Syphilis: The Great Imitator

**EPISODE II**
PRACTICAL PEARLS FOR PRACTICING CLINICIANS

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Learning Objectives:
- Upon completion of this content the learner will be able to:
- Describe the changing epidemiology of infection and list populations at high risk for syphilis.
- List the stages of disease and describe clinical manifestations of each stage of syphilis.
- List and describe the direct microscopic and serologic tests for syphilis and their application and interpretation in the diagnosis of infection.
- Discuss the clinical management of syphilis to include treatment, follow-up, and partner management.
- Describe the relationship between syphilis and HIV infection.

This curricular outline is a modification of one developed by the Curriculum Committee of the National Network of STD/HIV Prevention Training Centers. This project was funded through a grant by the US Centers for Disease Control and Prevention.

For the full text, please go to: [http://www.stdhivtraining.org/resource.php?id=53&ret=resource_search](http://www.stdhivtraining.org/resource.php?id=53&ret=resource_search)

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**Neurosyphilis:**
- Central nervous system invasion occurs early in infection in 30-40% of patients; however most patients eventually clear this site of infection with conventional therapy.
- Asymptomatic neurosyphilis can occur at any stage. Early forms of neurosyphilis usually occur a few months to a few years after infection. Clinical manifestations include acute syphilitic meningitis, a basilar meningitis that typically involves cranial nerves VI, VII and VIII, or meningovascular syphilis, an endarteritis that presents as a stuttering stroke-like syndrome and seizures.
- Late forms of neurosyphilis usually occur decades after infection and are rarely seen. Clinical manifestations of parenchymatous involvement include general paresis and tabes dorsalis.
- Ocular involvement can also be early or late. Uveitis may be the most common early presentation.

**Transmission:**
- Major routes of transmission are sexual and vertical (in utero from infected pregnant woman via hematogenous spread to her fetus).
- Risk of infection after sexual exposure is about 30%.
- An infected individual is most contagious to sexual partners during the primary and secondary stages of his/her infection when lesions or rash are present, and much less so in subsequent stages.

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**Time Line: Untreated Syphilis**

<table>
<thead>
<tr>
<th>Time</th>
<th>Stage</th>
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<tbody>
<tr>
<td>10-80 days</td>
<td>Primary</td>
</tr>
<tr>
<td>21 days</td>
<td>Secondary</td>
</tr>
<tr>
<td>6 wks to 6 mos</td>
<td>Tertiary</td>
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<tr>
<td>2 to 40 yrs</td>
<td>Latent</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Latent</th>
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</thead>
<tbody>
<tr>
<td>Early Latent &lt;12 mos</td>
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<tr>
<td>Late Latent &gt;12 mos</td>
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</table>
Diagnosis

History:
- History of syphilis.
- Known contact to an early case of syphilis. Typical signs or symptoms of syphilis in the past 12 months.
- Most recent serologic test for syphilis.
- Physical examination of oral cavity, lymph nodes, skin of torso, palms and soles, neurologic including cranial nerves especially II, VI, VII, VIII, in addition to the genitalia and perianal area.

Laboratory:
- Identification of Treponema pallidum in lesions on tissue via Darkfield microscopy. (Not available to us.)
- Direct fluorescent antibody - T. pallidum (DFA-TP). (Not available to us)
- 2-3 day turnaround, so patient needs to return for Tx.

Serological tests
- Nontreponemal tests: VDRL (Venereal Disease Research Laboratory), RPR (Rapid Plasma Reagin), TRUST (Toluidine Red Unheated Serum Test), USR (Unheated Serum Reagin):  
  1) Principles:  
     a) Measure IgM and IgG antibody directed against a cardiolipin-lecithin-cholesterol antigen.  
     b) Not specific for T. pallidum.
     c) Reaction may be microscopic (VDRL) or macroscopic (RPR).
     d) VDRL and RPR titers are not equivalent. RPR titers tend to be higher and are not directly comparable to VDRL titers for monitoring response to therapy. RPR may be slightly more sensitive and the longer duration of infection, the wider divergence between the RPR and VDRL.
     e) TRUST and USR are comparable to the VDRL.

Advantages:
- Rapid (RPR) and inexpensive.
- Easy to perform and can be done in clinic or office (RPR).
- Quantitative.
- Used to follow response to therapy.
- Can be used to evaluate possible reinfection.

Disadvantages:
- May be insensitive in certain stages (particularly primary and late latent).
- Biological false positive reactions. Febrile illnesses and recent immunizations.
- Chronic causes include injection drug use, autoimmune and chronic diseases.
- Rarely, a phenomenon called “the prozone effect” may cause a false negative reaction. The prozone effect occurs when the reaction is overwhelmed by antibody excess and may happen in late primary or in secondary syphilis. If clinical suspicion of secondary syphilis is high, the lab should dilute the serum to at least 1/16 dilution to rule out the prozone effect.

[Note: All positive non-treponemal tests need to be confirmed with a treponemal test for initial diagnosis.]

Treponemal test:
- TP-PA (Treponema pallidum Particle Agglutination).
- FTA-ABS (Fluorescent Treponemal Antibody-Absorbed).

Principles:
- Measures antibody (IgM and IgG) directed against T. pallidum antigens by particle agglutination (TP-PA) or immunofluorescence (FTA-ABS).

Test depends on serum dilution and absorption for specificity.
- Quantitative.
- Usually reactive for life, even after adequate treatment. However, some individuals treated early in their infections (before the secondary stage) may serorevert.

4. Sensitivity of serological tests in untreated syphilis:

30 y/o Woman requesting birth control
Sexual Risk Assessment

“The 5 Ps”

- Partners (number, gender, timeline)
- Practices (what goes where??)
- Protection from STIs (condom use, under which circumstances, etc...)
- Prevention (of pregnancy)
- Previous history of STIs

Latent syphilis:
No clinical manifestations. Only evidence is positive serologic test for syphilis.

Categories:
- early latent: <1 year duration.
- late latent: ≥1 year duration or of unknown duration.

Criteria for early latent syphilis:
- Documented seroconversion in comparison with a serologic titer obtained within the year preceding the evaluation.
- Unequivocal symptoms of primary or secondary syphilis reported by patient in past 12 months.
- Contact to an infectious case of syphilis in the past 12 months.
- A 4-fold increase in serologic titer in comparison with a titer within the past 12 months may represent a case of early latent syphilis or relapse of a previously treated case.

Relapses of secondary lesions in up to 25% of cases, usually within the first year.

Current therapy

Primary, secondary, early latent:
- Benzathine penicillin G 2.4 million units IM once.
- Non-pregnant, penicillin-allergic:
  - Close follow-up of persons receiving any therapy other than Benzathine penicillin G is essential because efficacy is not well documented.
  - Doxycycline 100 mg po twice daily for 2 weeks, or Tetracycline 500 mg po 4 times daily for 2 weeks, or
  - Some experts recommend ceftriaxone 1 gm IM/IV daily for 8-10 days as alternative therapy.
- Preliminary data suggest that azithromycin 2 gm as a single oral dose may be an effective alternative. Use in HIV-infected persons has not been studied, so if used, it should be done cautiously with close follow-up.
- Some experts recommend that HIV-infected persons with primary, secondary, or early latent syphilis be treated with benzathine penicillin G 2.4 million units IM at 1-week intervals for 3 weeks.

Later, unknown duration, or tertiary without neurologic involvement and normal CSF exam, if performed:
- Benzathine penicillin G 2.4 million units IM weekly for 3 consecutive weeks.
- Non-pregnant, penicillin-allergic:
  - Close follow-up of persons receiving any therapy other than Benzathine penicillin G is essential because efficacy is not well documented.
  - Doxycycline 100 mg po twice daily for 4 weeks, or Tetracycline 500 mg po 4 times daily for 4 weeks.

For further delineation of current therapeutic interventions for Neurosyphilis, Congenital Syphilis and Tertiary Syphilis, please see 2010 CDC STD treatment Guidelines @ http://www.cdc.gov/std/treatment/2010/

Jarisch-Herxheimer reaction:
Self-limited reaction to anti-treponemal therapy, characterized by fever, malaise, nausea/vomiting; may be associated with chills and exacerbation of secondary rash.
- Occurs within 24 hours after therapy and usually resolves within 24 hours.
- Patients should be warned it is not an allergic reaction to penicillin and can be treated with symptomatic support.
- More frequent after the treatment with penicillin and treatment of early syphilis, especially at the secondary stage.
- Pregnant women, in particular, should be informed of this possible reaction, that it may precipitate early labor, and to call obstetrician if problems develop.
Epidemiologic treatment
Sexual contacts to 1º, 2º or early latent syphilis or syphilis of unknown duration with titer of ≥1:32:
- Draw syphilis serology.
- Perform physical exam.
  Treat all as for early syphilis, at the time of test, unless the nontreponemal test result is known and negative, and last sexual contact with the index case is > 3 months.
- Azithromycin 1 gm po is currently being studied as an epidemiologic treatment.

Partner management: Refer all cases of primary, secondary, early latent syphilis, syphilis of unknown duration with a titer of ≥ 1:32, or a recent (within the past year) 4-fold increase in nontreponemal serologic titer to local health department Disease Intervention Staff for interview and partner elicitation and partner follow-up for counseling, evaluation, and treatment.

Follow-Up
1. Follow-up titers should be compared to the nontreponemal titer obtained on day of treatment.
2. Primary and secondary syphilis: clinical evaluation at 1-2 weeks and 1 month after treatment to ensure improvement and resolution of symptoms. Serological (quantitative VDRL or RPR) evaluation at 6 and 12 months.
3. Latent: serological (quantitative VDRL or RPR) evaluation at 6, 12, and 24 months.
4. HIV-infected patients clinical and serological evaluation at 3, 6, 9, 12, and 24 months for primary and secondary syphilis and at 6, 12, 18, and 24 months for latent syphilis.

Recommend HIV test for all patients with syphilis and consider retesting in 3-6 months, if initially negative.

Effect of HIV infection on syphilis:
- Syphilis and HIV infections commonly coexist.
- In general, clinical course is similar to non-HIV infected patients.
- Serological tests for syphilis are equivalent in sensitivity in HIV-infected and non-HIV-infected persons in the vast majority of patients. If clinical suspicion is high for syphilis and the serologic tests are negative, then biopsy of the lesion or rash is recommended.
- Conventional therapy is usually effective.
- Some investigators feel that patients may be more likely to present with symptomatic neurosyphilis.

Co-infections
- HIV
  - 39% of cases co-infected (15/38)
  - All MSM
  - 3 newly dx
- Other STDs
  - GC (1)
  - CT (1)
  - GC/CT (1)

All also HIV+

For further delineation of current therapeutic interventions for those things not covered today, please see 2010 CDC STD treatment Guidelines @
http://www.cdc.gov/std/treatment/2010/

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