Syphilis: Reemergence of the Great Pretender? (It never really left!)

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Learning Objectives

After attending this presentation, learners will be able to:

- Describe the natural history of syphilis
- Initiate a diagnostic work up for syphilis
- Manage syphilis

Other treponemal pathogens:
- T. pallidum spp. pertenue (yaws)
- T. pallidum spp. endemicum (bejel)
- T. carateum (pinta)
Cannot be cultivated in vitro

**Mucous patches**
Condylomata lata/Condyloma latum

Late or Tertiary Syphilis

- **Neurosyphilis**
  - can occur throughout the entire time course of syphilis infection and present as many things: meningitis, ocular/otic, behavioral, cognitive, autonomic, sensory, motor

- **Cardiovascular**
  - involves vasovasorum of the aorta. Saccular aneurysm of the ascending aorta-AR, stenosis of the coronary ostia

- **Late benign or 'gummatous'**
  - indolent granuloma like lesions of skin, bone and soft tissue

Neurosyphilis

- Early CNS invasion-clinical implications?
- Acute Symptomatic Meningitis
- Asymptomatic Meningitis
- Meningovascular events
- General Paresis
- Tabes dorsalis
- Gumma
- Ocular and otic

- Neurosyphilis should be considered for anyone with serologic evidence of syphilis and neuropsychiatric and/or ocular or otic disease
Ocular Syphilis

- Eye involvement occurs most frequently in secondary syphilis and late syphilis
- Almost every part of the eye can be involved.
- The vast majority of eye problems associated with syphilis are also associated with many other infectious and non-infectious diseases.
- Therefore—there are almost no eye findings that are absolutely specific for syphilis.

CDC April 2015 Clinical Advisory:
Ocular Syphilis Alert - CA, WA, other states
- 24 cases, majority HIV-infected MSM
- Few HIV-uninfected men and women
- Significant sequelae including blindness
- Loss of vision, blurring vision, floaters, a blue tinge in vision, flashing lights
- Careful neurologic exam in syphilis patients
- Patients with syphilis and ocular complaints need immediate ophthalmologic evaluation!!
- LP should be performed in patients with syphilis and ocular complaints
- Prior research has suggested neuropathogenic strains—undocumented here

CDC, MMWR November 4, 2016
- Following April 2015 report, eight jurisdictions (CA, FL, IN, MD, NYC, NC, TX, WA) reviewed syphilis surveillance and case data
- 388 suspected ocular syphilis were identified: 157 in 2014 and 231 in 2015 (0.93% and 0.65%)
- 93% men (high proportion MSM)
- 51% HIV co-infected
- 84% had symptoms: 54% blurry vision; 28% vision loss
- 158 (41%) had a specific dx: uveitis (n=72); retinitis (n=20); optic neuritis (n=18) and retinal detachment (N=6)
- Of 136 patients with available data, 64 (47%) had one eye involved and 72 (53%) had both eyes involved
- 174 had CSF results, 122 (70%) had +CSF VDRL
198 HIV-positive patients
- Higher median RPR titer in HIV+ compared to HIV- (256 vs 128)
- More often had LP (57% vs. 41%)
- More often treated with IV penicillin (67% vs. 44%)
- Both had similar reactive CSF VDRL, both eyes involved
  - Compared to patients with higher CD4, those with CD4 <500 were more likely to have LP (66% vs 45%) had reactive CSF VDRL (84% vs. 50%) and had both eyes involved (36% vs. 7%)

### Diagnostics: Traditional Serologic Testing

**Two-step testing:**

- **NTST:** Non-Treponemal Serologic Test (e.g. RPR, VDRL)
  - can be quantified
  - rises with active disease or failed therapy
  - declines with successful therapy or latency

  **If reactive then followed by**

- **TST:** Treponemal Serologic Test (e.g. FTA, TPPA, Treponemal IgG)
  - not quantifiable
  - life long reactivity

### Screening for Syphilis: Updated Evidence Report and Systematic Review for the US Preventive Service Task Force

**Table 1:** Sensitivity and Specificity of Serologic Tests for Syphilis

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Negative</td>
<td>78/79-97/100</td>
<td>94/96-99/100</td>
</tr>
<tr>
<td>Total Positive</td>
<td>72/93-94/95</td>
<td>73/79-85/90</td>
</tr>
<tr>
<td>Syphilis IgG</td>
<td>89/95-98/100</td>
<td>90/92-95/99</td>
</tr>
<tr>
<td>Syphilis IgM</td>
<td>90/95-96/99</td>
<td>92/95-98/99</td>
</tr>
<tr>
<td>TPHA</td>
<td>88/91-95/95</td>
<td>95/99-100</td>
</tr>
<tr>
<td>FTA</td>
<td>88/94-98/98</td>
<td>94/99-100</td>
</tr>
<tr>
<td>VDRL</td>
<td>78/92-88/98</td>
<td>90/95-99/99</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- TPHA: Treponema pallidum hemagglutination assay
- FTA: Fluorescent treponemal antibody absorption test
- VDRL: Venereal Disease Research Laboratory test
- HIV: Human Immunodeficiency Virus

- **RT-PCR:** Rapid antigen detection

- **USPSTF:** United States Preventive Services Task Force

- **USPSTF Recommendation:**
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- **Outcomes:**
  - 
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- **Notes:**
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- **References:**
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- **Funding:**
  - 
  - 

- **Conflict of Interest:**
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- **Copyright:**
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Treponemal Serologic Tests (TSTs) as Screening Tests - 'Reverse Algorithm'

- **EIA (T. pallidum sonicate or recombinant antigen)**
- **Low cost, automation, standardization etc.**
- **More sensitive and more specific than traditional NTSTs**
- **Doesn’t distinguish new, old, treated or untreated**
- **Recent CAP survey- 63% used traditional algorithm (Rhoads et al Arch Pathol Lab Med 2017)**

**Testing and Treatment Approach**

- **EIA Reactive**
  - TPPA Reactive
  - TPPA NR
  - BFP
  - Unless previously treated:
    - Stage and Rx by CDC recs

**CDC Screening Recommendations**

- **All pregnant women at 1st prenatal**
- **Retest pregnant women early in third trimester and at delivery if high risk**
- **MSM at least annually**
- **MSM every 3-6 months if high risk**
- **HIV if sexually active at first visit and annually**
- **HIV more frequently if high risk**
Screening in Pregnancy

- Screen at first prenatal assessment
- At every encounter consider risk and consider screening
- Screen infants at delivery
- Screen where stillborn after 20 weeks
- Screen at 28 weeks (NYC DOHMH)
To Treat is to Stage

- Primary, Secondary and Early Latent
  Benzathine penicillin 2.4million units IM once

- Late Latent and Latent of Unknown Duration*
  Benzathine penicillin 2.4million units IM once weekly for three weeks

- Late Tertiary Syphilis Except Neurosyphilis -
  R/O Neurosyphilis then same as latent syphilis

  -*If missed dose can continue series:
  if <9 days non-pregnant (levels decline)
  If <7 days pregnant
  Otherwise start all over!

Alternatives to Penicillin

- Tetracyclines (Doxycycline)
  - Two weeks for early or four weeks for latent
  - Ceftriaxone
  - Dose and duration unclear

  *Pregnant women should be treated with the penicillin regimen appropriate for their stage of infection.
  *There are no alternatives to penicillin in pregnancy
  *Jarish-Herxheimer reaction
  *HIV infected patients should receive the same therapy as HIV uninfected patients

Who needs an LP to Rule Out Neurosyphilis?

- "If you think about doing an LP then do an LP"
- Diagnosis requires CSF evaluation
- CDC STD Rx Guideline:
  - neurologic or ophthalmic signs or symptoms,
  - evidence of active tertiary syphilis (e.g., aortitis and gumma),
  - treatment failure-definition?
  - HIV: RPR>1:32 and/or CD4 <350???
CSF Abnormalities

- CSF VDRL - highly specific, variably sensitive
- CSF WBC - lymphocytic pleocytosis/ not specific in HIV+
- CSF protein
- CSF FTA-ABS - sensitive, not approved for this use
- PCR?
- Cytokines?

Neurosyphilis Treatment

- Aqueous PCN G 18-24mu qd in divided doses for 10-14 days (follow with Rx for latent)
- Alternative: procaine pcn G 2.4mu IM daily + probenecid 500mg po qid 10-14days
- Ceftriaxone - dose? Duration?
- Doxycycline?
- Amoxicillin + probenecid?

Do you need to do an LP in someone who only has eye symptoms and no neurological symptoms?

- Current CDC recs - treat ocular syphilis as if neurosyphilis even if CSF is negative
- If the CSF VDRL is positive in someone who has eye symptoms, you can make a DEFINITIVE diagnosis of ocular syphilis (that's really the only way to make a DEFINITIVE diagnosis)
- At least 70% of patients with ocular syphilis will have evidence of neurosyphilis on LP
- If there is evidence of neurosyphilis follow up LPs every 6 months
Post Rx follow-up for all stages

- Partner notification
- HIV testing
- Two fold declines in non treponemal serologic test like the RPR over 3-6m early and 12-24m in latent
- Some titers never go away
- Some titers don't decline properly
- CSF WBC should resolve 3-6 months, VDRL over a much longer period

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**From: Single Dose Versus 3 Doses of Intramuscular Benzathine Penicillin for Early Syphilis in HIV: A Randomized Clinical Trial**

**Intention-to-treat and per-protocol analyses of the comparison between a single dose vs 3 doses of 2.4 million units of intramuscular benzathine penicillin G (BPG) for early syphilis in human immunodeficiency virus-infected individuals.**

Abbreviation: BPG, benzathine penicillin G.

**Figure Legend:**


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"That which makes me shudder when at the very entrance to the Mosque I observe that it is written: "Mondays and Thursdays tuberculosis; Wednesdays and Fridays syphilis." In every Metro station there are grinning skulls that greet you with "Defendez-vous contre la syphilis!" Wherever there are walls, there are posters with bright venomous crabs heralding the approach of cancer. No matter where you go, no matter what you touch, there is cancer and syphilis. It is written in the sky; it flames and dances, like an evil porter. It is written in the air; it is written in our hearts. It is written on the moon; it is written on the moon, but a dead thing like the moon."

— Henry Miller, *Tropic of Cancer* (1934)
Question-and-Answer