STDs—Revenge of the Syph

Meena Ramchandani, MD, MPH
Assistant Professor of Medicine, University of Washington
Medical Director, PHSKC STD clinic
meenasr@uw.edu

Slides courtesy: Matt Golden, Julie Dombrowski, Sue Szabo, Sheila Lukehart

Updated 5/29/2019
Disclosures

• Meena Ramchandani does not have relationships with a commercial interest related to the content of this educational activity.
Overview

• Epidemiology
• Signs, symptoms
• Staging of disease
• Lab testing
• Treatment
• Complications
• Links to online learning courses
Just a rough estimate, to get a feel for your practice, how many patients have you seen with syphilis in the last 1-2 months?

A) 0
B) <3
C) 3-6
D) >6
How many neurosyphilis cases have you seen or been involved in taking care of?

A) 0
B) <3
C) 3-6
D) >6
Primary and Secondary Syphilis — Rates of Reported Cases by Sex and Male-to-Female Rate Ratios, United States, 1990–2017

- 88% of all P&S syphilis cases in the U.S. in 2017 occurred in men
- 80% of male syphilis cases in MSM (when sex of sex partner known)
- However, 2016-2017, cases increased by 25% in women!
Congenital Syphilis — Reported Cases by Year of Birth and Rates of Reported Cases of Primary and Secondary Syphilis Among Women Aged 15–44 Years, United States, 2008–2017

ACRONYMS: CS = Congenital syphilis; P&S = Primary and secondary syphilis.

- 918 cases of congenital syphilis in the US in 2017 (~600 in 2016)
- 64 still births (41 in 2016)
- Repeat RPR in 3rd trimester - >1 partner, nonmonogamous partners, substance use, homeless
Syphilis infections (all stages) increased 6.4% in 2018

Syphilis, North Dakota 2014-2018

Source: NDDoH Division of Disease Control
• 72% of syphilis infections were male
66% of syphilis infections were between 20-34 years old

Syphilis case counts by gender, North Dakota 2018

Source: NDDoH Division of Disease Control
Black/African Americans had the highest rate of syphilis in 2018

Syphilis rates by race, North Dakota 2014-2018

Source: NDDoH Division of Disease Control
Syphilis was reported in 14 counties

Map is shaded by rate per 100,000 and labeled by case count, 2018
Syphilis Disease: Transmission

- Chronic sexually transmitted infection caused by *Treponema pallidum*
- Infection through small breaks in skin or mucous membranes
- Risk of developing syphilis after sexual contact 10-60% (average about 30%)
- Highest risk with contact to early syphilis; Lesions with many treponemes transmit most effectively.
Rapid Dissemination of Syphilis via the Lymphatics and Blood
Syphilis – A Brief Refresher

- Few hours: mucosal surface -> lymph -> bloodstream
- Chancre ~ 3 weeks (10-90 days) spontaneously heals 1-6 weeks later

**INFECTION WITH T. PALLIDUM**

- Growth of organisms at site of infection, dissemination to various tissues including central nervous system

**PRIMARY SYPHILIS**

- Chancre at site of infection, regional lymphadenopathy

**SECONDARY SYPHILIS**

- Disseminated rash, generalized lymphadenopathy

**LATENT SYPHILIS**

- Recurrence of secondary syphilis symptoms in up to 25% of individuals

**NO FURTHER COMPLICATIONS**

**TERTIARY SYPHILIS**

- Gumma, cardiovascular syphilis, late neurological complications
Primary Syphilis
Atypical Primary Syphilis
Chancre
Typical Primary Syphilis

• Nontreponemal tests (RPR, VDRL) **negative** in 15-25% cases of primary syphilis

• Chancres can occur anywhere inoculated by direct contact (fingers, mouth)

• 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.
Secondary Syphilis
Few hours: lymph -> bloodstream

Chancre ~ 3 weeks (10-90 days) spontaneously heals 1-6 weeks later

15% overlap

3-6 weeks after chancre

**INFECTION WITH T. PALLIDUM**

- Growth of organisms at site of infection, dissemination to various tissues including central nervous system
- Chancre at site of infection, regional lymphadenopathy

**PRIMARY SYPHILIS**

**SECONDARY SYPHILIS**

- Disseminated rash, generalized lymphadenopathy
- Recurrence of secondary syphilis symptoms in up to 25% of individuals

**LATENT SYPHILIS**

- 72%
- 28%

**NO FURTHER COMPLICATIONS**

**TERTIARY SYPHILIS**

- Gumma, cardiovascular syphilis, late neurological complications
Secondary/Systemic Syphilis: Condyloma 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
• Pearl: WET warts generally aren’t warts!
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

- Really rare: lues maligna – necrotic skin lesions
Patient Case

• Your patient is a 37 year old male to female who presents to your clinic for routine testing.

• She has no symptoms, but has a positive RPR titer of 1:8 found on routine screening.

• Her confirmative TPPA is also reactive.

• She tests on occasion, and her last test was negative 2 years ago.
How would you clinically stage her disease?

A) Primary syphilis
B) Secondary syphilis
C) Early latent syphilis
D) Late latent syphilis
Latent Syphilis
Latent Syphilis: New or Old?

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

• Early Latent: Infected less than one year
  • Negative syphilis serology in past year
  • Known contact to an early case of syphilis

• Late Latent (infected > 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

- RPR titer of 1:8, what does that mean?
- Why the TPPA?
Serological Testing for Syphilis

Nontreponemal

RPR, VDRL

(Quantitative, goes down with treatment)

Treponemal

MHATP, FTA-ABS, TPPA, EIA/CIA

(Good for screening but once positive, positive for life)
Syphilis Screening Algorithm

• Traditional: 2 serologic tests
  • Screen with nontreponemal test (RPR or VDRL)
  • Confirm with a treponemal specific test (TPPA, MHATP)

- RPR or VDRL
  - TP-PA
    - + Syphilis (past/present)
    - - Syphilis unlikely
  - - No e/o syphilis
Reverse Sequence Syphilis Screening

- Screen with treponemal specific EIA
- Confirm with RPR
- If conflict: resolve with older treponemal test (TPPA)

Treponemal Test (EIA/CIA or TP-PA) +/- duplicate

Quantitative Non-trep Test (RPR)

2nd Trep test

NO disease or False Negative*

False Pos Trep Test vs. False Neg

DISEASE old vs. new

DISEASE - old vs. late/early

- Do not use EIA in patients with a history of syphilis and in newborns
- False negatives occur in early disease. If high clinical suspicion, repeat tests.
Dilutions of Serum to Obtain RPR Titer
# 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</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>
Case

• 29 yo pregnant woman seen for first pregnancy visit. Her syphilis screening comes back with a reactive RPR (1:2) and a syphilis IgG that is positive.

• She recalls that she was treated for secondary syphilis 2 years ago. You obtain records and see that her initial titer was 1:256.

• After treatment, the RPR had fallen to 1:16 at six months, then to 1:2 at 1 year.

• The titer remained at 1:2 two years later.
What is a compelling reason to treat her again?

A) Her syphilis IgG is positive
B) She is pregnant after an episode of syphilis
C) The RPR is still reactive at 2 years post-treatment
D) She doesn’t need treatment
Answer

What is a compelling reason to treat her again?

A. Her syphilis IgG is positive

B. She is pregnant after an episode of syphilis

C. The RPR is still reactive at 2 years post-treatment

D. She doesn’t need treatment
Serofast state

- **Serofast reaction** = persistent positivity of RPR for years to lifelong at steady state
  - See often in HIV+ patients but also HIV- and pregnancy
  - Does not mean new infection
  - New infection would be diagnosed by an INCREASE in RPR in these patients
  - The syphilis IgG or EIA test will always be positive
Syphilis Treatment
# Syphilis Treatment

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<th>Stage</th>
<th>Treatment</th>
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<tr>
<td>Primary, Secondary or Early Latent*</td>
<td>2.4 million units Benzathine PCN IM x 1</td>
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<td></td>
<td>PCN Allergy- Doxy 100mg bid x 14 days (or tetracycline 500 mg QID x 14 days)</td>
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<tr>
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<td>2.4 million units Benzathine PCN IM q week for 3 weeks</td>
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<td>PCN Allergy- Doxy 100mg bid x 28 days (or tetracycline 500 mg QID x 28 days)</td>
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</table>

Don’t use other PCN formulations!  
Don’t use azithromycin  
PCN ONLY FOR PREGNANT
Jarisch-Herxheimer reaction

- Acute febrile reaction after initiation of antibiotics for the treatment of spirochete infections.
- Death of these bacteria $\rightarrow$ endotoxins and lipoproteins.
- Fever, malaise, nausea, vomiting, chills, exacerbation of rash.
- Especially in secondary.
- Within 24 hours, resolves in 24 hours.
- The intensity of the reaction indicates the severity of inflammation.
- Self-limiting. Supportive care.

Tell patients they might experience this.
Patient Case

• Your patient, a 47 year old married man, presents with a penile lesion of 4 weeks duration, a generalized rash, sore throat, fever, headache and malaise.

• Your exam reveals palmar and plantar lesions in addition to his reported exanthem, as well as oral mucous patches and generalized lymphadenopathy.
Follow Up Visit

• You treated him with 2.4 MU of Benzathine Penicillin LA for secondary syphilis.
  • He had reported no CNS symptoms at his initial visit.

• His quantitative RPR was 1:512 on the day he came in with his primary chancre and rash. His HIV test was negative.

• His follow up blood test at 3 months post treatment is 1:64. Hmmm.... 1:64....
What would you do?

A) Treat again with a single dose of benzathine penicillin 2.4 MU IM

B) Treat with three weekly doses of benzathine penicillin 2.4 MU IM

C) Perform a lumbar puncture

D) Nothing. Repeat testing in 3 months
What did you decide?

• A drop in titer from 1:512 down to 1:64 is an appropriate eight fold* (3 dilution) decline.

• (A titer < four fold (TWO dilutions) is considered evidence of treatment)

1:512 \rightarrow 1:256 \rightarrow 1:128 \rightarrow 1:64 \rightarrow 1:8 \rightarrow 1:1
Follow up

• HIV negative: retesting at 6 & 12 months for primary and secondary (6, 12 and 24 months for latent disease)

• HIV positive: Evaluated clinically and serologically at 3, 6, 9, 12, and 24 months after therapy.

• Public Health Seattle & King County practice is to test at 3 months (or 1 month), reinfection risk is high
  • Assure continued engagement with care
  • Rescreen for all STIs (HIV!!!)
IMPORTANT: Contacts to syphilis (sex partners)

• Primary, secondary, early latent: treat sex partners as early syphilis x 90 days (even if serology negative)

• **The contact should be treated with first dose of 2.4 million units Benzathine PCN IM without waiting for test results, don’t wait for serology. Just treat.
  • Those >90 days → do serology and treat if positive

• Talk to health department re those w late latent syphilis and partners
  • Depends on titer
  • Depends on local epi data
Neurosyphilis can occur at any stage.

INFECTION WITH T. PALLIDUM

Ψ PRIMARY SYPHILIS

Ψ SECONDARY SYPHILIS

Ψ LATENT SYPHILIS

Ψ NO FURTHER COMPLICATIONS

Ψ TERTIARY SYPHILIS

Growth of organisms at site of infection, dissemination to various tissues including central nervous system

Ψ Chancre at site of infection, regional lymphadenopathy

Ψ Disseminated rash, generalized lymphadenopathy

Ψ Recurrence of secondary syphilis symptoms in up to 25% of individuals

Ψ Gumma, cardiovascular syphilis, late neurological complications

Not rare

Extraordinarily rare
Neurosyphilis

• Invasion of central nervous system by *T. pallidum*
• Increased protein, WBC in CSF; or reactive CSF VDRL
• Untreated, can progress to meningovascular syphilis (stroke), late neurologic complications
• Ocular syphilis can lead to permanent blindness
• Otosyphilis can lead to permanent hearing loss
• Imperative to screen everyone diagnosed with syphilis

• Patients should have lumbar puncture and treatment for Neurosyphilis
Neurosyphilis – Screening Questions

• Changes in vision? (blurry vision)
• Changes in hearing?
• Tinnitus?
• Headaches?
• Stiff neck?
• Photophobia?
• Discomfort, redness or burning of eyes?
• Other concerning changes: gait changes, sensory loss, cranial nerve abnormalities.

Negative LP does not rule out ocular or otosyphilis

Opthalmologic & Otologic (ENT) referrals
# Syphilis Treatment

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<th>Treatment</th>
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<td>Late Latent or unknown duration</td>
<td>2.4 million units Benzathine PCN IM q week for 3 weeks&lt;br&gt;PCN Allergy- Doxy 100mg bid x 28 days (or tetracycline 500 mg QID x 28 days)</td>
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<tr>
<td>Neurosyphilis (includes oto or ocular)</td>
<td><strong>Aqueous crystalline PCN G 3-4 MU IV q4 or continuous x 10-14d</strong>&lt;br&gt;Or&lt;br&gt;Procaine PCN 2.4 million units IM + Probenecid 500mg po qid x 10-14 days</td>
</tr>
</tbody>
</table>
CSF in Neurosyphilis

- Pleocytosis
  - >5 for HIV neg WBC/ul
  - Difficult to distinguish from HIV

- Protein concentration
  - >45 mg/dL

- CSF-VDRL
  - Specific, but not sensitive

- CSF FTA-ABS
  - Sensitive, but not specific
Neurosyphilis

- Patient should be treated promptly with Benzathine penicillin G (Bicillin L-A) - will treat secondary disease
- Risk of loss to follow-up (= transmission potential)
- Don’t delay treatment to arrange LP but try to do LP (important for diagnosis and response to therapy in the future)
- **Urgent** evaluation by Ophthalmology or ENT if symptoms
If positive screen and no history of treatment:

- Penicillin effective for preventing transmission to fetus and treating fetal infection
- Treat with penicillin appropriate for stage of infection
  - Primary, secondary, early latent: benzathine penicillin G 2.4 million units x 1
  - Late latent or unknown duration: benzathine penicillin G 2.4 million units weekly x 3 weeks
- Assess for neurologic symptoms at any stage of infection
- Reassess titers at 28-32 weeks and delivery
- If mother’s titer is reactive at deliver, infant titer must be checked
Congenital Syphilis

- Transplacental infection can occur
  - Any time during gestation
  - Any stage of syphilis

- Results in spontaneous abortion, stillbirth, infant with active or latent syphilis
Screening Recommendations: North and South Dakota

• Pregnant women **three times** throughout pregnancy
  • first prenatal exam, third trimester, delivery.

• Men who have sex with men at least annually, more often if at increased risk

• Persons living with HIV

• Persons at increased risk
## Who to Screen: King County

<table>
<thead>
<tr>
<th>Group</th>
<th>Risk Criteria</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MSM</strong></td>
<td>- Lower risk – Sexually active men outside of mutually monogamous relationships</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Higher risk (based on risk in past year)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Bacterial STI</td>
<td>Annually</td>
</tr>
<tr>
<td></td>
<td>- Methamphetamine or popper use</td>
<td>Every 3 months</td>
</tr>
<tr>
<td></td>
<td>- Condomless anal sex with HIV+/Unknown Status partner</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- &gt;10 sex partners</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- On PrEP</td>
<td></td>
</tr>
<tr>
<td><strong>Pregnant women</strong></td>
<td>- All women</td>
<td>- 1&lt;sup&gt;st&lt;/sup&gt; prenatal visit</td>
</tr>
<tr>
<td></td>
<td>- Homeless women, commercial sex, methamphetamine, cocaine or heroin use</td>
<td>- 1&lt;sup&gt;st&lt;/sup&gt; prenatal visit, 28–32 weeks’ gestation &amp; at delivery</td>
</tr>
<tr>
<td><strong>Persons with bacterial STIs</strong></td>
<td>- Focus on MSM and gonorrhea</td>
<td></td>
</tr>
<tr>
<td><strong>Homeless persons</strong></td>
<td>- Any sex outside of long-term mutually monogamous relationship</td>
<td>Annually</td>
</tr>
<tr>
<td><strong>Methamphetamine users &amp; sex workers</strong></td>
<td>- Any sex outside of long-term mutually monogamous relationship</td>
<td>Every 3 months</td>
</tr>
</tbody>
</table>
Syphilis and HIV/Other STDs

• All patients who have syphilis should be tested for HIV infection.

• Consider screening persons with syphilis for other STDs, based on risk.

• MSM with syphilis and HIV negative should be counseled to start PrEP (pre-exposure HIV prophylaxis)
STDs predict future HIV risk among MSM

Rectal GC or CT

1 in 15 MSM were diagnosed with HIV within 1 year.*

Primary or secondary Syphilis

1 in 18 MSM were diagnosed with HIV within 1 year.**

No rectal STD or syphilis infection

1 in 53 MSM were diagnosed with HIV within 1 year.*

*STD Clinic Patients, New York City. Pathela, CID 2013:57;
**Matched STD/HIV Surveillance Data, New York City. Pathela, CID 2015:61

Slide courtesy of Jessica Frasure Williams, NCSD
Syphilis Statistics: North and South Dakota

49% of cases were symptomatic at time of testing

84% of cases were tested for HIV

16% of cases were HIV positive

Risk factors of those interviewed (67)
- 9% report injection drug use
- 49% report sex while high/intoxicated
- 48% report sex with an anonymous partner
## Summary: Approach to Syphilis

<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) &amp; pregnancy – Vaccinate for HPV if age &lt;26</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 antiretrovirals and suppressed?</td>
</tr>
<tr>
<td></td>
<td>- If HIV negative - Recommend PrEP</td>
</tr>
<tr>
<td>5) Define follow-up plan</td>
<td>- Assure &gt;2 titer (4 fold) decline over 6-12 months</td>
</tr>
<tr>
<td>6) Report to health department</td>
<td>- Helps assure partner treatment, decrease transmission, optimizes care</td>
</tr>
</tbody>
</table>
## Syphilis Staging & Treatment

<table>
<thead>
<tr>
<th>Stage (or complicated)</th>
<th>Criteria for staging</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Chancre</td>
<td>2.4 million units Benzathine PCN IM x 1 PCN Allergy - Doxy 100mg bid x 14 days</td>
</tr>
<tr>
<td>Secondary</td>
<td>Rash, mucous patches, condyloma lata</td>
<td></td>
</tr>
<tr>
<td>Early Latent* (Early nonprimary nonsecondary)</td>
<td>No symptoms 1 or 2, &amp; ≥1 of the following:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1) Documented 2 titer ↑ in RPR/VDRL in last year</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2) Clear history of chancre or rash c/w syphilis in past year</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3) Contact to partners with 1, 2 or EL syphilis</td>
<td></td>
</tr>
<tr>
<td>Late Latent or unknown duration</td>
<td>Absence of symptoms 1 or 2 and does not meet criteria for early latent</td>
<td>2.4 million units Benzathine PCN IM q week for 3 weeks PCN Allergy - Doxy 100mg bid x 28 days</td>
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STD Resources

University of WA STD Prevention Training Center
  • www.uwptc.org

National Network of STD/HIV Prevention Training Centers
  • www.nnptc.org

CDC Treatment Guidelines
  • www.cdc.gov/std/treatment

American Social Health Association (ASHA) booklets, books, handouts, the Helper
  • www.ashastd.org
  • (800) 230-6039

NNPTC National STD Curriculum
  • www.std.uw.edu
National STD Curriculum

Funded by a grant from the Centers for Disease Control and Prevention

https://www.std.uw.edu/
Extra Slides
Causes of Biological False Positive Results (BFP)

• Other infections: HIV, malaria, leprosy, other spirochete infections.

• Older age, autoimmune disorders, cardiovascular disease, pregnancy, recent immunizations.

• False-positive results for the FTA-ABS and TPPA are rare, but are more common for the EIA/CIA.

• Therefore: confirmed by a second, different, treponemal test.

References: