Syphilis Basics: Part 1 of 3
Chase Cannon, MD, MPH

Overview
- Part 1
  - Clinical manifestations of syphilis
  - Staging of disease
  - Lab testing
  - Treatment

- Part 2: Deeper dive on complicated syphilis
- Part 3: Congenital syphilis

Disclosures
- Chase Cannon does not have relationships with a commercial interest related to the content of this educational activity.

Caveat: Language is evolving, and though our aim is to change accordingly, we acknowledge that CDC guidelines are written using binary language with respect to gender.
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A deep-rooted quandary

• Varied clinical manifestations, reporting practices
• CDC 2015 Guidelines: “A presumptive diagnosis of syphilis requires use of two tests: a nontreponemal test ... and a treponemal test...”
• Non-standardized or non-validated diagnostic algorithms
• Direct methods not widely available
• I have this positive result... Now what?

2021 CDC STI Treatment Guidelines

• Experts convened in Atlanta, GA from 11-14 June 2019
• Incorporation of new data/evidence
• More focus on challenges in syphilis management
  • Enhanced discussion about algorithms
  • Ocular syphilis
  • CSF follow-up
  • Expanded risk factors for testing in pregnant people

Syphilis: Disease transmission

• Chronic sexually transmitted infection caused by Treponema pallidum
• Infection through small breaks in skin or mucous membranes
• Risk of contracting syphilis per sexual contact 10-60% (average about 30%)
• Highest risk with contact to early syphilis
• Lesions with many treponemes transmit most effectively
Syphilis grows on you

- Progresses in stages with intervening periods of no disease activity
- Invades all parts of body, including central nervous system (CNS)
- Incubation time is 10 – 90 days, average ~ 3 weeks

Patient Case

- A 52 y/o man comes to your clinic with a painless penile lesion that appeared 3 days ago. He denies any other symptoms and reports regular STI screening (last negative 4 months ago).
- He reports approximately 10 male sexual partners in the last month. Occasional condom use. Mostly meets men on the apps now since COVID.
Patient Case

- Exam findings
  - 2 somewhat indurated but non-tender ulcers on the lateral shaft.
  - Firm non-tender LAD in R inguinal region
  - Oral exam and skin inspection are normal
- You order syphilis serologies but don’t have access to rapid testing.

Audience poll 2!

Syphilis: a bird’s-eye view

- Few hours: mucosal surface → lymph → bloodstream
- Chancre
  - ~3 wks (10-90 d); spontaneously heals 1-6 wks later
- Growth of organisms at site of infection, dissemination to various tissues including central nervous system
- Chance of infection, regional lymphadenopathy
- Disseminated rash, generalized lymphadenopathy
- Recurrence of secondary syphilis symptoms in up to 25% of individuals
- Gamma, cardiovascular syphilis, late neurological complications
Primary Syphilis

- Chancre can occur anywhere inoculated by direct contact (fingers, mouth, anus)
- Nontreponemal tests (RPR, VDRL) negative in 15-25% cases of primary syphilis
- Don’t need definitive diagnosis to treat: if you think it’s early syphilis → TREAT. Loss to follow up and spread of infection can be high.
Atypical primary syphilis

Secondary Syphilis

Cervical chancre

Syphilis: a bird’s-eye view
Secondary syphilis

- Generalized rash: evanescent, copper color, macular → reddish, papular, palms/soles
- Condylomata lata
- Mucous patches
- Fever (usually low grade), malaise, generalized lymphadenopathy
- Lasts 2-6 weeks

Secondary syphilis: Condylomata lata

- High numbers of treponemes
- May occur at any moist body site
- Highly contagious
- Fleshy, flat-topped appearance may help distinguish from warts, but often mistaken for latter
- Pearls: WET warts generally aren’t warts! Malodorous
Secondary Syphilis: Mucous patches

Secondary syphilis: Less common

- Alopecia (5%)  
  - Due to infection of hair follicles  
  - Patchy, “moth-eaten”  
- Loss of lateral eyebrows
- Liver, kidney, spleen involvement
- Uveitis

Patient Case

- A 37 y/o transgender woman presents to your clinic for routine testing.
- She has no symptoms but has a positive RPR titer of 1:8 on routine screening.
- Her confirmatory TP-PA is also reactive.
- Her serologies were negative 2 years ago.

Audience poll 3!
Latent Syphilis

Latent syphilis: new or old?

- Defined by positive treponemal serology in the absence of clinical manifestations

  - **Early Latent**: Infection identified <1 year
    - Negative syphilis serology in past year
    - Known contact to an early case of syphilis

  - **Late Latent**: Infection identified >1 year or unknown duration
    - No syphilis serology in past year
    - No contact to syphilis case or history of signs/symptoms in past year

Patient Case, cont.

- RPR titer of 1:8 -- what does that mean?
- Why the TP-PA?
Syphilis diagnosis and testing

Syphilis diagnostics

- Definitive: dark field microscopy, molecular testing (PCR)
- Highly suggestive: histopathology
- POC testing: Syphilis Health Check™

Serological testing for syphilis

Nontreponemal
- RPR, VDRL, TRUST
  (Quantitative, titers decrease with treatment)

Treponemal
- FTA-ABS, TP-PA, EIAs, CIAs
  (Good for screening but once positive, positive for life)

Treponemal tests

- FTA-ABS, TP-PA, EIAs, CIAs
- The FTA-ABS and TP-PA measure IgG and IgM reactivity to whole organisms
- The EIAs and CIAs measure antibodies to recombinant T. pallidum proteins
- Treponemal test results are expressed qualitatively (reactive or nonreactive) in the US
Nontreponemal tests

- **RPR, VDRL tests**
  - Originally developed using beef/ox heart emulsion in 1905
  - Measure IgG and IgM antibodies to a cardiolipin-lecithin-cholesterol antigen
  - Nonspecific evidence of tissue damage

- **Results expressed as a titer**
  - Higher titers reflect greater disease activity
  - Success of therapy: decline in titer
  - Even without treatment, nontreponemal titers will decline over time

Serial dilutions for quantitative RPR

Syphilis screening algorithms

- **Traditional**
  - Screen with nontreponemal test (RPR or VDRL)
  - Confirm with a treponemal specific test (TP-PA, EIA)

- **Reverse**
  - Screen with treponemal specific EIA
  - Confirm with RPR
  - If conflict: resolve with different treponemal test (TP-PA)

- CDC does not “endorse” or “recommend” either; based on your local lab and admin decision
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Traditional algorithm

- Non treponemal test (e.g. RPR)
  + Syphilis unlikely
  - Treponemal test (e.g. TP-PA)
    + Syphilis (past or present)
    - Syphilis unlikely

Reverse sequence algorithm

- Syphilis unlikely
  + Treponemal test (e.g. FTA or CFA)
    - Quantitative non-treponemal test (e.g. RPR)
      + Syphilis (past or present)
      - 2nd treponemal test (e.g. TPHA)
        + Syphilis (past or present)
        - Syphilis unlikely

Natural history timeline

Audience poll 4!
### Sensitivity of Serological Tests for Syphilis

<table>
<thead>
<tr>
<th>Test</th>
<th>Primary</th>
<th>Secondary</th>
<th>Tertiary</th>
</tr>
</thead>
<tbody>
<tr>
<td>VDRL</td>
<td>70%</td>
<td>99%</td>
<td>56%</td>
</tr>
<tr>
<td>RPR</td>
<td>80%</td>
<td>99%</td>
<td>56%</td>
</tr>
<tr>
<td>FTA-ABS</td>
<td>85%</td>
<td>100%</td>
<td>98%</td>
</tr>
<tr>
<td>TPPA</td>
<td>65%</td>
<td>100%</td>
<td>95%</td>
</tr>
</tbody>
</table>

### Detour for titers...

- **A fourfold change or two dilutions** represents a clinically significant difference
  - 1:32 → 1:4 (decreased 8-fold or 3 dilutions 1:16, 1:8, 1:4)
  - 1:2 → 1:16 (increased 8-fold or 3 dilutions 1:4, 1:8, 1:16)
- **Divide largest number by smallest. Must be ≥ 4 to be significant**
  - 1:2048 titer decreases to 1:256 after treatment. Appropriate response?
- **Ensure same nontreponemal test is used!**

### False negative tests

- **Early syphilis (primary)**
- **Prozone phenomenon** (with nontreponemal testing)
  - High antibody concentration in serum prevent ab/ag lattice formulation
  - Repeating the test using a diluted specimen

### Causes of Biologic False Positive results (BFP)

- Other infections: HIV, HSV, malaria, leprosy, other spirochetal infections
- Older age, autoimmune disorders, cardiovascular disease, pregnancy, recent immunizations (flu, PNA, etc.), IVDU
- False-positive results occur, but are rare overall
  - FTA-ABS and TP-PA (< 0.50%)
  - EIA/CIA (≤ 1%)
- **Confirm with a second, different treponemal test**

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False positive syphilis testing after COVID vaccination

Possible False RPR Reactivity with BioPlex 2200 Syphilis Total & RPR Test Kit Following a COVID-19 Vaccine - Letter to Clinical Laboratory Staff and Health Care Providers

Syphilis Treatment

Primary, Secondary or Early Latent*

- 2.4 million units benzathine PCN IM x 1
- PCN Allergy: Doxy 100mg bid x 14 days (or tetracycline 500 mg QID x 14 days)
- Ceftriaxone 1 gm daily IV x 10 days

Don’t use other PCN formulations!
PCN ONLY IN PREGNANCY

Alternatives: Azithromycin not recommended, insufficient data for amoxicillin + probenecid

Syphilis Treatment

Primary, Secondary or Early Latent*

- 2.4 million units benzathine PCN IM x 1
- PCN Allergy: Doxy 100mg bid x 14 days (or tetracycline 500 mg QID x 14 days)

Late Latent or unknown duration

- 2.4 million units benzathine PCN IM weekly for 3 weeks
- PCN Allergy: Doxy 100mg bid x 28 days (or tetracycline 500 mg QID x 28 days)
- Ceftriaxone IM/IV daily x10d? – consult an ID specialist

Efficacy of alternative therapies not well-studied in HIV patients
Jarisch-Herxheimer reaction

- Acute febrile reaction after initiation of antibiotics for the treatment of spirochetal infections.
- Death of bacteria → release of endotoxins and lipoproteins
- Sx: fever, malaise, nausea, vomiting, chills, exacerbation of rash
- Most frequent in secondary stage
- Occurs and resolves within 24 hours
- The intensity of the reaction indicates the severity of inflammation
- Self-limiting, supportive care

Warn/counsel patients about this.

Who to screen and when

<table>
<thead>
<tr>
<th>Risk Criteria</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSM</td>
<td></td>
</tr>
<tr>
<td>• &quot;Lower risk&quot; – Sexually active men outside of mutually monogamous relationships</td>
<td>Annually</td>
</tr>
<tr>
<td>• &quot;Higher risk&quot; (based on RFs in past year)</td>
<td>Every 3 months</td>
</tr>
<tr>
<td>- Bacterial STI</td>
<td></td>
</tr>
<tr>
<td>- Methamphetamine use</td>
<td></td>
</tr>
<tr>
<td>- Condomless anal sex with HIV+/unknown status partner</td>
<td></td>
</tr>
<tr>
<td>- &gt;10 sex partners</td>
<td></td>
</tr>
<tr>
<td>- On PrEP</td>
<td></td>
</tr>
<tr>
<td>Pregnant individuals</td>
<td>Testing should be performed three times; at the first prenatal visit, at 28-36 weeks gestation and at delivery</td>
</tr>
<tr>
<td>Persons with bacterial STIs</td>
<td>Focus on MSM and gonorrhea</td>
</tr>
<tr>
<td>Persons living homeless or unstably housed</td>
<td>Any sex outside of long-term mutually monogamous relationship</td>
</tr>
<tr>
<td>People who use methamphetamine &amp; sex workers</td>
<td>Any sex outside of long-term mutually monogamous relationship</td>
</tr>
</tbody>
</table>

General approach to syphilis management

<table>
<thead>
<tr>
<th>Question or Task</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Does the patient have evidence of complicated syphilis?</td>
<td>Determine need for additional work-up</td>
</tr>
<tr>
<td>2) What is the syphilis stage?</td>
<td>Determines therapy</td>
</tr>
<tr>
<td>3) Test for other STIs (HIV, GC/CT, Trich) &amp; pregnancy. Vaccinate for HPV?</td>
<td>Define need for other therapy or special follow-up</td>
</tr>
<tr>
<td>4) Define HIV treatment or prevention plan</td>
<td>- If HIV positive: Is patient on ART and suppressed? - If HIV negative: Recommend PrEP</td>
</tr>
<tr>
<td>5) Define follow-up plan</td>
<td>Assure &gt;2 titer (4-fold) decline over 12-24 months, or sooner if MSM, pregnant or HIV+</td>
</tr>
<tr>
<td>6) Report to health department</td>
<td>Helps assure partner treatment, decrease transmission, optimizes care</td>
</tr>
</tbody>
</table>

Incidence of New HIV Diagnoses in MSM with Bacterial STI, WA State and New York City

<table>
<thead>
<tr>
<th>Population</th>
<th>Annual Risk HIV Infection, WA State</th>
<th>Annual Risk New York City</th>
</tr>
</thead>
<tbody>
<tr>
<td>All MSM</td>
<td>0.4-0.6%</td>
<td></td>
</tr>
<tr>
<td>Rectal gonorrhea</td>
<td>4.1-4.36</td>
<td>6.7</td>
</tr>
<tr>
<td>Rectal chlamydia</td>
<td>1.59-2.31</td>
<td></td>
</tr>
<tr>
<td>Early syphilis</td>
<td>2.8-3.74</td>
<td>5.6</td>
</tr>
<tr>
<td>Urethral gonorrhea</td>
<td>1.63-1.99</td>
<td></td>
</tr>
<tr>
<td>Pharyngeal gonorrhea</td>
<td>1.08-1.26</td>
<td></td>
</tr>
<tr>
<td>Urethral chlamydia</td>
<td>0.62-0.77</td>
<td></td>
</tr>
</tbody>
</table>

Part 1: Take home points

- Maintain high suspicion for syphilis – any person who is sexually active in high incidence/prevalence areas
- Diagnosis is clinical (P&S) or serologic (latent)
- Low threshold for presumptive treatment
  - Clinical symptoms c/w possible case
  - All contacts to bacterial STI (treat before test results)
- Understand the syphilis screening algorithms
- Phone a friend! UW STD PTC, local PHD, etc.

Resources

University of WA STD Prevention Training Center
  - www.uwptc.org
National Network of STD/HIV Prevention Training Centers
  - www.nnptc.org
2021 CDC STI Treatment Guidelines
  - www.cdc.gov/std/treatment-guidelines
American Social Health Association (ASHA) booklets, books, handouts, the Helper
  - www.ashastd.org
  - (800) 230-6039
NNPTC National STD Curriculum
  - www.std.uw.edu

Thank You!
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