“The Great Pretender” — Have You Missed a Syphilis Diagnosis?

Tuesday, April 2, 2013
Supported By

Centers for Disease Control and Prevention
STD-Related Reproductive Health Training and Technical Assistance Centers, Regions VI, IX, and X

Co-Provided By

This event is presented by Cardea Services in collaboration with the Seattle STD/HIV Prevention Training Center and CAI.
Learning Objectives

By the end of this webinar participants will be able to:

• Describe the changing epidemiologic trends of syphilis infections
• Describe diagnosis of each stage of syphilis
• Discuss the clinical management of syphilis
Faculty

• **Sheila A. Lukehart, PhD**
  Professor of Medicine and Global Health and Director of STD & HIV Research Training Program, University of Washington

• **Edward W. Hook III, MD**
  Professor of Medicine, Epidemiology and Microbiology, University of Alabama at Birmingham; Director, Division of Infectious Diseases, Director, STD Control Program, Jefferson County (Alabama) Department of Public Health; Program Medical Director, AL-NC STD/HIV Prevention Training Center

• **Melanie Taylor, MD, MPH**
  Captain, US Public Health Service, Centers for Disease Control and Prevention; CDC Assignee, Arizona Department of Health Services & Maricopa County Department of Public Health; CDC Assignee, Indian Health Service
Essentials of Syphilis

Sheila Lukehart, PhD
Depts. of Medicine & Global Health
University of Washington
Outline of talk

- Overview of syphilis
- Epidemiology
- Clinical manifestations
- Diagnostic tests
- Treatment
Syphilis

- Chronic sexually transmitted infection caused by Treponema pallidum
- Characterized by episodes of active clinical disease interrupted by periods of subclinical (latent) infection
- Early manifestations involve primarily skin, mucosal surfaces; late manifestations may affect any organ system
Natural History of Untreated Syphilis

- **INFECTION**
  - Chancre, regional lymphadenopathy
  - 2 - 6 WK

- **PRIMARY**
  - Rash, generalized lymphadenopathy
  - 1 - 3 MO

- **SECONDARY**
  - 1 - 3 MO

- **LATENT**
  - 70% 30%
  - 2 - 50 YR

- **LIFETIME LATENCY**

- **TERTIARY**
  - Gumma
  - Cardiovascular syphilis
  - Paresis, Tabes dorsalis

- **CNS Invasion**
  - Asymptomatic neurosyphilis
  - Meningeal syphilis, Cranial Nerves
  - Meningovascular syphilis

- **LATENT**
  - 70%
  - 30%
  - 2 - 50 YR

- **LIFETIME LATENCY**

- **TERTIARY**
  - Gumma
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Syphilis 1940-Present, USA

![Graph showing the number of syphilis cases from 1940 to 2010. The graph compares total syphilis cases and primary and secondary syphilis cases.](image-url)
Epidemiology of Syphilis: U.S.

- 2011 cases
  - Primary, Secondary: 13,970*
  - All stages: 46,042
  - Congenital: 360

*More than doubled since 2000
Infectious Syphilis – by Gender

Reported cases

- **Women**
- **Men**
P&S in Women and Congenital Syphilis
# Epidemiology of P&S Syphilis

## Race and Ethnicity

<table>
<thead>
<tr>
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<th>White non Hispanic</th>
<th>White Hispanic</th>
<th>African American</th>
<th>AI/AN</th>
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<td>15.5</td>
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<td>Male</td>
<td>4.4</td>
<td>8.5</td>
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<tr>
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<td>0.3</td>
<td>0.6</td>
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2011 rate per 100,000
## Epidemiology of P&S Syphilis
### Race and Ethnicity

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2011 rate per 100,000

- White non Hispanic
- White Hispanic
- African American
- AI/AN
Etiology

- *Treponema pallidum* subsp. *pallidum*
  - Venereal syphilis
  - Corkscrew-shaped, microaerophilic, noncultivable
  - Fragile outside of host
Syphilis

- **Mode of Transmission**
  - Direct contact with infectious lesion
  - Primary and secondary stages are infectious

- **Incubation Period**
  - 9-90 days, average is 2-6 weeks
Primary Syphilis

- Painless, indurated chancre: genital, anal, or oral
- Firm regional lymph nodes
- Lasts 1-5 weeks; heals spontaneously
Primary Chancre
Chancres
Healing chancre
Chancre
Chancre
Chancre
Secondary Syphilis

- 15% have persisting/healing chancres
- Generalized rash: Macular, papular, pustular, or combination
- Generalized lymphadenopathy (88%)
- Mucous patches (10%)
- Condylomata lata (10%)
Secondary Syphilis

- Headache, fever, malaise
- Alopecia, liver or kidney involvement
- Lasts 2-6 weeks; resolves spontaneously
- Historically, 25% have recurrent secondary symptoms, within one year
Macular syphilis
Papular Syphilis
Secondary Syphilis—Soles
Secondary Syphilis
Secondary Syphilis—Mucous patches
Secondary Syphilis—Condylomata lata
Latent Syphilis

- No clinical manifestations
- Positive serologic tests for syphilis
- < 1 year – early latent
- > 1 year – late latent
- 2/3 of patients with untreated syphilis remain in latent stage for life
Neurosyphilis

- CNS invasion occurs early in infection
  - Up to 40% of persons with early syphilis
- Invasion is independent of concurrent HIV infection
Early Neurosyphilis

- Very common if one looks for it
  - Asymptomatic (abnormal CSF findings)
  - Meningeal
  - Meningovascular

- Clinical manifestations may be more severe with HIV coinfection
Natural History of Untreated Syphilis

INFECTION

PRIMARY 50-95%

SECONDARY 67-95%

EARLY LATENT 83-95%

LATE LATENT 10-40%

CONGENITAL SYPHILIS
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
- Adequate treatment of pregnant women during 1\textsuperscript{st} or 2\textsuperscript{nd} trimester is effective for fetus
Congenital Syphilis: Outcome

- Stillbirth or miscarriage 17-40%
- Perinatal death 10-23%
- Live infected infant 2-33%
- Prematurity or low birthweight 20-33%
- Any adverse outcome 49-80%
Syphilis: Diagnosis

- Clinical manifestations
- Identification of *Treponema pallidum*
- Serological testing
Clinical Diagnosis

Genital ulcers can be confusing to diagnose
Herpes
Chancroid
What is this?
Direct Detection of *T. pallidum*

- Darkfield microscopy
- IF staining
- PCR

- None of these is widely available
Syphilis Serology

- **Nontreponemal tests—Lipid antigens**
  - Used for screening, quantitation
  - RPR – Rapid Plasma Reagin
  - VDRL – VD Research Laboratory

- **Treponemal tests—Protein antigens**
  - Recommended to confirm reactive RPR or VDRL
  - May remain positive after rx
  - Serodia TP-PA: Particle agglutination
  - FTA-ABS: Fluorescent Treponemal Antibody-Adsorbed
  - EIA/CIA
# Sensitivity of Serological Tests in Untreated Syphilis

## Stage of Disease

<table>
<thead>
<tr>
<th>% Positive</th>
<th>Primary</th>
<th>Secondary</th>
<th>Latent</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPR, VDRL</td>
<td>80</td>
<td>100</td>
<td>95</td>
</tr>
<tr>
<td>TP-PA, EIA</td>
<td>89</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>FTA-ABS</td>
<td>84</td>
<td>100</td>
<td>100</td>
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</table>
Use of EIA/CIA Tests for Screening

- Increasingly common in large labs
- High false positivity rate in low-risk populations
- How to interpret reactive EIA/CIA screening tests?
Syphilis Treatment

- Benzathine penicillin G: 2.4 mu IM weekly
  - x1 for early
  - x3 for late latent

- Pen allergic:
  - Doxycycline, 100 mg PO bid for 14 (or 28) days
  - or
  - Tetracycline, 500 mg PO qid for 14 (or 28) days
Syphilis Therapy: Pregnancy

- Treat according to stage of disease
- Follow-up should include monthly quantitative nontreponemal serologic tests
- Pen allergic: Erythromycin is no longer recommended; desensitize and treat with penicillin
Syphilis Therapy: Contacts

- Contacts to early syphilis in the preceding 3 months should be treated as for early syphilis
Syphilis Therapy—Azithromycin?

- Oral azalide antibiotic
- Single dose (2 g early syphilis)
- Clinical failures seen
- Associated with mutations in 23S rDNA
- Strains with resistance mutations are widespread
- Prevalence of strains with mutations is regional
Criteria for Efficacy of Treatment

- Resolution of clinical manifestations
- Decline in VDRL or RPR titer
  - Primary, secondary: four-fold decline by 3-6 months
  - Early latent: four-fold decline by 6 months
  - Late latent: No increase in titer or if initially ≥ 32, four-fold decrease by 6-12 months
Reasons for Serological Testing For Syphilis

Screening

Diagnostic Testing

Monitoring Outcomes of Therapy
NATURAL HISTORY OF SYPHILIS

Exposure ... 1° → 2° → Latent → 3°

20-50%

33% 25% 33%
RPR Titers At Time Of Early Syphilis Diagnosis By Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Median RPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>1:32</td>
</tr>
<tr>
<td>Secondary</td>
<td>1:128</td>
</tr>
<tr>
<td>Early Latent</td>
<td>1:32</td>
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</table>
Case 1

A 43 YO HIV infected male returns to clinic for scheduled follow-up. On examination he has patchy hair loss which has occurred over the past 6 weeks. His CD4 count is 420/mm³, his viral load is <20, and his RPR which was negative 6 months ago is now reactive at 1:32

What is the appropriate diagnosis and management for this patient at this time?
HIV/STD Potential Interactions

1. STDs as markers for HIV risk
2. STDs as risk factors for HIV/acquisition transmission
3. Alterations of clinical +/or laboratory manifestations of STDs due to coexistent HIV infection
4. Decreases susceptibility to STD therapy due to coexistent HIV infection
TREATMENT OF EARLY SYphilis IN HIV-INFECTED AND UNINFECTED PERSONS

Proportion of Subjects with RPR Decline <2 Dilutions

<table>
<thead>
<tr>
<th></th>
<th>3 Mo.</th>
<th>6 Mo.</th>
<th>12 Mo.</th>
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<tr>
<td>Treatment Group</td>
<td></td>
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<td>HIV-Status</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Positive</td>
<td>38% (76)*</td>
<td>28% (69)</td>
<td>21% (61)</td>
</tr>
<tr>
<td>Negative</td>
<td>24% (287)</td>
<td>19% (259)</td>
<td>16% (219)</td>
</tr>
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*P < 0.05

2010 STD TREATMENT GUIDELINES
Syphilis in HIV Infected Patients

Treat as Recommended for Patients Without HIV Infection

Closer Follow-up
(3, 6, 9, 12, and 24 mos)
Case 2

A 34 YO male returns to clinic for scheduled follow-up. Six months ago he was diagnosed with early latent syphilis and treated with 2.4 Mu of benzathine penicillin G. At that time his RPR was reactive at 1:8.

His previous partners were treated and he has been monogamous since treatment. His repeat RPR remains positive at 1:8.

What is the appropriate diagnosis and management for this patient at this time?
Reasons for Serological Testing For Syphilis

Screening

Diagnostic Testing

Monitoring Outcomes of Therapy
Error of RPR VDRL Tests - ± 1 dilution

Meaningful change is 2 dilution (or 4-fold) change in titer
  e.g. 1:2 → 1:4 or 1:1, no meaningful change
  1:2 → 1:8, meaningful change

Quantitative RPR or VDRL test, results are not interchangeable

Two dilution decline in titer indicates response to therapy however, failure to decline ≥ 2 dilutions does not necessarily mean patient has failed treatment
TREATMENT OF EARLY SYPHILIS IN HIV-INFECTED AND UNINFECTED PERSONS

Proportion of Subjects with RPR Decline <2 Dilutions

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Rolfs et al, NEJM
1997; 337:307-14
Response To Early Syphilis Therapy at 3 Months Following Benzathine Penicillin G or Azithromycin Treatment (n=470)

- Serological Cure: 78.5% (369)
- Serofast: 20.4% (96)
- Serological Failure: 1.1% (5)

Hook et al, JID 2010; 201: 1729-35
Factors Associated With Serological Response To Therapy

Younger Age
Earlier Stage of Disease (1°>2°>EL)
Jarisch-Herxheimer Reaction
Higher Baseline Titer (within stage)

Not Associated – Gender, Race, Prior syphilis,

Sena et al CID 2011; 53: 1092-9
Serofast Syphilis Response To Repeat Therapy

Of 82 early syphilis patients who were serofast 6 months following treatment with benzathine penicillin or azithromycin and retreated with single injections of benzathine penicillin, 2.4 Mµ at 12 months following initial therapy:

22 (27%) – had > 2 dilution RPR declines from their baseline titer

11 (13%) had > 2 dilution RPR declines from their 6 month titer

Serological cure was:

Associated with higher baseline (and 6-month) RPR titers

Not associated with gender, age, syphilis stage or initial therapy

Case 3

A 54 YO woman is diagnosed with syphilis of unknown duration based on an RPR reactive at a 1:4 dilution and a reactive treponemal IgG assay. There are no signs of syphilis and no prior serological tests for syphilis in nearly 20 years. Physical examination is normal.

Planned therapy with benzathine penicillin, 2.4Mug weekly for three weeks is initiated. She presents 12 days following her initial penicillin injection, stating that she was unable to keep her 1 week appointment.

What should the next course of action be?
2010 STD TREATMENT GUIDELINES
Early vs. Late Latent Syphilis

**Early Latent Syphilis**
Documented Seroconversion Past Year Unequivocal history of 1°, 2° syphilis symptoms, past year
Sex partner with 1°, 2°, or EL syphilis, past year

**Late Latent Syphilis**
All others
(STD Titers Do Not Differentiate Early vs. Late Latent Syphilis)
MEASURING SYPHILIS INCIDENCE

Year 1  Year 2  Year 3

ACTUAL  3      3      3
MEASURED 1      3      5

- Red: Time syphilis acquired
- Green: Time syphilis diagnosed/detected
2010 CDC STD TREATMENT GUIDELINES
Late Latent and Tertiary Syphilis

• Benzathine Penicillin G 2.4 Mu IM weekly* x 3

• **Penicillin Allergy**
  • Doxycycline 100 mg PO, BID x 28

• Intradose interval of 10-14 days acceptable without re-starting therapy
Pharmacologic considerations suggest that an interval of 10-14 days between doses of benzathine penicillin for late syphilis or latent syphilis of unknown duration might be acceptable before restarting the sequence of injections. Missed doses are not acceptable for pregnant patients receiving therapy for late latent syphilis.
Syphilis Therapy: Goals

Cure of disease: improvement of clinical signs and symptoms; prevention of disease progression

Prevention of disease transmission

Reduction of risk for HIV acquisition
Quantitative nontreponemal serological tests should be repeated at 6, 12, and 24 months.

CSF exam should be performed for:
1) A 4-fold increase in titers;
2) An initial titer >1:32 fails to decline 4-fold;
3) Signs or symptoms attributable to syphilis develop.
Latent Syphilis:
Response To Therapy
Su bebé es un REGALO

Protéjalo de la sífilis.
El tratamiento temprano en las embarazadas puede disminuir la posibilidad de complicaciones serias en los bebés. Obtenga cuidado prenatal desde el principio y pídale a su médico el examen de la sífilis.

Llame al 800-833-4642 para más información sobre cómo obtener cuidado prenatal.

Melanie Taylor MD, MPH
Medical Epidemiologist
CDC/NCHHSTP/DSTDP

April 2, 2013

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Division of STD Prevention
Case 1: 23 yo pregnant woman 37 weeks gestation

- First prenatal visit
- EIA positive
- RPR negative
- Physical exam normal
- She denies prior syphilis diagnosis or treatment
- What additional testing should she receive?
Pregnancy: EIA+/RPR-

- What additional testing should she receive?
  A. Repeat RPR
  B. Syphilis IgM
  C. Repeat EIA
  D. TP-PA or FTA-ABS
Assessing EIA results

• Her TP-PA returns positive.
• She is given a presumptive diagnosis of latent syphilis and is treated with 3 weekly injections of benzathine penicillin.
• She delivers a healthy infant at 40 weeks.
• Should the infant be treated? (<30 day treatment interval)
“Syphilis tests” over time

What does this test result mean?
1. Past infection—treated?
2. Past infection—untreated?
3. Current infection?
4. False positive reaction?

Current recommendation: Treat, if not previously treated

Tom Peterman, MD, MS (CDC/DSTDP)
Dilemma

- Should an infant born to an untreated mother with these lab findings be treated?
  - A positive EIA
  - Negative RPR
  - Positive TP-PA or FTA-ABS

- Diagnostic workup of the infant still recommended but if negative:
  - No current treatment recommendation
Mother to child transmission of syphilis when mother is RPR negative:

- 23,863 patients with congenital syphilis reported to CDC during 1991-2009.
- 106 RPR negative mothers, no confirmed evidence of CS or stillbirth deliveries
- No convincing evidence of syphilis transmission from mothers with persistently negative non-treponemal (RPR) test results

Case 2: 19 year old female

- Was called by the health department and told to report to your clinic for testing and treatment
- Partner of high-risk MSM case
- Single painless vaginal lesion on exam
- Urine pregnancy test positive
- Penicillin allergic
Case 2: Management Considerations

- 70%-100% likelihood of transmission to infant during maternal primary stage.
- Presumptive treatment with 2.4 MU of benzathine penicillin is needed.
- She reports her allergy to PCN as hives and difficulty breathing.
- What is the next management step?
Pregnant Woman with Primary Syphilis and Penicillin Allergy

- What is the next step in management?
  A. Penicillin desensitization, followed by immediate treatment with 2.4 MU BZN PCN
  B. Same day treatment with 2.4 MU BZN PCN IM in clinic
  C. Hospitalization and PCN challenge with IV aqueous PCN
  D. Referral to immunologist for allergy testing and documentation of true PCN allergy
Treatment of Pregnant Women with Syphilis

- Penicillin is the only recommended treatment
  - No other proven alternative
- Desensitization is standard of care for those that are penicillin allergic
- Treatment is the same as for non-pregnant
  - Some experts recommend giving two shots of benzathine penicillin to women with early syphilis
- Jarisch-Herxheimer reaction may cause premature labor or fetal distress

2010 CDC STD Treatment Guidelines www.cdc.gov/std
Penicillin Desensitization

### Oral Desensitization Protocol for Patients with a Positive Skin Test*

**Observation period:** 30 minutes before parenteral administration of penicillin

**Interval between doses:** 15 minutes

**Cumulative dose:** 1.3 million units

<table>
<thead>
<tr>
<th>Penicillin V Suspension Dose*</th>
<th>Amounts (units/mL)</th>
<th>mL</th>
<th>Units</th>
<th>Cumulative Dose (units)</th>
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<td>1</td>
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<td>9</td>
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<td>80,000</td>
<td>8.0</td>
<td>640,000</td>
<td>1,296,700</td>
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* Elapsed time is 3 hours and 45 minutes.
† The specific amount of drug was diluted in approximately 30 mL of water and then administered orally.


Case 2: Management Considerations

- Following desensitization, she receives 2.4 MU benzathine penicillin
- Initial RPR 1:256
- She returns for follow-up 3 months later; now 22 weeks gestation
- RPR titer is 1:256
- Reports two new sexual partners

What are the management considerations?
Case 2: Management Considerations

• Inadequate titer response
• Possible re-exposure, re-infection or treatment failure
• Does she need repeat treatment with benzathine penicillin?
• Does she need repeat desensitization?
Case 3: Delivery

- Re-treatment (2.4 MU PCN) at 23 weeks
- Delivers a live-born infant at 26 weeks
- The infant's RPR is 1:32
- Long bones are normal
- Infant's CSF VDRL is positive with a titer of 1:8
- What is the recommended management?
Infant with CSF VDRL titer of 1:8

- What should be included in the management of this infant?
  A. Benzathine penicillin 50,000 units/kg IM in a single dose
  B. Benzathine penicillin 2.4 MU IM single dose
  C. Aqueous crystalline penicillin G 100,000-150,000 units/kg/day for 10 days
  D. Retest mother, if RPR equal or less than infants RPR titer of 1:32, no treatment needed
Infant evaluation should include the following:

- CSF VDRL, cell count and protein
- CBC
- Long bone x-ray
- Serum RPR
- (Darkfield examination)

2010 CDC STD Treatment Guidelines www.cdc.gov/std
Delivery Outcomes

- Asymptomatic
- Stillborn
- Low birth weight (IUGR)
- Premature delivery
- Birth defects
- Non-immune hydrops fetalis
- Spontaneous abortion
Early Congenital Syphilis
Signs and Symptoms

- Skin lesions
- Mucous membrane lesions
- Long bone abnormalities
- Anemia
- Hepatosplenomegaly
- CSF abnormalities/meningitis
- Rhinitis (rare)
Congenital Syphilis
Congenital Syphilis

(Hepatosplenomegaly & skin lesions)
Case 3: Treatment

- The infant receives aqueous crystalline penicillin G 100,000-150,000 units/kg/day administered as 50,000 units/kg/dose IV q 12 hours during the first 7 days of life and q 8 hours thereafter for a total of 10 days.
- Follow-up testing is scheduled for 3 months.
Infants Requiring Treatment:

- Infants with objective findings
- Infants born to mothers who:
  - Had untreated syphilis at delivery
  - Had serologic evidence of relapse or re-infection
  - Were treated with erythromycin or other non-penicillin regimen during pregnancy
  - Treated \( \leq 4 \) weeks before delivery
  - Poor or no documentation of treatment history
  - Adequately treated, but insufficient follow-up with repeat testing
Prevention Recommendations

• Test mother for syphilis
  – First prenatal visit
  – During third trimester (risk)
  – At delivery

• Testing and treatment history of sex partners
Every baby is a GIFT

Help your patients protect theirs.
Remember to test all expectant mothers for syphilis.
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For more information please contact Centers for Disease Control and Prevention

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Questions?
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