CHAPTER-X
SYPHILIS

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Trepananoma pallidum

D. Clinical Infection: Syphilis

Transmission
- Usually through sexual contact from an infected individual by invading intact mucous membranes or abraded skin

Pathogenesis
- Disease of blood vessel & perivascular areas
- Primary lesion due to inflammation at site of inoculation
- Secondary lesion due to inflammation of ectodermal tissues
- Tertiary lesion due to diffuse chronic inflammation to organ systems
Trepananoma pallidum

D. Clinical Infection: Syphilis

3. Clinical Manifestations
   - **Primary Disease**
     - **Chancre**: single lesion, non-tender & firm with a clean surface, raised border & reddish color
     - Usually on the cervix, vaginal wall, anal canal
     - Draining lymph nodes enlarged & non-tender
Pathogenesis of T. pallidum

- Tissue destruction and lesions are primarily a consequence of patient’s immune response.
- Syphilis is a disease of blood vessels and of the perivascular areas.
- In spite of a vigorous host immune response, the organisms are capable of persisting for decades.
  - Infection is neither fully controlled nor eradicated.
  - In early stages, there is an inhibition of cell-mediated immunity.
  - Inhibition of CMI abates in late stages of disease, hence late lesions tend to be localized.
Pathology

Penetration:
- *T. pallidum* enters the body via skin and mucous membranes through abrasions during sexual contact
- Also transmitted transplacentally

**Dissemination:**
- Travels via the lymphatic system to regional lymph nodes and then throughout the body via the blood stream
- Invasion of the CNS can occur during any stage of syphilis
Pathology

- The bacteria rapidly enter the lymphatic's, are widely disseminated via the bloodstream and may lodge in any organ. The exact infectious dose for man is not known, but in experimental animals fewer than ten organisms are sufficient to initiate infection.
STAGES OF SYPHILIS

1. Primary
2. Secondary
3. Latent
   - Early latent
   - Late latent
4. Late or tertiary
   - May involve any organ, but main parts are:
     - Neurosyphilis
     - Cardiovascular syphilis
     - Late benign (gumma)
Untreated syphilis may be a progressive disease with primary, secondary, latent and tertiary stages. *T. pallidum* enters tissues by penetration of intact mucosae or through abraded skin.
Primary syphilis

a) One or more painless chancre (indurated raise edges & clear bases) that erupt in the genitalia, anus, nipples, tonsils or eyelids.

b) Starts as papule and then erode

c) Disappear after three to six weeks even without treatment.

d) Lymphadenopathy that is either unilateral or bilateral
Trepananoma pallidum

D. Clinical Infection: Syphilis

3. Clinical Manifestations

iii. Latent disease

a. Early latent (1st 4 years)
   • No signs & symptoms of active syphilis but remain seroactive

b. Late latent (after 4 years)
   • If untreated, 60% continue to be asymptomatic while 40% progress to tertiary stage
Chancre

The chancre usually heals spontaneously within 3-6 weeks, and **2-12 weeks later the symptoms of secondary syphilis develop.** These are highly variable and widespread but most commonly involve the skin where macular or pustular lesions develop, particularly on the trunk and extremities. The lesions of secondary syphilis are highly infectious.
Progress of Disease

- Relapse of the lesions of secondary syphilis is common, and latent syphilis is classified as early (high likelihood of relapse) or late (recurrence unlikely). Individuals with late latent syphilis are not generally considered infectious, but may still transmit infection to the fetus during pregnancy and their blood may remain infectious.
Trepananoma pallidum

D. Clinical Infection: Syphilis

3. Clinical Manifestations
   • Primary Disease
     • Chancre: single lesion, non-tender & firm
       with a clean surface, raised border & reddish color
     • Usually on the cervix, vaginal wall, anal canal
     • Draining lymph nodes enlarged & non-tender
PRIMARY SYPHILIS
(The Chancre)

- Incubation period 9-90 days, usually ~21 days.
- Develops at site of contact/inoculation.
- Classically: single, painless, clean-based, indurated ulcer, with firm, raised borders. Atypical presentations may occur.
- Mostly anogenital, but may occur at any site (tongue, pharynx, lips, fingers, nipples, etc...)
- Non-tender regional adenopathy
- Very infectious.
- May be darkfield positive but serologically negative.
- Untreated, heals in several weeks, leaving a faint scar.
Pathogenesis of T. pallidum (cont.)

Secondary Syphilis

- Secondary disease 2-10 weeks after primary lesion
- Widely disseminated mucocutaneous rash
- Secondary lesions of the skin and mucus membranes are highly contagious
- Generalized immunological response
Treponema pallidum

D. Clinical Infection: Syphilis

3. Clinical Manifestations

iv. Tertiary Disease

a. Gummas (3-10 years after secondary disease)
   • Non-progressive, localized dermal lesions
   • Benign tertiary syphilis
   • Pronounced immunologic host reaction

b. Neurosyphilis (>5 years after primary disease)
   • Paralytic dementia, tabes dorsalis, amyotropic lateral sclerosis, meningovascular syphilis, seizures, optic atrophy, gummatous changes of the cord
Congenital syphilis results from transplacental infection.

*T. pallidum* septicemia in the developing fetus and widespread dissemination.

Abortion, neonatal mortality, and late mental or physical problems resulting from scars from the active disease and progression of the active disease state.
Treponema pallidum and Immunity

D. Clinical Infection: Syphilis

4. Immunity

- Syphilis has persistent infection for decades in spite vigorous host response due to:
  - Dense coat (with fibronectin, transferrin, cerruloplasmin)
  - Evasion from PMN detection
  - Inhibition of cell-mediated immunity
- Relative but unreliable protection from reinfection in untreated patients
- Minor protection from reinfection in treated patients
Congenital Syphilis

- Passed from mother to fetus during pregnancy
  - Abnormally shaped teeth
  - Nasal septum collapses
  - Skeletal abnormalities
1. History and clinical examination.
2. Dark-field microscopy: special technique use to demonstrate the spirochete as shiny motile spiral structures with a dark background.

The specimen includes oozing from the lesion or sometimes L.N. aspirate. It is usually positive in the primary and secondary stages and it is most useful in the primary stage when the serological tests are still negative.
Diagnosis of syphilis

Direct detection of spirochetes:
- Darkfield microscopy
  (motile bugs + experience + prompt examination)
- Silver stain

- Culture: not used
- Serology: non-specific and specific tests
Serologic Tests

- Reveal patients immune status *not* whether they are currently infected
- Use lipoidal antigens rather than *T. pallidum* or components of it; *non-treponemal antigen tests*
- RPR; rapid plasma reagin
- VDRL; Venereal Disease Research Laboratory
Treponema pallidum

Laboratory diagnosis

- Serologic testing
  - Nontreponemal Tests (uses Cardiolipin-lecithin as antigen)
    a. Complement-fixation tests (Wasserman & Kolmer test)
    b. Flocculation tests (Venereal Disease Research Laboratory, (VDRL), Hinton & rapid reagin tests)
Serologic Tests

- Positive within 5 to 6 weeks after infection
- Strongly positive in secondary phase
- Strength of reaction is stated in dilutions
- May become negative with treatment or over decades
F. Laboratory diagnosis

- Serologic testing
  - Treponemal Tests (uses syphilitic tissue as complement-fixing antigen)
    - Reiter Protein Complement Fixation
      - Antigen is an extract from nonvirulent treponeme (Reiter strain)
      - Nonreactive in late stages of syphilis
Non-treponemal tests

- Antigen: **cardiolipin** (beef heart) + lecithin + cholesterol
- Detect nonspecific antibody (Reagin): a mixture of IgM & IgG direct against some normal tissue antigens
- **VDRL** (Venereal Disease Research Laboratory) test for serum and CSF samples
Venereal Disease Research Laboratory - VDRL

- Flocculation test, antigen consists of very fine particles that precipitate out in the presence of reagin.
- Utilizes an antigen which consists of cardiolipin, cholesterol and lecithin.
  - Antigen very technique dependent.
  - Must be made up fresh daily.
- Serum must be heated to 56 C for 30 minutes to remove anti-complementary activity which may cause false positive, if serum is not tested within 4 hours must be reheated for 10 minutes.
- Calibrated syringe utilized to dispense antigen must deliver 60 drops/mL +/- 2 drops.
Each preparation of antigen suspension should first be examined by testing with known positive or negative serum controls.

The antigen particles appear as short rod forms at magnification of about 100x. Aggregation of these particles into large or small clumps is interpreted as degrees of positivity.

Reactive on left, non-reactive on right.
Rapid Plasma Reagin Test - RPR

- General screening test, can be adapted to automation.
- **CANNOT** be performed on CSF.
- Antigen
  - VDRL cardiolipin antigen is *modified with choline chloride* to make it more stable
  - attached to charcoal particles to allow macroscopic reading
  - antigen comes prepared and is very stable.
- **Serum or plasma** may be used for testing, serum is not heated.
Treponema pallidum

Laboratory diagnosis

- Serologic testing
  - ii. Treponemal Tests (uses syphilitic tissue as complement-fixing antigen)
    - a. Treponema Pallidum Immobilization (TPI)
      - Reaginic antibody & complement immobilize a suspension of living and motile treponemes maintained in rabbit testes & determined by darkfield microscopy
      - Difficult, expensive, requires living organisms
      - Positive for nonvenereal treponematoses, bejels, yaws & pinta
F. **Laboratory diagnosis**

- **SEROLOGIC TESTING**
  
  ii. **Treponemal Tests** *(uses syphilitic tissue as complement-fixing antigen)*
  
  b. **Reiter Protein Complement Fixation**
    
    - Antigen is an extract from nonvirulent treponeme *(Reiter strain)*
    
    - Nonreactive in late stages of syphilis
Specific serological tests of syphilis

A. Reiter protein complement fixation test.
B. Fluorescent Treponemal antibody/absorption test, FTA/ABS. the most specific and most sensitive.
C. Treponema pallidum haemagglutination test- TPHA-
D. Treponema pallidum immobilization test- TPI
Treponema pallidum haemagglutination (TPHA)

- Adapted to micro techniques (MHA-TP)
- Tanned sheep RBCs are coated with T. pallidum antigen from Nichol’s strain.
- Agglutination of the RBCs is a positive result.
Specific serological tests of syphilis

- A. Reiter protein complement fixation test.
- B. Fluorescent Treponemal antibody/absorption test, FTA/ABS. the most specific and most sensitive.
- C. Treponema pallidum Haemagglutination test- TPHA-  D. Treponema pallidum immobilization test- TPI
F. Laboratory diagnosis

   Serologic testing

   ii. Treponemal Tests (uses syphilitic tissue as complement-fixing antigen)

   c. Fluorescent Antibody Tests / Fluorescent Treponemal Antibody Absorption (FTA-ABS) Test
      • Uses lyophilized Nichols strain organisms as antigen → mixed with antitreponemal antibody (from test serum) in a slide → flourescein isothiocyanate-labeled antihuman Ig → presence of antibody determined by darkfield microscopy
      • Used to diagnosed congenital syphilis & late stage syphilis, confirmation of nontreponemal tests
Fluorescent Treponemal Antibody Absorption Test (FTA-ABS)

- Diluted, heat inactivated serum added to Reiter’s strain of *T. pallidum* to remove cross reactivity due to other Treponemes.
- Slides are coated with Nichol’s strain of *T. pallidum* and add absorbed patient serum.
- Slides are washed, and incubated with antibody bound to a fluorescent tag.
- After washing the slides are examined for fluorescence.
- Requires experienced personnel to read.
- Highly sensitive and specific, but time consuming to perform.
Positive FTA Test for Syphilis Viewed with a Fluorescent Microscope
Serologic Tests

- To improve sensitivity and specificity tests using a specific treponemal antigen devised
- MHA-TP: microhemagglutination assay for *T. pallidum*
- FTA-ABS: fluorescent treponemal antibody absorption test
- All positive nontreponemal test results should be confirmed with a specific treponemal test
Treponema pallidum

F. Laboratory diagnosis
   - Serologic testing
     ii. Treponemal Tests (uses syphilitic tissue as complement-fixing antigen)
       d. Haemagglutination Tests
          a. Microhemagglutination assay – T. pallidum (MHA-TP)
Biologic False-Positive Test Results

- Positive STS in persons with no history or clinical evidence of syphilis
- Acute BFP: those that revert to negative in less than 6 months
- Chronic BFP: persist > 6 months
BFP Test Results in Syphilis

- Acute BFP
- Vaccinations
- Infections
- pregnancy

- Chronic BFP
- Connective tissue disease (SLE)
- Liver disease
- Blood transfusions
- IVDA
Advantage of VDRL:

- cheap, easy to perform
- quantitative, screen test
- monitor disease course
- trace therapeutic effect, become “-” in 6-18 m after effective treatment.
Treatment of Late Syphilis

- Late syphilis:
  - benzathine penicillin 2.4 million units intramuscularly weekly for 3 weeks.
  - procaine penicillin 1.2 million units intramuscularly daily for 21 days
  - Tetracycline or erythromycin 500 mg 4 times a day – or doxycycline 100 mg x2- by mouth for 30 days

- Jarrisch-Herxheimer reaction

- Follow-up
Prevention & Treatment of Syphilis

- **Penicillin remains drug of choice**
  - WHO monitors treatment recommendations
  - 7-10 days continuously for early stage
  - At least 21 days continuously beyond the early stage
- **Prevention with barrier methods** (e.g., condoms)
- **Prophylactic treatment of contacts** identified through epidemiological tracing