Syphilis: Clinical Aspects, Epidemiology, and Control

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Overview

- History of Syphilis
- Transmission, Pathogenesis, and Stages of Syphilis
- Diagnostic Tests
- Treatment and Partner Management
- Epidemiology
- Public Health and Syphilis
History of Syphilis
The Great Pox

- Epidemic in late 15th century Europe
- Rapid spread and severe symptoms in early stages
- Epidemic coincided with Columbus’ return from America in 1493
  - ? endemic but unrecognized
  - ? A gift from the new world
Syphilis…Discovery of its Cause

- 1903: Infection successfully transmitted to monkeys
- 1905: Identification of the bacterium *Treponema pallidum* ("Spirochaeta pallida")
- 1906: Darkfield microscopy
Treponema pallidum
Initial Treatment Strategies

- Mercury treatment
- Potassium Iodide
- Arsphenamine (arsenic derivative)
- Bismuth compounds
- Fever therapy
  - Malaria infection with *Plasmodium vivax*
- Penicillin: 1943
Transmission, Pathogenesis, and Stages of Syphilis
Transmission (1)

- Contact with infectious, moist lesion(s), most commonly during oral, anal or vaginal sex

- Less common through casual skin-to-skin contact eg. foreplay, finger play

- Mother-to-child transmission

- Cannot be spread by use of toilet seats, swimming pools, hot tubs, shared clothing or eating utensils
Transmission (2)

- During early (primary and secondary) syphilis, efficiency of transmission ~ 30%.

- Perinatal transmission can occur:
  - at any time during pregnancy
  - at any stage of the disease

- Syphilis can infect infants of untreated mothers. Chance of vertical transmission by stage of infection:
  - primary syphilis = 50%
  - early latent syphilis = 40%
  - late latent syphilis = 10%
  - tertiary syphilis = 10%
Pathogenesis

- Multiplies at the site of inoculation & forms a chancre (1<sup>o</sup>)
- Spread to local lymph nodes & then to the blood stream (2<sup>o</sup>)
- Can involve of many body organs (2<sup>o</sup> and latent)
- Late disease (tertiary) → infection/inflammation of the blood vessels in the central nervous system and cardiovascular systems or poorly formed lesions (gumma)
Syphilis
Distribution of the Organism
Primary Syphilis

- Chancre:
  - Appears 10-90 days after infection
  - Typically single, painless, clean-based lesion with rolled edges
Primary Syphilis
Chancre, Tongue
Secondary Syphilis

Signs and Symptoms

- Usually occurs 3-6 weeks after primary chancre
  - Rash (75-90%)
  - Generalized lymph node swelling (70-90%)
  - Constitutional symptoms (50-80%)
  - Mucous patches (5-30%)
  - Condyloma lata (5-25%)
  - Patchy alopecia or hair loss (10-15%)
  - Symptoms of neurosyphilis (1-2%)
  - Less common: meningitis, hepatitis, arthritis, nephritis
Rashes of Secondary Syphilis

Macular

Papular

Palmar

Dr. Joseph Engelman, San Francisco City Clinic

STD Atlas, 1997
Rash of Secondary Syphilis

Dr. Joseph Engelman, San Francisco City Clinic
Rash of Secondary Syphilis

STD Atlas, 1997
Palmer/Plantar Rash of Secondary Syphilis
Other Manifestations of 2º Syphilis

Condyloma lata

Mucous patches

Condyloma lata

Dr. Joseph Engelman, San Francisco City Clinic

Mosby STD Atlas, 1997
Secondary Syphilis
Condyloma Lata, Perianus
Secondary Syphilis
Moth-Eaten Alopecia (Hair Loss)
Latent Syphilis

- No clinical manifestations: only evidence is positive serologic tests
- 60-85% remain asymptomatic for years without treatment
- Divided into two stages for treatment purposes:
  - Early latent syphilis: <1yr duration
  - Late latent syphilis: >1yr duration
Syphilis Staging Flowchart

Symptoms or Signs?

YES

1º (Ulcer)  2º (Rash, etc)

PRIMARY  SECONDARY

NO

LATENT

ANY IN PAST YEAR?
Negative syphilis serology
Known contact to an early case of syphilis
Good history of typical signs/symptoms

YES

EARLY LATENT

NO

UNKNOWN or LATE LATENT
Tertiary Syphilis

- 70% of untreated patients remain asymptomatic
- 30% of untreated patients progress to tertiary stage in 5-20 years
  - Gummas: destructive lesions of soft tissue, cartilage, internal organs and bone
  - Cardiovascular involvement: aortic aneurysm, aortic insufficiency
  - Central nervous system involvement: general paresis, tabes dorsalis, optic atrophy
- Progressive inflammatory disease
Neurosyphilis

- Central nervous system invasion occurs early in infection in 30-40% of patients
- Asymptomatic neurosyphilis can occur at any stage of syphilis
- Early symptomatic forms (months to a few years)
  - Acute meningitis
  - Meningovascular (stuttering stroke)
- Late symptomatic forms (> 2 years)
  - General paresis
  - Tabes dorsalis
Syphilis and HIV Transmission/Acquisition

• How can syphilis or other STDs increase HIV transmission?
  • Reducing physical barriers
  • Increasing the number of receptor cells
  • Increasing HIV viral load in genital lesions, semen or both

• Genital ulcers → 3 to 11-fold increased HIV acquisition*

*Wasserheit STD 19:261; 1992
Diagnostic Tests
Diagnostic Tests for Syphilis

- Darkfield / DFA-TP
- PCR
- VDRL/RPR
- FTA-abs / TP-PA (MHA-TP)
- EIA
T. pallidum on Darkfield
T. pallidum by DFA-TP
Syphilis Serology

- Non-treponemal tests
  - VDRL (Venereal Disease Research Laboratory)
  - RPR (Rapid Plasma Reagin)
  - TRUST (Toluidine Red Unheated Serum Test)
  - USR (Unheated Serum Reagin)

- Treponemal tests
  - TP-PA (Treponema Pallidum Particle Agglutination)
  - FTA-abs (Fluorescent Treponemal Antibody - Absorbed)
  - EIA (Enzyme Immunoassay)
Non-Treponemal Tests

- VDRL and RPR are most commonly used
- Detect Abs against cardiolipin-lecithin-cholesterol antigens; not specific for *T. pallidum*
RPR Test for Syphilis

Soluble Antigen, Antibody, and Chromogen

Antigen–Antibody Complex

STD Atlas, 1997
Uses of Non-Treponemal Tests

- Screening
- Evaluation of patients with symptoms or possible re-infection
- Follow-up assessment after treatment
Non-Treponemal Tests

Advantages

- Rapid & inexpensive compared to treponemal tests
- Easy to perform
- Quantitative (can be titered)
  - Used to follow response to therapy
  - Can evaluate possible reinfection
Non-Treponemal Tests

Disadvantages

- Biological false positive reactions (BFPs)
  - Viral illnesses including HIV, recent immunizations, IDU, autoimmune and chronic diseases

- False negative reactions
  - Prozone effect
  - Early primary and late latent stages
Treponemal Tests

- Specific for *T. pallidum*
- Measure antibody (IgM & IgG) directed against *T. pallidum* antigens by particulate agglutination (TP-PA) or immunofluorescence (FTA-abs)
- May remain positive after treatment
- More sensitive and specific than non-trep. tests
- More expensive and labor intensive
- Can not quantitate…not useful for following response to treatment
Step 1
Antigen
Treponema pallidum

Patient's specimen containing antibody (diluted 1:5 in sorbent)

Antigen-antibody complex

+  

Step 2
The treponeme is coated with antibody. This coating can be "stained" with a conjugate.

Conjugate (Fluorescein-conjugated animal antiserum to human globulin)

Fluorescence (2nd antigen-antibody complex)
**LA County Screening**

Non-Treponemal Test (RPR, VDRL)

- **NEG**
  - NO disease or False Negative*

- **POS**
  - Confirm with Treponemal Test

  - **NEG**
    - BFP
  - **POS**
    - DISEASE

*False negative RPRs can occur early in infection. Re-screen in 1 month if recent exposure.
## Sensitivity of Serologic Tests According to Stage

<table>
<thead>
<tr>
<th>Test</th>
<th>1°</th>
<th>2°</th>
<th>Latent</th>
<th>Tertiary</th>
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<tr>
<td>VDRL/RPR</td>
<td>74-87%</td>
<td>100%</td>
<td>88-100%</td>
<td>37-94%</td>
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<tr>
<td>FTA-ABS</td>
<td>70-100%</td>
<td>100%</td>
<td>100%</td>
<td>96%</td>
</tr>
<tr>
<td>MHA-TP*</td>
<td>69-90%</td>
<td>100%</td>
<td>97-100%</td>
<td>94%</td>
</tr>
</tbody>
</table>

*MHA-TP and TP-PA probably perform equivalently
Serologic Pitfalls in the Diagnosis of Syphilis

- Negative nontreponemal test may occur early in primary or late in tertiary - check FTA-ABS or TP-PA
- **Prozone phenomenon**: false negative due to lack of agglutination with high antibody levels
- **Serofast**: persistent, low-level positive titer after adequate treatment
Syphilis Screening Guidelines

- Targeted screening of at risk populations
  - Patients with other STDs
  - Correctional settings
  - Drug treatment settings
  - HIV+
  - MSMs in outbreak areas or high risk
Treatment
and
Partner Management
Syphilis: Treatment
Penicillin G

- Intravenous or intramuscular injection of penicillin G is the preferred drug for treatment of all stages of syphilis
- Benzathine penicillin G, aqueous procaine penicillin or aqueous crystalline penicillin can be used
  - Bicillin-LA (not CR)
Syphilis: Treatment
Primary, Secondary & Early Latent

- **Recommended regimen:**
  - Benzathine penicillin G 2.4 million units IM once

- **Non-pregnant penicillin-allergic adults** *

  * Data to support the use of alternatives to penicillin are limited and if used, close follow-up is essential
  - Doxycycline 100mg orally twice daily for two weeks or
  - Tetracycline 500mg orally 4 times a day for two weeks or
    - Adherence is poor (i.e., dosing and gastrointestinal effects)
  - Ceftriaxone 1 g IM daily x 8-10 d or
  - (Azithromycin 2 g po)...not recommended in CA

* Efficacy in HIV + persons not studied so use with caution
Syphilis Resistant to Azithromycin!

Macrolide Resistance in Treponema pallidum in the United States and Ireland

Sheila A. Lukehart, Ph.D., Charmie Godornes, B.S., Barbara J. Molini, M.S., Patricia Sonnett, B.S., Susan Hopkins, M.D., Fiona Mulcahy, M.D., Joseph Engelman, M.D., Samuel J. Mitchell, M.D., Ph.D., Anne M. Rompalo, M.D., Christina M. Marra, M.D., and Jeffrey D. Klausner, M.D., M.P.H.

Impact of Azithromycin Resistance

- In San Francisco, the frequency of azithromycin-resistant *T. pallidum* isolates increased from 4% during 2000–2002 to 37% during 2003
- San Francisco STD clinic discontinued use of azithromycin for treating syphilis infection
- Notified San Francisco medical providers of azithromycin treatment failures
  - Recommendation to use Benzathine penicillin G
  - Doxycycline as alternative in PCN-intolerant
- National notification via *MMWR*
- *Not included in 2006 CDC Treatment Guidelines as a recommended treatment for syphilis*
Syphilis: Treatment
Late Latent and Unknown Duration

- **Recommended regimen:**
  Benzathine Penicillin G 7.2 million units total, given as 3 doses of 2.4 million units each at 1 week intervals

- **Non-pregnant penicillin-allergic adults** *
  - Doxycycline* 100mg orally two times a day for 4 weeks or
  - Tetracycline* 500mg orally four times a day for 4 weeks

*Close follow-up essential and efficacy in HIV+ not studied so use with extreme caution
Syphilis: Treatment

Neurosyphilis

- **Recommended regimen:**
  - Aqueous Crystalline Penicillin G 18-24 million units IV daily administered as 3-4 million IV every 4 hrs for 10 -14 days

- **Alternative regimen:**
  - Procaine Penicillin G 2.4 million units IM daily plus Probenecid 500 mg PO daily, both for 10-14 days
Syphilis: Treatment
Pregnancy

- Penicillin is the only adequate form of treatment for syphilis in pregnancy
  - Penicillin-allergic patients → Hospitalize, desensitize & treat with penicillin
  - Erythromycin is not accepted as alternative drug in penicillin-allergic patients
Partner Evaluation for Syphilis Exposure Periods

- All partners within the following time periods require evaluation:
  - $1^o$: 90 days + duration of symptoms
  - $2^o$: 6 months + duration of symptoms
  - Early latent: 1 year

- Partners of patients with syphilis of unknown duration and titers $\geq 1:32$ should also be evaluated
Management of Contacts

- Contacts to primary, secondary or early latent syphilis
  - Persons exposed *within 90 days* preceding the diagnosis in a sex partner might be infected even if seronegative: **Treat presumptively**
  - Persons exposed >90 days before the diagnosis should be treated presumptively if serologic tests are unavailable or follow up is uncertain; **if serologic tests are negative no treatment is needed**
Syphilis: Management of Contacts Late Syphilis

- Long term sex partners should be evaluated clinically and serologically for syphilis and treated on the basis of findings
Harm Reduction

- Abstain from sex until treatment is finished and until partners have been evaluated and treated
- Use condoms consistently and correctly
- Minimize # of sex partners
- Avoid sex while under the influence of alcohol or drugs to decrease risky behavior
- Avoid having sex with partners with genital ulcers/lesions or rashes
- Get check-ups every 6 months if engaging in sex with more than one sex partner
Epidemiology and Public Health Aspects of Syphilis Prevention and Control
Syphilis — Reported cases by stage of infection: United States, 1941–2007

Cases (in thousands)

- P&S
- Early Latent
- Total Syphilis

<table>
<thead>
<tr>
<th>Year</th>
<th>P&amp;S</th>
<th>Early Latent</th>
<th>Total Syphilis</th>
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<tbody>
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<td>240</td>
<td>120</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>2006</td>
<td>0</td>
<td>0</td>
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Primary and secondary syphilis — Rates by state: United States and outlying areas, 2007

Note: The total rate of P&S syphilis for the United States and outlying areas (Guam, Puerto Rico and Virgin Islands) was 3.8 per 100,000 population. The Healthy People 2010 target is 0.2 case per 100,000 population.
Rates per 100,000 Population
US, CA, and LA County 2001 - 2007

P&S Syphilis

- United States (1)
- California (2)
- LA County (3)
<table>
<thead>
<tr>
<th>Year</th>
<th>Chlamydia</th>
<th>Gonorrhea</th>
<th>P&amp;S Syphilis</th>
<th>EL Syphilis</th>
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<td>2006[1]</td>
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<td>1,030,911</td>
<td>358,366</td>
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<td>135,827</td>
<td>33,740</td>
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<td>LA</td>
<td>42,943</td>
<td>11,162</td>
<td>866</td>
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<tr>
<td>% CA</td>
<td>31.6%</td>
<td>33.1%</td>
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<td>% US</td>
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<td>LA**</td>
<td>44,030</td>
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<tr>
<td>% CA</td>
<td>31%</td>
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<td>45.1%</td>
<td>49%</td>
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<tr>
<td>% US</td>
<td>4%</td>
<td>2.8%</td>
<td>8%</td>
<td>7%</td>
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Distribution of Reported STD in Los Angeles County, 2008

- Chlamydia: 48,059 (79.9%)
- Gonorrhea: 8,980 (15.9%)
- PID: 201 (0.3%)
- Congenital syphilis: 20 (0.03%)
- Late latent syphilis: 1,422 (2.4%)
- Early latent syphilis: 758 (1.3%)
- P&S Syphilis: 719 (1.2%)
Syphilis in Los Angeles County, 2008

- In 2008, 1476 early syphilis cases were reported to health department in LAC
  - 719 primary and secondary syphilis
  - 758 early latent
- MSM comprised approximately 2/3 of cases, of whom 60% are also HIV-positive.
Primary & secondary syphilis — Rates: Total & by sex:
U.S., 1988–2007 & the Healthy People 2010 target

Note: The Healthy People 2010 target for P&S syphilis is 0.2 case per 100,000 population.
Primary & Secondary Syphilis, Rates by Gender
California, 1996–2007*

Gender Disparity in Reported Early Syphilis Rates per 100,000 Population, LA County, 2008

P&S Syphilis Rate per 100,000 Population

Early Latent Syphilis

Male

Female

Los Angeles Department of Public Health, STD Program
Age Disparity in Reported Early Syphilis Rates per 100,000 Population, LA County 2008

P&S Syphilis Rate per 100,000 Population

Early Latent Syphilis

Los Angeles Department of Public Health, STD Program
Race/Ethnicity Disparity in Reported Early Syphilis Rates per 100,000 Population, LA County, 2008

Los Angeles Department of Public Health, STD Program
Trends in Early Syphilis Cases by Sexual orientation, Los Angeles County, January 2001 - December 2005

Number of cases

MSM/W  MSM  MSW  WSM

2001 2002 2003 2004 2005
Percent of Interviewed Men who Have Sex with Men Primary & Secondary Syphilis Cases Reporting Meeting Partners, by Venue, California, 2001–2006

Note: The difference between bathhouses and sex clubs is the presence of private rooms; sex clubs do not have private rooms.
Trends in Venue Use for Sexual encounter of Early Syphilis Cases, Los Angeles County, 2001 -2005
Providers must report syphilis cases within one working day by completing a Confidential Morbidity Report (CMR)
Prevention and Control Measures

- Case finding
- Disease and health event investigation
- Case management
- Health education
- Counseling
- Referral and follow-up
- Collaboration
- Advocacy
Resources

- 2006 STD Treatment Guidelines: www.cdc.gov/std

- Los Angeles County STD Program website: www.lapublichealth.org/std

- California STD-HIV Prevention Center: www.stdhivtraining.org
Questions?

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