SPIROCHETES

Syphilis, one of the classic venereal diseases, was described in writings from antiquity and was responsible for a great European epidemic in the late 15th century. Its sexual mode of transmission was recognized in the 16th century. Over the centuries, syphilis has changed from an acute, often fatal disease to a more chronic illness with serious complications. Syphilis is noted for its large variety of clinical presentations and for its progression through two infectious (primary and secondary) stages and a long latent period followed by a noninfectious (tertiary) stage.

Syphilis is caused by the spiral bacterium (spirochete), *Treponema pallidum*. In addition to syphilis, two other genera of spirochetes, *Borrelia*, including the agents of Lyme borreliosis and Relapsing Fever, and *Leptospira*, the agent of leptospirosis, are pathogenic for humans.

1. **Structural characteristics of spirochetes:**
   a. Helical morphology
   b. Flexible peptidoglycan cell wall
   c. One of more axial fibrils which wind around the cell wall of the organism
      i. Covered by outer membrane (like gram negative bacteria)
      ii. Probably responsible for peculiar rotation and flexion motility
   d. *Treponema* and *Leptospira* are thin and not visible by light microscopy
      i. Seen by darkfield microscopy
   e. *Borrelia* are larger and seen in stained preparations

2. **Pathogenic spirochetes overview:**

<table>
<thead>
<tr>
<th>Name</th>
<th>Visible by Light Microscopy</th>
<th>Vector/Reservoir</th>
<th>Transmission</th>
<th>Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Treponema pallidum</em></td>
<td>No (darkfield)</td>
<td>None</td>
<td>Intimate sexual contact</td>
<td>Syphilis</td>
</tr>
<tr>
<td><em>Leptospira</em></td>
<td>No (darkfield)</td>
<td>Rats, mice</td>
<td>Contact with or ingestion of water containing contaminated urine</td>
<td>Leptospirosis</td>
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<tr>
<td></td>
<td></td>
<td>wild rodents, dogs, swine, cattle</td>
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<tr>
<td><em>Borrelia recurrentis, 15 other species</em></td>
<td>Yes</td>
<td>V. louse, tick R. Wild rodents</td>
<td>Ticks or lice Ticks</td>
<td>Relapsing fever</td>
</tr>
<tr>
<td><em>Borrelia burgdorferi</em></td>
<td>Yes</td>
<td>V. tick R. Mouse, deer</td>
<td>Tick</td>
<td>Lyme borreliosis</td>
</tr>
</tbody>
</table>
3. *Treponema pallidum*:

a. **Morphology, staining, and structural characteristics:**

   i. Spiral organism, 6-20 μm long x 0.1-0.2 μm wide with regular spirals 1 μm apart
      1. Seen on darkfield exam or by immunofluorescence in fresh tissue. Cannot be seen by standard microscopic techniques
   ii. Structure
      1. Outer membrane does not contain lipopolysaccharide
   iii. Growth and cultivation
      1. Cannot be cultured except for several generations in cultured rabbit epithelial cells
      2. Generation time: 30 hours
      3. Very sensitive to drying and heat
      4. Microaerophilic, survives 3-5% oxygen

b. **Virulence factors and determinants of pathogenicity:**

   i. Passes through intact mucus membrane or abraded skin
   ii. Multiplies locally in subepithelial tissue and disseminates to lymph nodes and other organs
   iii. Symptoms and signs when critical mass of organisms reached at site Primary lesion – 3-90 days after initial infection
   iv. Pathologic lesion is obliterative endarteritis
   v. Hypersensitivity and autoimmune responses may play a role in later disease
   vi. Primary and secondary stages are self-limiting. Each are followed by periods of latency with mechanism of latency not determined
   vii. Immunity to reinfection after treatment of early syphilis is not sufficient to prevent reinfection
   viii. Immunity after treatment of later stages is more substantial
   ix. After latent period, late destructive disease develops in one-third of people

c. **Epidemiology**

   i. Intimate sexual contact with infective primary or secondary lesions (genitals, anus, lip)
      1. Risk of transmission about one in three contacts
   ii. Passes through placenta resulting in congenital infection
   iii. Accidental transfusion (rare)
   iv. Lesions of primary and secondary syphilis are contagious
   v. No sexual spread > 4 years after acquiring infection
vi. US has seen increased rates of syphilis yearly since 2003. Remarkable increase in men who have sex with men (particularly when co-infected with HIV) and more recently in women.

d. Primary Clinical Diseases

i. Primary syphilis
   1. Ulcerative lesion at the site of inoculation with regional adenopathy
      a. Painless papule (red bump) at the site of inoculation, which ulcerates called chancre (10-90 days after initial infection)
      b. Ulcer has smooth, heaped up margins and a crusted, dry base
      c. Liquid expressed from base is darkfield positive
   2. Firm local adenopathy
   3. Heals spontaneously

ii. Secondary syphilis
   1. Mucocutaneous rash with generalized lymphadenopathy and organ (liver, kidney, CNS) involvement
   2. Papulosquamous rash-entire body including palms and soles
   3. Moist areas-papules coalesce - condylomata lata
   4. Many other sites: hepatitis, aseptic meningitis, periostitis, nephritis (immune-complex type)
   5. Fever and generalized lymphadenopathy
   6. Heals spontaneously but may recur over the ensuing ?4 years (Most recurrences within the first year)
   7. One third of untreated cases spontaneously resolve the infection. The remainder progress to:

iii. Latent syphilis: positive treponemal test in the absence of clinical manifestations

iv. Tertiary syphilis -1/3 of untreated develop late syphilis
   1. Neurosyphilis
      a. Asymptomatic - evidence of infection in CSF without symptoms or signs
      b. Meningovascular - chronic meningitis which can affect major arteries to brain
      c. General Paresis - cortical degeneration of the brain with dementia*
      d. Tabes dorsalis - Demyelination of posterior columns and dorsal roots resulting in loss of pain, temperature and position sense in limbs with or without ataxia
   2. Cardiovascular involves destruction and arteritis of the proximal aorta and its branches causing aneurysms
   3. Late benign “gummatous” –granulomatous lesions in skin, mucocutaneous areas, bones, liver
v. Congenital syphilis
   1. Infection in utero - majority die in utero
   2. Normal at birth - multiorgan involvement becomes apparent later
   3. Rhinitis (snuffles), rash, bony and cartilaginous involvement (teeth, jaw, face), liver, spleen, lymph nodes and CNS
   4. Treatment during early pregnancy prevents congenital syphilis
   5. Routine serologic testing (screening) during pregnancy recommended

e. Diagnosis

i. MICROSCOPY
   1. Darkfield - primary and secondary lesions
   2. Immunofluorescence microscopy - monoclonal antibodies

ii. SEROLOGY (Mainstay of Diagnosis)
   1. Non-treponemal reaginic tests – Syphilis "reaginic" antibodies are IgG & IgM directed against cardiolipin, a lecithin-cholesterol mixture present on mitochondrial membrane
      a. Cardiolipin is a lipid extracted from beef heart. Reason for forming these antibodies is not known. The antibodies are not directed against *T. pallidum* specifically.
      b. VDRL - Venereal Diseases Research Laboratories
         i. Only test done on cerebrospinal fluid
     c. RPR - Rapid Plasma Reagin
        i. Most commonly performed on serum
     d. Tests are quantitated (diluted) and used to follow treated patients.
        i. Should revert to negative after successful treatment of primary (1 year) and secondary (2 years) syphilis.
        ii. Exception to this is HIV/AIDS where non-treponemal tests may remain positive at a low titer for life.
   2. Specific treponemal tests – Measure specific antibody against *T. pallidum*
      a. FTA-Abs - Fluorescent Treponemal Antibody - Absorption Test.
         i. Serum is absorbed with extracts of cultivated non-*T. pallidum* treponeme
         ii. Antigen is killed Reiter strain of *T. pallidum* on a slide
      b. TP-PA (Treponema pallidum particle agglutination) or TP-HA (Treponema pallidum hemagglutination)
         i. Treponemal antigens adsorbed onto erythrocytes or latex particles.
         ii. Agglutinated by serum containing antibody against *T. pallidum*.
      c. EIA and CIA (enzyme immunoassay, chemiluminescence immunoassay) – these are automated, inexpensive tests that are
now done in large laboratories and used to screen. A positive EIA should be confirmed with a quantitative nontreponemal test (e.g., FTA-Abs, TP-PA).

3. One of the specific tests should always be used to confirm a positive reaginic test. Specific treponemal tests remain positive for life

4. Now “reverse algorithm” in which positive treponemal test is confirmed with a nontreponemal test when EIA is used for screening

5. False positive non-treponemal serologic tests are relatively frequent

f. **Treatment**

i. Penicillin resistance is unknown in this exquisitely sensitive pathogen

ii. Long acting injectable formulation because of very long generation time, therefore Benzathine Penicillin G intramuscular injection is used

iii. Treatment schedules differ according to stage. Must use intravenous treatment for neurosyphilis.

iv. Alternate to penicillin – doxycycline – NOT FOR NEUROSYPHILIS OR PREGNANCY.

v. Jarisch Herxheimer Reaction - fever, chills, headache, flushing, muscle aches, and hypotension after treatment
  1. Release of toxic products from killed spirochetes
  2. Usually occurs within first few hours following first antibiotic dose
  3. Self-limiting and rarely serious, can use NSAIDS as needed

<table>
<thead>
<tr>
<th>Name</th>
<th>Agent</th>
<th>Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bejel</td>
<td><em>T. pallidum ss. Endemicum</em></td>
<td>Contaminated utensils</td>
</tr>
<tr>
<td>Yaws</td>
<td><em>T. pertenue</em></td>
<td>Direct lesion contact</td>
</tr>
<tr>
<td>Pinta</td>
<td><em>T. carateum</em></td>
<td>Direct lesion contact</td>
</tr>
</tbody>
</table>

4. **Borrelia:**

a. General structural and culture characteristics

i. Spirochetes, 3-30um x 0.2-0.5 um

ii. *Borrelia recurrentis* and other species of *Borrelia* that cause Relapsing Fever can be seen on Wright's or Giemsa stained blood smear

iii. Culture – challenging and rarely performed

1. *B. recurrentis*, others - fluid media containing blood serum or tissue

2. *B. burgdorferi*: artificial media - Barbour, Stoenner, Kelly broth

iv. Contain linear plasmids that code for outer membrane protein antigens
b. **Relapsing Fever** - Relapsing Fever is a systemic illness in which *Borrelia* are found in the bloodstream and multiple organs

i. Epidemic relapsing fever is caused by *B. recurrentis* and the vector is the body louse (humans are only reservoir)

ii. Endemic relapsing fever is caused by many other *Borrelia* species and the vector is the soft-bodied tick (*Ornithodoros*)

iii. Genetic (antigenic) diversity

1. *Borrelia recurrentis* and others can escape specific immunity by altering their antigenic structure during infection

2. Mechanism involves gene switch on a linear plasmid from silent locus to active expression locus (like *N. gonorrhoeae*)

3. Relapses of illness are caused by repeated multiplication of antigenic variants

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**Figure 1** A switch from serotype 7 to 21 by a *B. hermsii* cell. In the recombination, a silent vmp21 (dark cross-hatched pattern) and its 3' flanking region, which are located on the silent plasmid bp21S, replaces an active vmp7 (checkerboard) on the expression plasmid bp7E. In the process, the expression plasmid bp21E is created and bp21S is retained. The switch is unidirectional and nonreciprocal. The boundaries of the recombination are the Upstream Recombination Site (open box) at the 5' end of the vmp genes and Downstream Recombination Site (solid box) at the telomere of the expression plasmids and in the interior of the silent plasmids. The silent plasmid bp7S is not shown.

iv. **Epidemiology**

1. Epidemics of louse-borne relapsing fever occur primarily in Central and Eastern Africa in times of catastrophe such as war or famine or natural disaster

   a. Lice cause infection when they are crushed while they are attached on skin

2. Tick-borne relapsing fever occurs in mountain regions of western U.S. (and throughout the world)
a. Ticks become infected by feeding on animal reservoir (rodents) and then infect humans with tick bites

v. Clinical disease
   1. Recurrent predictable episodes of fever/rigors, chills, headache, myalgias, rash that last for 3 days, then recur 7 days later
   2. Relapses are sometimes less severe

vi. Diagnosis, treatment, and prevention
   1. Diagnosis is by visualization of spirochetes on light microscopy of a Giemsa or Wright stained blood smear
   2. Can also use darkfield microscopy
   3. Treatment with tetracyclines, macrolides
   4. Jarisch-Herxheimer reactions are very common

c. Lyme disease - Systemic disease resembling syphilis in its multiple stages and prominent involvement of the skin and CNS

i. Epidemiology
   1. Zoonosis in which deer and mice are primary reservoirs
   2. Spread by tick - *Ixodes ricinus* complex: *Ixodes scapularis* in northeastern and Midwestern U.S.; *I. pacificus* in western areas
   3. All tick stages feed on humans but nymph primarily responsible for transmission
   4. Animal reservoirs for spirochete and the tick include white-footed mouse (larva and nymph forms) and deer (adult form) but wide variety of species infected.

ii. Clinical disease
   1. Early localized - Erythema migrans (EM). Expanding erythematous skin lesion at site of tick bite
      a. Organisms can be identified in skin biopsy
      b. Accompanied by flu-like illness
   2. Early disseminated
      a. fever, systemic signs
      b. Neurologic: meningitis, radiculitis, facial nerve paralysis, other
      c. Heart – esp heart block
   3. Late - Involves CNS, joints, skin
      a. Neurologic: Encephalitis and encephalopathy
      b. Arthritis: develops in two-thirds weeks to years later
      c. Chronic skin lesions - Acrodermatitis chronica atrophicans

iii. Laboratory diagnosis and treatment
   1. Culture usually not available
   2. Serology – two-tiered system
5. Leptospirosis

a. Leptospirosis is a zoonosis affecting a variety of animal species. Humans acquire the organism by contact with infected animal urine (contaminated water most common).

b. Structural and culture characteristics
   i. Thin spirochetes - 6-20um x 0.1um
   ii. Two periplasmic flagella
   iii. Many different species and serovars
      1. The specific syndromes associated with each serotype are not distinctive and taxonomy is not definitive so they are just referred to as “Leptospirosis”
   iv. Can be cultivated in liquid media – very difficult

c. Epidemiology
   i. Zoonosis with many animal hosts: Rats, mice, wild rodents, dogs, swine, cattle
   ii. Transmission. Humans infected through indirect or direct contact of skin or mucous membranes with infected animal urine or with food or water contaminated with infected animal urine
   iii. Usually either occupational (vets, butchers, farmers) or recreational (waterskiing, triathlons, jet-skis) exposure

d. Clinical disease
   i. First stage (Bacteremia): fever, headache, muscle ache, abdominal pain, conjunctival suffusion
   ii. Second stage (Detectable antibody): aseptic meningitis or generalized illness with myalgias, headache, rash, uveitis
   iii. The stages blend in severe disease with prominent hepatitis, kidney involvement, and hemorrhage
   iv. Mortality in severe disease 5-10%

e. Diagnosis and treatment
   i. Serology is preferred using microscopic agglutination test (MAT) after first week of illness
   ii. Can be cultured with difficulty from blood, CSF, and urine (later)
   iii. Penicillin, ceftriaxone, or tetracycline is treatment