OBJECTIVES

• What/When/Why/Who?
• Natural history of disease
• Tests
• Things to remember
• Treatment
• Considerations
• Monitoring
WHAT IS SYPHILIS?

• Syphilis is a systemic, sexually transmitted disease (STD) caused by the *Treponema pallidum* bacterium.

• Two means of syphilis transmission: sexual and vertical
  – Sexual: direct contact with chancreles or with mucous membrane lesions
  – Vertical: From infected mother to her unborn baby via the bloodstream.
WHY THIS TALK?

The STATE of STDs in the United States in 2017

- 1.7 million cases of Chlamydia, 22% increase since 2013
- 555,608 cases of Gonorrhea, 67% increase since 2013
- 30,644 cases of Syphilis, 78% increase since 2013

Anyone who has sex is at risk, but some groups are more affected:
- Young people aged 15-24
- Gay & Bisexual Men
- Pregnant Women

Left untreated, STDs can cause:
- Increased risk of giving or getting HIV
- Long-term pelvic/abdominal pain
- Inability to get pregnant or pregnancy complications

Help interrupt the steady climb in STDs with these three steps:

TALK
Talk openly about STDs with your partners & healthcare providers.

TEST
Get tested. It’s the only way to know if you have an STD.

TREAT
If you have an STD, work with your provider to get the right medicine.
WHY THIS TALK?

• During 2019:
  – There were 129,813 reported new diagnoses of syphilis (all stages), compared to 37,968 new diagnoses of HIV infection in 2018 and 616,392 cases of gonorrhea in 2019.
  – The majority of P&S syphilis cases occurred among gay, bisexual, and MSM.
  – 1,870 cases of congenital syphilis were reported, compared to an estimated 65 cases of perinatal HIV infection during 2018.
    • ~106 cases per 100,000 live births – African Americans
    • ~65 cases per 100,000 live births – Latinos
    • ~22 cases per 100,000 live births – Caucasians
### Who do we screen?

<table>
<thead>
<tr>
<th>Test Pregnant Women:</th>
<th>Test MSM Patients:</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ at first prenatal visit</td>
<td>✓ annually if sexually active</td>
</tr>
<tr>
<td>✓ at beginning of 3rd trimester and at delivery, if at risk</td>
<td>✓ more frequently if at risk</td>
</tr>
</tbody>
</table>
NATURAL HISTORY
INCUBATION PHASE AND PRIMARY SYPHILIS

- Incubation phase
  - 3 - 90 days
  - Asymptomatic

- Primary
  - Chancre
  - Painless
  - *Usually* at site of exposure
  - Can heal without treatment
  - Highly infectious
SECONDARY SYPHILIS

- Diffuse maculopapular rash – trunk, extremities, palms and soles
- Start: 3 weeks - 6 months after primary infection
- Duration: 2 weeks to 3 months
- Systemic symptoms
- 25% have: condyloma lata or tongue mucous patches
- Highly infectious
SECONDARY SYphilIS
LATENT SYPHILIS

- This stage is characterized by the absence of any signs or symptoms of infection, but associated with positive serologic tests.

- Early
  - Reactive non treponemal and treponemal tests within 1 year of infection
  - P & S symptoms can re-occur → infectious

- Late Latent or Latent of Unknown Duration
  - Reactive non treponemal and treponemal tests more than 1 year after infection
  - Latent: potentially infectious
TERTIARY SYPHILIS = LATE SYPHILIS

- Progressive
- Not infectious
- Classic late presentations:
  - Dementia (general paresis)
  - Tabes dorsalis
- Aortitis and gummatous syphilis (nodular lesions more commonly present in the skin and bones).
NEUROSYPHILIS

• ANY stage
• Early
  • Usually after few years of infection, but can occur during P & S.
  • Manifests as meningitis (CN VI – VIII) or meningovascular syphilis (stroke-like).
• Late
  – Usually 10 – 30 years after onset, at the late latent stage.
  – Symptoms: paresis, dementia, muscle weakness, paralysis or tabes dorsalis.
<table>
<thead>
<tr>
<th>Neurosyphilis stage</th>
<th>Clinical presentation</th>
<th>Signs/symptoms</th>
<th>Onset</th>
<th>CSF leukocytes</th>
<th>CSF protein, mg/dL</th>
<th>Serum RPR</th>
<th>CSF VDRL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>Asymptomatic</td>
<td>None</td>
<td></td>
<td>Primary or secondary syphilis</td>
<td>&gt;5</td>
<td>&gt;45</td>
<td>Likely positive&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Meningitis, ocular (+HIV)</td>
<td>Meningeal symptoms, ocular, involvement of ≤1 cranial nerve</td>
<td>Typically within 1 year</td>
<td>200–400</td>
<td>100–200</td>
<td>Positive</td>
<td>Positive; may be negative in HIV+ patients</td>
</tr>
<tr>
<td>Early/late</td>
<td>Meningovascular</td>
<td>Headaches, dizziness, personality changes, stroke-like symptoms&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1–7 years (pre-antibiotic era)</td>
<td>10–100</td>
<td>100–200</td>
<td>Positive</td>
<td>Positive (almost always)</td>
</tr>
<tr>
<td>Late</td>
<td>General paresis</td>
<td>Progressive dementia leading to death in 2.5 years; dysarthria, facial and limb hypotonia, tremors, abnormal reflexes</td>
<td>10–25 years</td>
<td>25–75</td>
<td>50–100</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Tabes dorsalis</td>
<td>Sensory ataxia and lancinating pain; Argyll-Robertson pupil; absent lower extremity reflexes, impaired vibratory and position sense; less common: paresthesias and epigastric pain</td>
<td>20 years</td>
<td>10–50 and occasionally normal</td>
<td>45–75</td>
<td>Typically positive, but not always</td>
<td>Nonreactive up to 25%</td>
</tr>
</tbody>
</table>

Abbreviations: RPR = rapid plasma reagin; VDRL = Venereal Disease Research Laboratory.
<sup>a</sup>Unless recent infection.
<sup>b</sup>Middle cerebral artery most commonly affected.
<sup>c</sup>Pupils respond to accommodation but not to light.
OCULAR SYPHILIS

• ANY stage
• Symptoms: blurry vision, vision loss, pain, redness.
• May present as uveitis, retinitis, and optic neuritis.
• Do not delay treatment while waiting for results due to risk of blindness.
CONGENITAL SYPHILIS

- All pregnant women during 1st trimester
- All HIGH RISK pregnant women during:
  - 1st trimester
  - 28 weeks
  - At delivery
- When diagnosed, need immediate treatment
  - Treatment ≥30 days prior to delivery is likely to prevent cases of congenital syphilis (may not prevent stillbirth or CS in a gravely infected fetus).
- All women who deliver a stillborn (after 20 weeks) should be tested at time of delivery.
DIRECT DETECTION METHODS

• Dark-field microscopy, PCR, and direct fluorescent antibody testing for *T pallidum*.
• In some cases, these tests may allow the diagnosis of syphilis prior to a serologic response.
• Most clinical centers do not have access to these methods and must rely on clinical manifestations and serologic testing.
SEROLOGIC TESTS

• 2 different types based on the type of antigen the antibodies are directed against:
  – Treponemal tests detect antibody to *T. pallidum* proteins.
  – Nontreponemal tests detect antibodies directed against lipoidal antigens, damaged host cells, and possibly from treponemes.

• Both tests are used to confirm the infection and determine whether the disease is active.
TREPONEMAL TESTS

• These are:
  – Microhemagglutination assay for *T pallidum*
  – *T pallidum* particle agglutination
  – *T pallidum* hemagglutination assay
  – Fluorescent treponemal antibody absorbed (FTA-ABS) test
  – Chemoluminescence immunoassays
  – Enzyme immunoassays that detect Treponemal antibodies.

• Reported as reactive or nonreactive.

• Reactivity to a treponemal test implies infection, but it does not determine whether the infection is recent or remote or whether it has been treated or not.

• False-positive results with this type of test can occur and may be due to other infections or other inflammatory diseases, such as systemic lupus erythematosus.
NONTREPONEMAL TESTS

• Three types:
  – Rapid plasma reagin (RPR)
  – Venereal Disease Research Laboratory (VDRL) test
  – Toluidine red unheated serum test
• These tests usually react with immunoglobulin M and immunoglobulin G antibodies.
• The results of these tests are semi quantitative.
• Seroconversion occurs around 3 weeks, but can take up to 6 weeks.
  – Consequently, patients can present with primary syphilis and have initially negative serologic tests.
• Titers will normally decline over time, often to undetectable titers after successful treatment.
• False-positive nontreponemal tests have been described in systemic infections such as tuberculosis, rickettsial diseases, and endocarditis, and also during pregnancy.
PARADIGM SHIFT

• Traditionally: a positive nontreponemal was followed by a confirmatory treponemal test.

• However, automated and rapid treponemal testing has allowed the algorithm to be reversed.

• Now: accepted to order a treponemal test as the initial diagnostic tool.
  – Cost effective.
  – Not usually available.
**INTERPRETATION OF REACTIVE TESTS**

<table>
<thead>
<tr>
<th>Treponemal test</th>
<th>Nontreponemal test</th>
<th>Possible interpretations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonreactive</td>
<td>Nonreactive(^a)</td>
<td>1. Absence of syphilis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Very early syphilis before seroconversion</td>
</tr>
<tr>
<td>Reactive(^b)</td>
<td>Nonreactive</td>
<td>1. Prior treated syphilis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Untreated syphilis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. False-positive treponemal test(^c)</td>
</tr>
<tr>
<td>Reactive</td>
<td>Reactive with or without a measurable titer</td>
<td>1. Active syphilis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Recently treated syphilis with nontreponemal titers that have not yet become nonreactive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Treated syphilis with persistent titers(^d)</td>
</tr>
<tr>
<td>Nonreactive</td>
<td>Reactive(^a)</td>
<td>1. False-positive nontreponemal test</td>
</tr>
</tbody>
</table>

\(^a\) Usually not performed if the initial treponemal test is negative.

\(^b\) By 2 different methods if the nontreponemal test is nonreactive.

\(^c\) Commonly seen among African immigrants with previous exposure to endemic treponematoses.

\(^d\) Successful treatment is usually considered with a fourfold decline in titers (e.g., from 1:32 to 1:8).
CDC ALGORITHM FOR POSITIVE TREPONEMAL TEST AND NEGATIVE NON-TREPONEMAL TEST

Treponemal test positive; RPR or VDRL nonreactive

- Different treponemal test positive
  - If prior history of syphilis and no evidence of recent exposure, don't treat
  - If no prior history of syphilis and no evidence of recent exposure, treat for late latent syphilis

- Different treponemal test negative
  - No further evaluation or treatment is necessary
CSF EXAMINATION

• When:
  – Sustained (>2 weeks) fourfold increase or greater in titer is observed.
  – Initially high titer (≥1:32) fails to decline at least fourfold within 12–24 months of therapy.
  – Signs or symptoms attributable to (neuro) syphilis develop.
THINGS TO REMEMBER...

- Titers are used to monitor treatment success.
- May have false negative RPR.
- All patients with positive syphilis serologic tests & a presumptive diagnosis of syphilis need staging to determine the treatment regimen.
TREATMENT

• Primary, Secondary, or Early Latent (<1 year)
  – Benzathine penicillin G 2.4 million units IM in a single dose

• Late Latent (>1 year), Latent Syphilis of Unknown Duration, or Tertiary Syphilis with Normal CSF Examination
  – Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals

• Neurosyphilis, Ocular Syphilis
  – Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV every 4 hours or continuous infusion, for 10–14 days
  – Additional doses of benzathine penicillin are not indicated in patients with HIV infection.
  – Additional doses of penicillin in pregnant women with early syphilis may be indicted if evidence of fetal syphilis on ultrasound.
# TREATMENT ALTERNATIVES

<table>
<thead>
<tr>
<th>Disease stage</th>
<th>Primary treatment</th>
<th>Alternative treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary syphilis</td>
<td>Benz PCN 2.4 million units IM × 1 dose</td>
<td>Doxycycline 100 mg PO BID × 14 days</td>
</tr>
<tr>
<td>Secondary syphilis</td>
<td>Benz PCN 2.4 million units IM × 1 dose</td>
<td>Doxycycline 100 mg PO BID × 14 days</td>
</tr>
<tr>
<td>Early latent syphilis</td>
<td>Benz PCN 2.4 million units IM × 1 dose</td>
<td>Doxycycline 100 mg PO BID × 14 days</td>
</tr>
<tr>
<td>Late latent syphilis</td>
<td>Benz PCN 2.4 million units IM weekly × 3 doses</td>
<td>Doxycycline 100 mg PO BID × 28 days</td>
</tr>
<tr>
<td>Cardiovascular and gummatous syphilis</td>
<td>Benz PCN 2.4 million units IM weekly × 3 doses</td>
<td>Consult with infectious diseases physician recommended</td>
</tr>
<tr>
<td>Neurosyphilis</td>
<td>PCN G 18-24 million units IV daily × 10-14 days</td>
<td>Procaine PCN 2.4 million units IM daily + probenecid 500 mg PO QID for 10-14 days</td>
</tr>
</tbody>
</table>
CONSIDERATIONS

• Jarisch-Herxheimer Reaction
  – Acute febrile reaction with or without headache, myalgia, fever, and other symptoms within the first 24 hours after the initiation of any therapy for syphilis.
  – Most frequent among persons who have early syphilis, presumably because bacterial burdens are higher during these stages.

• Management of Sex Partners
  – Transmission: muco cutaneous syphilitic lesions
  – High risk partners are those who have had sex within:
    • 3 months plus the duration of symptoms for persons who receive a diagnosis of primary syphilis
    • 6 months plus duration of symptoms for those with secondary syphilis
    • 1 year for persons with early latent syphilis.
  – Who do we treat?
    • Within 90 days and negative serologic testing: treat
    • >90 days and:
      – Negative serologic tests: no treatment
      – Positive serologic tests: treat base on staging.
CONSIDERATIONS

• Treatment failure criteria:
  – Persistent signs or symptoms or recurrence.
  – At least a fourfold increase in nontreponemal test titer persisting for >2 weeks.
  – Re-treat, re-test for HIV infection.
  – DDx: re-infection.
CLINICAL AND SEROLOGICAL MONITORING

• P & S
  – At 6 and 12 months after treatment.
  – Retreatment: benzathine penicillin G 2.4 million units IM q week x 3.

• Latent Syphilis
  – At 6, 12, and 24 months after treatment.

• Neurosyphilis
  – If CSF pleocytosis was present initially, a CSF examination should be repeated every 6 months until the cell count is normal.
MONITORING HIV POSITIVE PATIENTS

• Primary and Secondary Syphilis among Persons with HIV Infection
  – Clinical and serological evaluations at: 3, 6, 9, 12, and 24 months after therapy.
  – Treatment failure: management same as HIV-negative.

• Latent Syphilis among Persons with HIV Infection
  – Clinical and serological evaluations at: 6, 12, 18, and 24 months after therapy.
  – Treatment failure: need CSF examination.

• Neurosyphilis among Persons with HIV Infection
  – Same as HIV-negative persons with neurosyphilis.
RESOURCES


