STI Clinical Update: Introduction to Syphilis

Kelly A. Johnson, MD, MPH
Public Health Medical Officer, STD Control Branch, California Department of Public Health
Assistant Professor of Medicine, Division of Infectious Diseases, University of California San Francisco
Clinical Faculty, California Prevention Training Center
Learning Objectives

STI update through case-based approach
Case Presentation

- 35-year-old bisexual male presents to your clinic with genital ulcers.
- The ulcers are a little bit painful. They are not pruritic. There are several of them.
- The patient’s physical exam reveals the following findings . . .
What is the most likely diagnosis?

- A. Genital herpes
- B. Primary syphilis
- C. Secondary syphilis
- D. Chancroid
- E. Pityriasis rosea
What is the most likely diagnosis?

- A. Genital herpes
- B. Primary syphilis
- C. Secondary syphilis
- D. Chancroid
- E. Pityriasis rosea
Syphilis Overview

- **Causative organism**: *Treponema pallidum*, spirochete bacterium
- **Transmission**: direct contact to infectious lesion, blood-borne, mother-to-child
- **Incubation**: ~3-4 weeks; range 10-90 days
- **Causes systemic infection, episodes of active disease interrupted by periods of latent infection**
Natural History of Syphilis

Incubation Period
3-4 weeks

30-50%

2-6 weeks

2-6 weeks

3-8 weeks

2-20 years

Exposure → Primary → Secondary → Latent → Tertiary

30%

25%

Transmission from mother to fetus can occur at any stage

Neuro and Ocular Syphilis can occur at any stage
Natural History of Syphilis: Primary Syphilis

- **Exposure**: 30-50%
- **Primary**: 2-6 weeks
- **Secondary**: 3-8 weeks
- **Latent**: 2-20 years
- **Tertiary**: 30%

**Chancre (ulcer)**
- Single, painless, indurated, clean-based lesion with rolled edges.
- Can go unrecognized, esp if in the rectum or vagina.
- Possible regional adenopathy (rubbery, bilateral, painless).
Primary Syphilis

Dr. Joseph Engelman, San Francisco City Clinic

Courtesy: SF City Clinic
Primary Syphilis
Primary Syphilis: Extranodal Chancres

Clinics in Dermatology, 2016

SFCC

Raguse et al. AIM 2012.
After examining the patient’s genital ulcers, the provider suspects genital herpes.

The patient is prescribed acyclovir.

His ulcers resolve entirely; he feels well.

He returns a few weeks later, this time with a diffuse but subtle non-pruritic rash.

The appearance of the rash is as shown:
What is the most likely diagnosis?

- A. Secondary syphilis
- B. Tinea versicolor
- C. Coxsackie virus (hand-foot-mouth disease)
- D. Atopic dermatitis
- E. Contact dermatitis
What is the most likely diagnosis?

- A. Secondary syphilis
- B. Tinea versicolor
- C. Coxsackie virus (hand-foot-mouth disease)
- D. Atopic dermatitis
- E. Contact dermatitis
Natural History of Syphilis: Secondary Syphilis

Incubation Period
- Primary: 3-4 weeks
- Secondary: 2-6 weeks
- Latent: 3-8 weeks
- Tertiary: 2-20 years

Exposure: 30-50%

Secondary signs:
- Rash (75-90%),
  - Involving palms/soles (60%)
- Generalized lymphadenopathy (70-90%)
- Constitutional symptoms (50-80%)
- Mucous patches (5-30%)
- Condyloma lata (5-25%)
- Patchy alopecia (10-15%)
- Symptoms of neurosyphilis (1-2%)
Secondary Syphilis: Rash
Secondary Syphilis: Mucous Patches

Courtesy: Gregory Melcher, UC Davis
Susan Philip, SF DPH & UCSF
Mucus Patches: Differential Diagnosis

Oropharyngeal candidiasis / Thrush

Oral hairy leukoplakia

Secondary Syphilis: Patchy Alopecia
Secondary Syphilis: Condyloma lata

Courtesy: Gregory Melcher, UC Davis
Susan Philip, SF DPH & UCSF

Differential diagnosis: Condyloma acuminata

https://www.std.uw.edu/go/pathogen-based/hpv/core-concept/all#clinical-manifestations
Back to our case...

- After evaluating the patient’s rash, the provider suspects contact or allergic dermatitis.
- A topical steroid is prescribed.
- The patient is adherent to steroid treatment.
- His rash resolves and he feels well.
The patient returns for a routine physical exam and check-up a few months later. He has no acute concerns. A sexual history is not taken, and he is not screened for sexually transmitted infections.
Natural History of Syphilis: Early latent

- **Exposure**: 30-50%
- **Primary Phase**: 2-6 weeks
- **Secondary Phase**: 3-8 weeks
- **Latent Phase**: 2-20 years
- **Tertiary Phase**: 30%

**Incubation Period**
- Exposure: 3-4 weeks
- Primary: 2-6 weeks
- Secondary: 3-8 weeks
- Latent: 2-20 years

**Early latent**
- Latent with evidence of infection within the past 12 months
- Otherwise: Considered Late-Latent or Unknown

**Duration**
Back to our patient . . .

- Two years after resolution of his rash, the patient returns to clinic with slight hearing loss and new mild headaches.
- The provider tests the patient’s hearing in office and does not find any obvious deficits.
- No further testing is pursued.
- The patient is reassured that there is nothing to worry about.
- He is told to return to clinic if his symptoms worsen.
What is the most likely diagnosis?

For the hearing loss and headaches:

- A. Cholesteatoma
- B. Otitis media
- C. Neurosyphilis
- D. Age-related sensorineural hearing loss
What is the most likely diagnosis?

For the hearing loss and headaches:

- A. Cholesteatoma
- B. Otitis media
- C. Neosyphilis
- D. Age-related sensorineural hearing loss
Neuro and Ocular Syphilis can occur at any stage.
Neurosyphilis

- Can occur at **any** stage of syphilis
- **Early** manifestations (months to years after infection)
  - Cranial nerve dysfunction, meningitis, stroke, AMS, hearing or vision changes
  - Otosyphilis – hearing loss w/wo tinnitus
  - Ocular – range of visual symptoms
- **Late** manifestations (10-30 years after infection)
  - Tabes dorsalis and general paresis
- **Note:** in untreated HIV or AIDS- Neuro and ocular syphilis timelines are shortened considerably
- **All patients with syphilis should be assessed for neurological signs and symptoms**
  - Neuro exam, including assessment of ophthalmic and auditory symptoms
  - If clinical evidence of neurologic involvement is observed, perform LP
Case Continued

- The patient presents to the ED a few days after his last clinic discharge.
- His headaches have worsened to the point of becoming severe.
- The ED physician now does a CT brain and LP.
- A cerebrospinal fluid VDRL is sent as part of the routine work up for meningitis.
- The VDRL results positive, and the patient is diagnosed with neurosyphilis.
- He is admitted for treatment with IV penicillin.
Meanwhile, a few months after our patient’s last clinic visit, one of the patient’s female partners delivers an infant at 38 weeks pregnant.

The mother received no pre-natal care.

The newborn appears ill, with copious nasal discharge, hepatosplenomegaly, lymphadenopathy, a rash, and jaundice.

CSF analysis reveals a positive VDRL, confirming a diagnosis of congenital syphilis.
CDC: “Up to 40% of babies born to women with untreated syphilis may be stillborn, or die from the infection”

Early CS physical findings (birth-8 weeks, but up to 2 years)

- Hepatomegaly (enlarged liver)
- Splenomegaly (enlarged spleen)
- Snuffles (copious nasal secretions – infectious!)
- Mucocutaneous lesions (infectious!)
- Pneumonia Alba
- Osteochondritis
- Pseudoparalysis
- Edema
- Rash, lymphadenopathy
- Hemolytic anemia or thrombocytopenia

Courtesy CDC Public Health Image Library
Congenital Syphilis Physical Findings:
Late (2 years +)

- **Interstitial keratitis** (5–20 years of age)
- **Eighth cranial nerve deafness** (10–40 years of age)
- **Hutchinson teeth** (peg-shaped, notched central incisors)
- **Mulberry molars**
- **Anterior bowing of the shins**
- **Frontal bossing**
- **Saddle nose**
- **Rhagades** (perioral fissures)
- **Clutton joints** (symmetric, painless swelling of the knees)

Mathematical model: Early Rx = Fewer CS Infant Deaths

% CS deaths preventable by treating pregnant women with syphilis at a given gestational age.


Around 70% of CS stillbirths were likely avoidable if treatment was given by 21 weeks’ gestation.
Natural History of Syphilis

- **Incubation Period**: 3-4 weeks
- **Primary**: 2-6 weeks
- **Secondary**: 3-8 weeks
- **Latent**: 2-20 years
- **Tertiary**: 30%

**Transmission from mother to fetus** can occur at any stage.

**Chancre (ulcer)**
- Single, painless, indurated, clean-based lesion with rolled edges.
- Can go unrecognized, esp if in the rectum or vagina
- Possible regional adenopathy (rubbery, bilateral, painless)

**Secondary signs**
- Rash (75-90%),
- Involving palms/soles (60%)
- Generalized lymphadenopathy (70-90%)
- Constitutional symptoms (50-80%)
- Mucous patches (5-30%)
- Condyloma lata (5-25%)
- Patchy alopecia (10-15%)
- Symptoms of neurosyphilis (1-2%)

**Early latent**
- Latent w/evidence of infection within the past 12 months
- Otherwise: Considered Late-Latent or Unknown Duration

**Latency**
- Early latent
- Late latent

**Neuro and Ocular Syphilis can occur at any stage**
Syphilis Diagnosis
Syphilis Diagnostics

What test(s) is/are needed to diagnose syphilis?

- A) A treponemal test, such as a treponema pallidum particle agglutination (TPPA), Enzyme immunoassay (EIA), or chemiluminescence immunoassay (CIA) detecting antibodies to syphilis
- B) A non-treponemal test such as an RPR or VDRL
- C) Both a non-treponemal test and at least one treponemal test
What test(s) is/are needed to diagnose syphilis?

- A) A treponemal test, such as a treponema pallidum particle agglutination (TPPA), Enzyme immunoassay (EIA), or chemiluminescence immunoassay (CIA) detecting antibodies to syphilis
- B) A non-treponemal test such as an RPR or VDRL
- C) Both a non-treponemal test and at least one treponemal test
Serology and stage: Need both a treponemal AND a non-treponemal tests

Non-treponemal tests
- Examples: RPR and VDRL
- Quantitative tests, allowing for assessment of disease burden, treatment adequacy, and reinfection
- Non-specific (can be positive in patients with other conditions)

Treponemal tests
- Examples: TPPA, TPHA, FTA-ABS, EIA, CIA
- Detect antibodies specific to T. pallidum
  - Antibodies usually stay positive for life after initial infection
  - Not quantitative; cannot be used to assess for reinfection or response to treatment
Serologic Screening for Syphilis: Traditional vs Reverse Algorithms

**Traditional**
- Quantitative RPR
  - RPR+
    - TP-PA or other trep. test
      - TP-PA+ Syphilis (past or present)
      - TP-PA- Syphilis unlikely
  - RPR-

**Reverse Screening Algorithm**
- EIA/CIA+ or CIA-
  - Quantitative RPR
    - RPR+
      - EIA/CIA+ Syphilis (past or present)
    - RPR-
      - TP-PA
        - TP-PA+ Syphilis (past or present)
        - TP-PA- Syphilis unlikely

Evaluate clinically, determine if treated for syphilis in the past, assess risk of infection, and administer therapy according to guidelines if not previously treated.

If incubating or primary syphilis is suspected, treat with benzathine penicillin G 2.4 million units IM x 1 and/or repeat in 2-4 weeks.

If at risk for syphilis, repeat RPR in 2 to 4 weeks.
Traditional screening algorithm

Quantitative RPR

RPR+

TP-PA or other trep. test

TP-PA+
- Syphilis (past or present)

TP-PA-
- Syphilis unlikely

RPR-
Reverse Screening Algorithm

Evaluate clinically, determine if treated for syphilis in the past, assess risk of infection, and administer therapy according to guidelines if not previously treated.

If incubating or primary syphilis is suspected, treat with benzathine penicillin G 2.4 million units IM x 1 and/or repeat in 2-4 weeks.

If at risk for syphilis, repeat RPR in 2 to 4 weeks.
Clinical Interpretation of Syphilis Screening Algorithms: A Resource for Local Health Jurisdictions

What about patients with a history of syphilis, how do you interpret non-treponemal (RPR/VDRL) titers?

• Higher numbers correspond to higher level of antibodies in patient’s serum

• **Two-fold change:** Generally considered within margin of error of test

• **Four-fold change:** Sustained for at least 2 weeks considered to be significant

• Compare titers using the **same** serologic test: RPR often higher than VDRL

<table>
<thead>
<tr>
<th>Titers</th>
<th>1:1024</th>
<th>1:512</th>
<th>1:256</th>
<th>1:128</th>
<th>1:64</th>
<th>1:32</th>
<th>1:16</th>
<th>1:8</th>
<th>1:4</th>
<th>1:2</th>
<th>1:1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change</td>
<td>2-fold</td>
<td></td>
<td></td>
<td></td>
<td>4-fold</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Syphilis Treatment
Primary, Secondary, and Early Latent Syphilis

Benzathine penicillin G* 2.4 million units IM in a single dose

*Bicillin L-A is the trade name. DO NOT use bicillin C-R!

Alternatives (non-pregnant penicillin-allergic adults):
- Doxycycline 100 mg po bid x 2 weeks
- Tetracycline 500 mg po qid x 2 weeks
- Ceftriaxone 1 g IV or IM qd x 10-14 d
Syphilis of Late Latent or Unknown Duration

Benzathine penicillin G 2.4 million units IM weekly* x 3

*Maximum 10-14 day interval in non-pregnant patients (7-9 days ideal)
*7-day interval optimal in pregnancy

Alternatives (non-pregnant penicillin-allergic adults):
- Doxycycline 100 mg po bid x 4 weeks
- Tetracycline 500 mg po qid x 4 weeks
Syphilis in Pregnancy

Penicillin is the only treatment for syphilis in pregnancy

- Treat with the penicillin regimen appropriate for stage of infection
  - Some experts recommend a 2nd dose of benzathine penicillin G 2.4 mu IM (7 days after 1st dose in early syphilis for pregnant people)
- Pregnant people with history of penicillin allergy should be desensitized and treated with penicillin
- All patients with syphilis should be tested for HIV
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

Alternative Regimen (use only if compliance with therapy can be ensured)

- Procaine penicillin G 2.4 million units IM once daily PLUS
- Probenecid 500 mg orally four times a day, both for 10–14 days
Importance of Day of Treatment Titer

Higher peak titer at treatment, but not checked

RPR 1:256  RPR 1:1024  RPR 1:256

Day of initial lab test  Day of treatment  Day of follow up titer to assess response

Establishes baseline to compare response post treatment
Frequently forgotten and without baseline makes assessment of titer response difficult
Conclusions

1) Syphilis presents differently in different stages of disease and can easily be misdiagnosed.

2) Left untreated, patients progress through stages of active disease interspersed by periods of latent disease.

3) The outcomes of untreated primary, secondary, and latent syphilis can be as severe as congenital syphilis, neurosyphilis, and ocular syphilis.

4) Neurosyphilis and maternal-fetal syphilis transmission can occur at any stage of disease.

5) The diagnosis of syphilis involves both treponemal and non-treponemal tests.

6) Syphilis is treated differently depending on the stage of disease; penicillin is the drug of choice.

7) Remember to include syphilis on your differential diagnoses and to screen broadly.
CDC Indications for HIV PrEP

HIV PrEP should be offered to sexually active individuals with syphilis (and/or any other bacterial STI) diagnosed or reported in the past 6 months

Thank you/Questions

Acknowledgements:
Kathy Jacobson, MD
Ina Park, MD, MAS
Sharon Adler, MD
Roz Plotzker, MD, MPH
Eric Tang, MD, MPH
Alyson Decker, MPH
Stephanie Cohen MD, MPH
Oliver Bacon, MD, MPH