recurrentis* escapes immune recognition by altering antigenic structure during infection
  - Gene switch from silent to expression locus (like *N. gonorrhoeae*) on plasmid
  - Relapses caused by emergence and multiplication of antigenic variants
Lyme Disease

<table>
<thead>
<tr>
<th>Species of Borrelia</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borrelia burgdorferi</td>
<td>US and Europe</td>
</tr>
<tr>
<td>B. garinii, B. afzelii</td>
<td>Europe and Asia</td>
</tr>
</tbody>
</table>

Lecture Objectives

- Recognize the primary insect vectors, animal reservoirs, and geographic distribution for *Borrelia burgdorferi*
- From a clinical description, distinguish between the early and late stages of Lyme disease

*Borrelia burgdorferi* epidemiology

- Leading vector-borne disease in U.S.
- 95% of cases are in two geographic areas:
  - Northeast and Mid-Atlantic states (Maine to Virginia)
  - Upper Midwest (Minnesota and WI)

[https://www.cdc.gov/lyme/index.html](https://www.cdc.gov/lyme/index.html)
Borrelia burgdorferi: epidemiology

- White-tailed deer and white-footed mouse are primary animal reservoirs
- Spread by hard ticks
  - *Ixodes scapularis* – NE and Midwestern U.S.
  - *Ixodes pacificus* – Western U.S.

https://www.cdc.gov/lyme/index.html
Lyme disease: clinical manifestations

• Early stage (3-30d post bite):
  – Erythema migrans – Expanding erythematous target-shaped lesion at site of tick bite
  • Can culture from biopsy
  • Often accompanied by flu-like illness – fever, chills, malaise, myalgias

• Early disseminated
  – Within days to weeks of primary infection
  – Fatigue, headache, fever
  – Arthritis and arthralgia (60%)
  – Myalgia
  – Erythematous skin lesions
  – Cardiac dysfunction (conduction block)
  – Neurologic: facial nerve paralysis or other cranial neuropathies, radiculopathy, meningitis, and rarely encephalomyelitis

CID, 2006; 43: 1089.
**Lyme disease: clinical manifestations**

- Late-stage manifestations:
  - Recurrent/relapsing arthritis in large joints
  - Acrodermatitis chronica atrophicans (more common in Europe)

**Lecture Objectives**

- Describe the two-tier serologic testing for Lyme disease and recognize limitations of testing for early Lyme disease

**Lyme disease: diagnosis**

- Serum serology is a two-tiered testing system:
  1. Initial screening immunofluorescence assay (EIA, ELISA, IFA)
     - If negative you are done (unless within 4 weeks of tick bite or erythema migrans rash)
  2. High rate of false + so must be confirmed with a second Western Blot test
     - Specific IgG and IgM antibodies
     - IgM should only be used if <4 months from exposure

Lyme disease: diagnosis

- Nervous system Lyme disease diagnosis
  - Can see lymphocytic pleocytosis and elevated protein in CSF
  - Specific serology (IgG and IgM) from CSF
  - Also PCR available from CSF (reference laboratory)

Lyme disease: treatment and prevention

- Treatment:
  - Early: doxycycline, amoxicillin, cefuroxime x 10-14 days
  - Late: oral as above except for CNS Lyme (ceftriaxone IV may be preferred)
- Post-Lyme Disease Syndrome:
  - Poorly understood constellation of non-specific symptoms following treatment
  - Fatigue, subjective cognitive deficits, arthralgias, myalgias
  - No evidence for chronic infection and antibiotics do not help
- Prevention
  - Insect repellent, clothing, tick checks

Lecture Objectives

- Distinguish between epidemic and endemic relapsing fever with regard to vectors, animal reservoirs, and geographic distribution.
- Recognize the characteristic clinical manifestations and preferred method of diagnosis for relapsing fever
Relapsing Fever

<table>
<thead>
<tr>
<th>Organism</th>
<th>Vector</th>
<th>Reservoir</th>
<th>Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. recurrentis</td>
<td>Body louse</td>
<td>Humans</td>
<td>Epidemic (louse-borne)</td>
</tr>
<tr>
<td>15 other Borrelia</td>
<td>Soft tick Ornithodoros</td>
<td>Rodents, e.g., chipmunks</td>
<td>Endemic (tick-borne)</td>
</tr>
</tbody>
</table>

Relapsing fever: epidemiology

- **Epidemic – Louse-borne**
  - Crushed lice transmit disease through skin/membranes
  - Crowded, unsanitary conditions (war, famine, natural disaster)
  - Central and East Africa
    - Ethiopia, Eritrea, Somalia, Sudan

- **Endemic – Tick-borne**
  - Tick bites can be very brief and often unrecognized
  - Worldwide distribution
    - Mountain U.S. (WA, CA)

504 cases – 1990-2011 from 12 western states
Relapsing fever: clinical manifestations

- Epidemic and endemic present essentially the same
- Abrupt onset fever, chills, myalgias, headache with bacteremic phase
- Splenomegaly and hepatomegaly
- Resolves in 3-7 days and then recurs a week later
  - Single relapse for epidemic
  - As many as 10 relapses for endemic
  - Relapses are less severe
- Mortality high for louse-borne epidemic disease

Relapsing fever: diagnosis, treatment, prevention

- Diagnosis:
  - Giemsa or Wright stained blood smear
  - Serology not helpful due to antigenic phase variation
- Treatment:
  - Tetracyclines (preferred) or penicillins
  - Jarisch Herxheimer reactions common
- Prevention:
  - Insect repellant, clothing
  - Rodent control, delousing sprays, hygiene

https://www.cdc.gov/relapsing-fever/clinicians/index.html
Question 2

A 24 year old man seeks care in the Emergency Department for recurrent fever. He has noted very high fever to 104 with severe headache and chills. This lasts a few days, then remits for about a week, and then returns. He’s had three such episodes. About a week prior to fever onset, he was hiking in eastern Washington state and had tick bites noted. An astute ED physician suspects endemic (tick-borne) relapsing fever.

What is the preferred method of diagnosis for this infection?

A. Spirochetes observed on Wright/Giemsa stained blood smear
B. Serum serology with immunofluorescence assay
C. Blood culture
D. Serum nucleic acid testing (i.e., PCR)

Leptospirosis

Lecture Objectives

• Distinguish the unique structural and morphologic characteristics of spirochetes, including those specific to Treponema pallidum, Borrelia, and Leptospira.
• Identify the primary mode of transmission of Leptospirosis
• From a clinical description, diagnose Leptospirosis
**Leptospirosis: structural and culture characteristics**

- Thin, coiled spirochete with hook
- Many different species and serotypes so generally just referred to as “Leptospirosis”
- Culture is difficult but possible
  - Liquid media supplemented with vitamins, fatty acids, salts
  - Obligate aerobes

**Leptospirosis: pathogenesis**

- Zoonosis affecting a variety of animal species
  - Humans acquire the organism by contact with infected animal urine usually through contaminated water
- Penetrate intact mucous membranes or skin through small cuts or abrasions
- Spread via blood to all tissues and damages endothelium of small blood vessels
  - Meningitis, hepatitis, renal dysfunction, hemorrhage, myocarditis

**Leptospirosis: epidemiology**

- Worldwide distribution but only 100-200 US infections/year
- Zoonosis with many animal hosts
  - Rodents; dogs, pigs, cattle, horses
- Transmission
  - Contact with urine (or other body fluids, except saliva) from infected animals
  - Contact with water, soil, or food contaminated with the urine of infected animals
  - Recreational exposure to contaminated water (e.g., lakes) or occupational exposure (vets, farmers, hunters, butchers)
Leptospirosis: clinical manifestations

- Most infections not clinically apparent or diagnosed
- First stage (Bacteremia)
  - Fever, chills, headache, myalgias, conjunctival suffusion, abdominal pain
- Second stage (Immune)
  - Aseptic meningitis or generalized illness with myalgias, headache, uveitis and rash
- Severe – stages blend
  - Vascular collapse, thrombocytopenia, hepatitis, kidney involvement, hemorrhage
  - Mortality 5-10%

Leptospirosis: clinical manifestations

- "Icteric" Leptospirosis is called Weil's disease
  - Striking jaundice with hepatitis in severe Leptospirosis
  - Hepatic necrosis not seen and most do not develop liver failure

Weil's disease in a rat owner
Leptospirosis – diagnosis and treatment

- **Diagnosis**
  - Culture blood and CSF (early), urine (late)
  - Serology – Microscopic agglutination test (MAT) after first week
    - ELISA and IHA tests less standardized
    - PCR very sensitive in research laboratories
- **Treatment**
  - IV Penicillin or doxycycline