Syphilis Management
for Clinicians

Satellite Conference and Live Webcast
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Faculty

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Program Objectives

• Upon completion of this content, the learner will be able to:
  – List the stages of syphilis
  – Describe the signs and symptoms of syphilis
  – Discuss the impression criteria for determining treatment and follow-up

Syphilis Definition

• Sexually acquired infection
• Etiologic agent:

  Treponema pallidum

• Disease progresses in stages
• May become chronic without treatment
Syphilis Transmission

- Sexual and vertical
- Most contagious to sex partners during the primary and secondary stages

Microbiology

- Etiologic agent: *Treponema pallidum*, subspecies *pallidum*
  - Corkscrew-shaped, motile microaerophilic bacterium
  - Cannot be cultured in vitro
  - Cannot be viewed by normal light microscopy

Stages of Syphilis

- Primary Syphilis: 2 to 4 weeks after exposure, chancre present, highly infectious
- Secondary Syphilis: 2 to 8 weeks after chancre disappears, highly infectious

Stages of Syphilis

- Latent Syphilis – No signs and symptoms
  - Early Latent Syphilis <1 year duration
  - Late Latent Syphilis >1 year duration
  - Late Latent Syphilis of unknown duration

Stages of Syphilis

- Neurosyphilis
  - Early neurosyphilis <1 year duration
  - Late neurosyphilis >1 year duration
- Tertiary Syphilis >1 - 10 years
  - Neurosyphilis, cardiovascular and gummatous disease

Stages of Syphilis

- Serofast state
  - After adequate therapy, VDRL / RPR decline, but always reactive
Aspects of Syphilis Diagnosis

- Clinical history
- Physical examination
- Laboratory diagnosis

Clinical History

- Assess
  - 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

- Oral cavity
- Lymph nodes
- Skin of torso
- Palms and soles
- Genitalia and perianal area
- Neurologic examination
- Abdomen

Laboratory Diagnosis

- The use of only one type of serologic test is insufficient for diagnosis
  - Darkfield (secretion from lesion)
  - Serologic Tests
    - Two types
      - Nontreponemal (qualitative and quantitative) VDRL, RPR, TRUST, USR

Nontreponemal Serologic Tests

- Principles
  - Measure antibody directed against a cardiolipin - lecithin - cholesterol antigen
  - Not specific for *T. pallidum*

Nontreponemal Serologic Tests

- Titers usually correlate with disease activity and results are reported quantitatively
- May be reactive for life, referred to as “serofast”
Nontreponemal Serologic Tests

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

- Disadvantages
  - May be insensitive in certain stages
  - False-positive reactions may occur
  - Prozone effect may cause a false-negative reaction (rare)

Causes of False-Positive Reactions in Serologic Tests for Syphilis

<table>
<thead>
<tr>
<th>Disease</th>
<th>RPR/VDRL</th>
<th>FTA-ABS</th>
<th>TP-PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmune Diseases</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Dermatologic Diseases</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Drug Abuse</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Febrile Illness</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Glucosamine/chondroitin sulfate</td>
<td>Possibly</td>
<td></td>
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<tr>
<td>Leprosy</td>
<td>Yes</td>
<td>No</td>
<td></td>
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<tr>
<td>Lyme disease</td>
<td>Yes</td>
<td></td>
<td></td>
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<tr>
<td>Malaria</td>
<td>Yes</td>
<td>No</td>
<td></td>
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<tr>
<td>Pinta, Yaws</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Recent Immunizations</td>
<td>Yes</td>
<td>--</td>
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</tr>
<tr>
<td>STD other than Syphilis</td>
<td>Yes</td>
<td></td>
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</tr>
</tbody>
</table>

Source: Syphilis Reference Guide, CDC/National Center for Infectious Diseases, 2002

Treponemal Serologic Tests

- Principles
  - Measure antibody directed against *T. pallidum* antigens
  - Qualitative
  - Usually reactive for life
  - Titers should not be used to assess treatment response

Syphilis Screening at ADPH

- EIA
- VDRL
- TP-PA
Managing Discordant Syphilis Test Results

- Asymptomatic contact to early syphilis with non-reactive EIA
  - No further testing or clinical follow-up is required

- Symptomatic patient/contact with non-reactive EIA or VDRL
  - Offer treatment as early syphilis
  - Repeat test within 2-4 weeks after treatment or upon return to the clinic

- No history of previous adequate treatment with EIA or TP-PA reactive and VDRL non-reactive
  - Offer treatment
  - Repeat the test within 2-4 weeks or upon return to the clinic

Managing Discordant Syphilis Test Results

- Repeat VDRL non-reactive
  - No further testing or clinical follow-up required

Clinical vs. Surveillance DIS Staging

- Clinical
  - Purpose: Identify possible infection early and treat promptly to prevent spread
  - Key Points:
    - Clinical manifestations
      - EIA: ±
Clinical vs. Surveillance DIS Staging

- VDRL: ±
- TP - PA: ±

• No clinical Manifestations
- EIA: ±
- VDRL: ±
- TP - PA: ±

Clinical vs. Surveillance DIS Staging

- Surveillance DIS
  - Purpose: Report to CDC and contact tracing
  - Key Points:
    - EIA: ±
    - VDRL: Tittered
    - TP - PA: ±

Impression Criteria: Primary Syphilis

- Consistent Clinical Exam Findings:
  - Genital or non-genital single or multiple, painless, rubbery ulcer(s)
  - or lesion(s) that is highly suspicious for syphilis chancre

OR

Primary Syphilis

Penile Chancre

Source: CDC/NCHSTP/Division of STD Prevention, STD Clinical Slides

Primary Syphilis

Labial Chancre

Source: CDC/NCHSTP/Division of STD Prevention, STD Clinical Slides
Primary Syphilis
Perianal Chancre

Primary Syphilis
Chancre of the Tongue

Impression Criteria:
Secondary Syphilis
• Any of the Following Clinical Exam Findings:
  – Generalized or localized cutaneous eruption without explanation, generalized lymphadenopathy
  – Palmar and / or plantar rash

Secondary Syphilis
Papulosquamous Rash

Secondary Syphilis
Palmar / Plantar Rash
Clinical Manifestations

Secondary Syphilis
Generalized Body Rash

Source: Cincinnati STD/HIV Prevention Training Center

Secondary Syphilis
Papulo-pustular Rash

Source: CDC/NCHSTP/Division of STD Prevention, STD Clinical Slides

Secondary Syphilis
Condylomata lata

Source: CDC/NCHSTP/Division of STD Prevention, STD Clinical Slides

Secondary Syphilis
Nickel/Dime Lesions

Source: CDC/NCHSTP/Division of STD Prevention, STD Clinical Slides

Secondary Syphilis
Alopecia

Source: CDC/NCHSTP/Division of STD Prevention, STD Clinical Slides

Impression Criteria: Latent Syphilis

- May occur between primary and secondary stages, between secondary relapses, and after secondary stage
- No symptoms or findings consistent with primary or secondary syphilis
Impression Criteria: Latent Syphilis
- Categories:
  - Early latent: <1 year duration
  - Late latent: ≥1 year duration

Impression Criteria: Early Latent Syphilis
- Laboratory Findings:
  - Reactive Syphilis - EIA and / or TP-PA, with / without reactive VDRL or RPR
  PLUS
- No symptoms or findings consistent with primary or secondary syphilis
  PLUS

Impression Criteria: Early Latent Syphilis
- Any of the following within the past 12 months
  - History of symptoms consistent with primary or secondary syphilis
  - OR Documented Serologic conversion

Impression Criteria: Late Latent Syphilis
- Laboratory Findings:
  - Reactive Syphilis - EIA and / or TP-PA with/without reactive VDRL or RPR
  PLUS
- No symptoms or findings consistent with primary or secondary syphilis
  PLUS

Impression Criteria: Late Latent Syphilis
- Any of the following greater than 12 months in the past
  - History of symptoms consistent primary or secondary syphilis
  - OR Documented serologic conversion
Impression Criteria: Late Latent Syphilis
- OR A >4 - fold rise in RPR / VDRL titer in a person who has previously received adequate treatment for a syphilis infection
- OR History of exposure to primary, secondary, or early latent syphilis
- OR No possible exposure within the past 12 months

Latent Syphilis of Unknown Duration
- No history of exposure to primary, secondary, or early latent syphilis or treatment in the past
  AND
  - Insufficient information to determine the duration of infection or the most likely time of exposure

Latent Syphilis of Unknown Duration
- Reactive Syphilis - EIA or TP - PA with / without reactive VDRL or RPR
  PLUS
  - No signs or symptoms consistent with primary or secondary syphilis
  AND

Neurosyphilis
- Occurs when *T. pallidum* invades the central nervous system (CNS)
- May occur at any stage of syphilis
- Can be asymptomatic

Neurosyphilis
- Early neurosyphilis
  - Clinical manifestations can include acute syphilitic meningitis, meningovascular syphilis, and ocular involvement

Neurosyphilis
- Late neurosyphilis
  - Clinical manifestations can include general paresis, tabes dorsalis, and ocular involvement
Indications for CSF Examination

- Patients with syphilis who demonstrate any of the following criteria should have a prompt CSF evaluation:
  - Neurologic or ophthalmic signs or symptoms
  - Evidence of active tertiary syphilis (e.g., gummatous lesions)

- Treatment failure
- HIV infection with a CD4 count ≤350 and / or a nontreponemal serologic test titer of ≥1:32

Neurosyphilis Spirochetes in Neural Tissue

- Approximately 30% of untreated patients progress to the tertiary stage within 1 to 20 years
- Rare because of the widespread availability and use of antibiotics

Tertiary (Late) Syphilis

- Manifestations
  - Gummatous lesions
  - Cardiovascular syphilis
  - Neurosyphilis

Late Syphilis - Serpiginous Gummata of Forearm

Source: CDC/NCHSTP Division of STD Prevention, STD Clinical Slides
Late Syphilis Ulcerating Gumma

Source: CDC/NCHSTP Division of STD Prevention, STD Clinical Slides

Late Syphilis Cardiovascular

Source: CDC/NCHSTP Division of STD Prevention, STD Clinical Slides

Syphilis Treatment

<table>
<thead>
<tr>
<th>Syphilis / Pregnant</th>
<th>Recommended Regimens / Dose / Route</th>
<th>Alternative Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary, Secondary, Early Latent and Sex Partners</td>
<td>Benzathine penicillin G 2.4 million units IM in a single dose.</td>
<td></td>
</tr>
<tr>
<td>Not pregnant with True Penicillin Allergy</td>
<td>Doxycycline 100 mg PO BID x 14 days OR Tetracycline 500 mg PO QID x 14 days</td>
<td></td>
</tr>
<tr>
<td>Late latent/latent of unknown duration</td>
<td>Benzathine penicillin G 2.4 million units IM x 3 weeks</td>
<td></td>
</tr>
<tr>
<td>Not pregnant with True Penicillin Allergy</td>
<td>Doxycycline 100 mg PO BID x 28 days OR Tetracycline 500 mg PO QID x 28 days</td>
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Syphilis Treatment

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</tr>
<tr>
<td>True Penicillin Allergy</td>
<td>MUST BE REFERRED TO A HOSPITAL FOR DESENSITIZATION</td>
<td></td>
</tr>
</tbody>
</table>

Referral for Management

- All pregnant patients with “true penicillin” allergy for desensitization
- Patients with suspected neurosyphilis, tertiary syphilis or congenital syphilis for treatment

When to Offer Presumptive Treatment

- Symptomatic Patients
- Asymptomatic Patients
- Contacts
<table>
<thead>
<tr>
<th>Treat Symptomatic Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>• With signs and symptoms consistent with primary or secondary regardless of the syphilis serologic test results should be treated</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treat Asymptomatic Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Who have reactive syphilis (EIA and/or TP - PA) with/without reactive (VDRL/RPR) plus any of the following should be treated based upon the stage of the disease:</td>
</tr>
<tr>
<td>• History of symptoms consistent with primary or secondary syphilis OR</td>
</tr>
<tr>
<td>• History of recent exposure to primary or secondary syphilis or reinfection OR</td>
</tr>
<tr>
<td>• Inadequate serologic response to past treatment OR</td>
</tr>
<tr>
<td>• No history of past adequate treatment OR</td>
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<th>Treat Asymptomatic Patients</th>
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<tbody>
<tr>
<td>• No test results available to compare with previous test results OR</td>
</tr>
<tr>
<td>• ≥4-fold increase in VDRL/RPR titer in a patient with history of past adequate treatment</td>
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</table>

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<th>Treat Contacts</th>
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<tr>
<td>• To Primary, Secondary, or Early Latent Syphilis should be treated regardless of the syphilis serologic test results</td>
</tr>
<tr>
<td>• With verbal history or DIS referral of a patient who is a contact to Primary, Secondary, or Early Latent Syphilis regardless of the syphilis serologic test results</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treat Contacts</th>
</tr>
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<tbody>
<tr>
<td>• To Late Latent Syphilis or Latent Syphilis of Unknown Duration if the treponemal test result (EIA and/or TP - PA) is reactive, with/without reactive non-treponemal (VDRL/RPR) test results</td>
</tr>
<tr>
<td><strong>Syphilis Patient Follow-up</strong></td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>• Evaluate signs and symptoms</td>
</tr>
<tr>
<td>• Weekly penicillin therapy</td>
</tr>
<tr>
<td>• Confirm syphilis infection</td>
</tr>
<tr>
<td>• Response to treatment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Follow-up for Treated Primary and Secondary Syphilis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clinical evaluation: 2 Weeks</td>
</tr>
<tr>
<td>– Clinical manifestation with doxycycline or tetracycline treatment</td>
</tr>
<tr>
<td>• Serological Testing:</td>
</tr>
<tr>
<td>– At 6 and 12 months after treatment with penicillin therapy</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th><strong>Follow-up for Treated Primary and Secondary Syphilis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>– At 1, 3, 6, 9, 12 and 24 months after treatment with doxycycline or tetracycline treatment and HIV infected patients</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Follow-up Treatment for Latent (Early or Late) Syphilis or Syphilis of Unknown Duration</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Treatment:</td>
</tr>
<tr>
<td>– Every week for three weeks for penicillin therapy</td>
</tr>
<tr>
<td>• Serological Testing:</td>
</tr>
<tr>
<td>– At 6, 12, and 24 months after treatment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Response to Syphilis Treatment</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Adequate response</td>
</tr>
<tr>
<td>– Primary and secondary syphilis</td>
</tr>
<tr>
<td>• Decline in VDRL / RPR titer 2 dilutions (4 fold) within 6 months after therapy</td>
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</table>

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<thead>
<tr>
<th><strong>Response to Syphilis Treatment</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>– Latent (early or late) syphilis</td>
</tr>
<tr>
<td>• Decline in VDRL / RPR titer 2 dilutions (4 fold) within 6 months after therapy</td>
</tr>
<tr>
<td>• Inadequate response</td>
</tr>
<tr>
<td>• Rise in VDRL / RPR titer 2 dilutions (4 fold) or greater rise since initiation of therapy</td>
</tr>
</tbody>
</table>
Intervention for Inadequate Response

- Consider reinfection if risk of re-exposure exists
  - Repeat therapy
- Consider treatment failure if oral therapy was used or patient is HIV Positive

Intervention for Inadequate Response

- Refer patient for CSF exam, if needed
- Re-treat all stages as late latent syphilis, if risk for re-exposure is low and the presence of neurosyphilis has been ruled out

Conclusion

- Syphilis Management:
  - Diagnosis
    - Clinical Manifestations
    - Lab test results
  - Staging
  - Treatment
  - Follow-up
  - Clinical and surveillance staff TEAM

What Is On Your Mind?

Reference