Syphilis: Diagnosis, Treatment and Prevention

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Learning Objectives

- Describe the epidemiology of syphilis in the U.S.
- Describe the pathogenesis of *Treponema pallidum*
- Discuss the clinical manifestations of syphilis
- Identify methods used in the diagnosis of syphilis
- List the CDC-recommended treatment regimens for syphilis
- Summarize appropriate prevention counseling messages for patients with syphilis

Epidemiology

![Epidemiology Map](image)
Primary and Secondary Syphilis—Rates by Age and Sex, United States, 2011

<table>
<thead>
<tr>
<th>Age</th>
<th>Rate (per 100,000 population)</th>
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<tbody>
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Primary and Secondary Syphilis—Rates by Race/Ethnicity, United States, 2002–2011

- Blacks
- American Indians/Alaska Natives
- Asians/Pacific Islanders
- Hispanics
- Whites

Primary and Secondary Syphilis—Reported Cases* by Stage, Sex, and Sexual Behavior, United States, 2011

*Of the reported male cases of primary and secondary syphilis, 17.0% were missing sex of sex partner information.

MSM = men who have sex with men; MSW = men who have sex with women only.

Primary and Secondary Syphilis—Reported Cases* by Sex, Sexual Behavior, and Race/Ethnicity, United States, 2011

*Of the reported male cases of primary and secondary syphilis, 17.0% were missing sex of sex partner information; 2.4% of sex partner data were missing and 0.4% of race/ethnicity data were missing.

MSW = men who have sex with women only; MSM = men who have sex with men.
Clinical Stages of Syphilis

- **Exposure**: 9-90 days
- **Primary**: 4-10 weeks
- **Secondary**: > 12 months
- **Late Latent**: > 12 months
- **Early Latent**: ≤ 12 months
- **Tertiary**: 9-90 days
- **Late Latent**: > 12 months
- **Early Latent**: ≤ 12 months

Syphilis: Transmission

- **Major routes**: sexual and in utero from infected pregnant women to her fetus (vertical)
- **Risk of infection after 1 exposure**: 40%
- **Index patient** is most contagious to sexual partners during 1st and 2nd stage, less so in early latent stage

Syphilis: Pathogenesis

- **Penetration**:
  - Enters via skin or mucus membranes
  - Divides every 30-33 hours
  - Smaller the inoculum, longer the incubation period (9-90 days)
- **Dissemination**:
  - Before clinical signs/symptoms, it travels via lymphatic system to regional lymph nodes and then through body via blood
**Syphilis: Pathogenesis**

- Some spirochetes lodge at entry site, proliferate, sensitize lymphocytes and activate macrophages
- Primary lesion (chancre) results at this site of inoculation about 3-6 weeks after initial infection
- Chancre heals spontaneously, usually without scar, within 3-8 weeks

**Secondary syphilis**

- *T. pallidum* can traverse the tight junctions between endothelial cells to enter the perivascular spaces, where large number of treponemes and immune cells accumulate
- It can induce production of MMP-1, which degrades collagen and may facilitate access to and egress from the bloodstream, resulting in systemic spread
- Usually within 3 months of infection, symptoms of secondary syphilis appear

**Clinical Spectrum of Secondary syphilis**

- Eventually, the host suppresses the secondary infection enough so that no lesions are clinically apparent
- This is latency; 60-85% of patients remain asymptomatic
- Some progress to tertiary stage in 1-20 years
- Immunity is present with chronic infection but lost after treatment
Primary syphilis

- Chancre: appears 2-3 wks after exposure (range 3-90 days)
  - local lesion at site of inoculation
  - typically painless, indurated, clean base
  - 25% have multiple lesions
  - Regional adenopathy: classically rubbery, painless, bilateral

More primary syphilis...

Primary syphilis: Male chancre

Primary syphilis: Female chancre
Oral Chancre

Secondary Syphilis

- Onset 4-10 weeks following 1st and may overlap with it
- Rash:
  - macular, papular, pustular, combination;
  - usually nonpruritic
  - 60% or more involve palms and soles
- Mucus patches (5-30%)
  - flat patches in mouth, pharynx, genitals
More secondary syphilis...

- Condylomata lata (5-25%)
  - heaped, moist wart-like papules
  - in warm intertriginous areas
  - teeming with spirochetes
- Constitutional symptoms:
  - malaise, headache, slight fever, myalgia
  - liver/kidney involvement
  - patchy alopecia

Condylomata lata
Latent syphilis

- No clinical manifestations
- Only evidence is positive serology
- Early latent syphilis: <1 year duration
- Late latent syphilis: >1 year duration
- After 4 years patient is noninfectious; resistant to reinfection if not treated

Tertiary syphilis

- Late benign syphilis:
  - gummatous lesions in skeletal, spinal and mucosal areas, eye and viscera
  - average onset 4-12 years
- Cardiovascular syphilis:
  - endarteritis of aortic vasovasorum
  - present as aortic aneurysm, Aortic insufficiency
  - average onset 15 years
More tertiary syphilis…

Neurosyphilis

- CNS involvement occurs early
- Clinical manifestations may appear early or late and include:
  - Asymptomatic neurosyphilis, meningeal involvement (acute meningitis), meningovascular involvement, choreoretinitis, parenchymatous disease (paresis, tabes dorsalis, optic atrophy)

Congenital syphilis

- Vertical transmission can occur at any time during pregnancy and at any stage
- Among women with syphilis, perinatal transmission occurs in:
  - 50% with 1st and 2nd stages
  - 40% with early latent
  - 10% with late latent
  - 10% with tertiary

Adverse Fetal Outcomes among Pregnant Women with Untreated Syphilis

- 20% of children born to these mothers will be normal
- Intrauterine growth restriction
- Stillbirth (4%)
- Neonatal death
- Preterm birth
- Congenital infection and anomalies
Diagnosis

What’s recommended?

- Primary/Secondary Syphilis
  - Lesions?
    - Darkfield microscopy
    - Direct immunofluorescence
    - Polymerase chain reaction (PCR)
- Early Latent Syphilis
- Late Latent Syphilis
- Syphilis of Unknown Duration
- Late Syphilis

Diagnostic Points

- A positive darkfield or DFA of lesion exudate or tissue is a DEFINITIVE DX

- For presumptive diagnosis you need:
  + nontreponemal test (VDRL/RPR)
  AND
  + confirmatory treponemal test (FTA-ABS)

Syphilis - *Treponema pallidum* on darkfield

Few clinics have darkfield microscopes
Few clinicians know how to use them
Syphilis - Treponema pallidum on DFA

Few labs offer this test; takes time to perform

Selecting Syphilis Tests

Select and interpret lesion and serologic tests appropriately

- Lesion-based tests used only for Primary Stage
- Sensitivity and specificity of serology varies by stage
- Presence of antibody doesn’t distinguish past from present infection
- Quantitative Titers (RPR/VDRL) are used to evaluate response to therapy

Serologic Tests for Syphilis

- Two types
  - Non-Treponemal (qualitative) (RPR or VDRL)
  - Treponemal (qualitative and quantitative) (FTA-ABS, TPPA, TPI, ELISA, TPHA)
- Need both types to make an accurate diagnosis of syphilis

Screening Tests for Syphilis

Nontreponemal tests

- RPR Card Test: read directly
- VDRL Test: read via microscope
Serologic Tests for Syphilis

- Monitor titers to determine “cure”, “failure”, “reinfection/relapse”
- After therapy:
  - Cure = 4-fold (or 2 dilution) decrease (e.g. from 1:32 to 1:8)
  - Failure = no change or increase
  - Reinfection = documented titer response then a 4-fold increase

Natural History of Titer Decay

![Graph showing the natural history of titer decay over years from infection]
SEROLOGIC TITERS OF RPR/VDRL

1 : 1024
1 : 512
1 : 256
1 : 128
1 : 64
1 : 32
1 : 16
1 : 8
1 : 4
1 : 2
1 : 1

2-fold decline

Interpretation of Syphilis Tests

**Non-** T STS  T - STS  Possible diagnoses
RPR  FTA
Reactive  Non-reactive  False positive RPR
False negative FTA
Reactive  Reactive  New case – needs treatment
Old case – inadequately treated
Old case – reinfected
Congenital, other treponemal
Non-Reactive  Reactive  Old case – treated or untreated
Primary syphilis
Prozone reaction – rare
Non-reactive  Non-reactive  No syphilis
Incubating/early primary syphilis

Table 1. Sensitivity and Specificity of Serologic Tests for Syphilis

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity during stage of infection, % target</th>
<th>Specificity, % target</th>
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<tr>
<td></td>
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<td>Secondary</td>
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<td>Nonrecombinant tests</td>
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<td>VDL 2 [14]</td>
<td>76 (94–97)</td>
<td>100</td>
</tr>
<tr>
<td>TRUST 2 [14]</td>
<td>65 (57–75)</td>
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</tr>
<tr>
<td>RPR 14</td>
<td>86 (77–95)</td>
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<td>Early recombinant tests</td>
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<td>MHA TP 17</td>
<td>76 (69–83)</td>
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<td>MFA (17)</td>
<td>88 (80–100)</td>
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<tr>
<td>FTA-ABS (14)</td>
<td>94 (87–100)</td>
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<td>Enzyme immunoassays</td>
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<td>IgM ELISA 16</td>
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<tr>
<td>ICE [21]</td>
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*Note.* CUA, chemiluminescence assay; ELISA, enzyme-linked immunosorbent assay; EIA, enzyme immunoassay; FTA-ABS, fluorescent treponemal antibody-absorbed assay; ICE, immune capture EIA; MHA-TP, microhemagglutination assay for Treponema pallidum; N/A, not available; TPHA, T. pallidum hemagglutination assay; TPIA, T. pallidum particle agglutination; TRUDE, treponemal reagin/unreactive serum test.
Changing Times in Syphilis Serology

- Prevalence of syphilis is extremely low in many industrialized countries
- Labor costs have increased
- Introduction of treponemal tests which can be fully automated

Syphilis Laboratory testing and the EIA dilemma

- Two licensed tests for screening and confirmation
  - Trinity Captia Syphilis G (sonicated treponemes)
  - Trepchek G (cloned antigens)
- Increased use of treponemal EIA for screening; clinical management problems
- Quantitative non-treponemal testing to guide patient management; if test is negative, perform a second treponemal test to determine reactivity

Recommendations for laboratory syphilis testing algorithm with treponemal EIA (or CIA) as initial test

- A1 (EIA or CIA)
- A1+ → A1 – (Negative for syphilis)
- A2 (quantitative non-treponemal i.e. RPR)
- A1+ A2+ → Consistent with syphilis (past or current)
- A1+ A2 – → Treponemal test that uses a different Ag platform from A1 (i.e. TPPA, FTA-ABS)
- Positive Possible syphilis
- Negative Unconfirmed EIA

Biggest question?

- How to interpret a positive treponemal, but negative non-treponemal result!
  - Treatment?
  - Contact investigation?
  - Reporting?
CDC recommended algorithm for reverse sequence syphilis screening followed by nontreponemal test confirmation

What are the implications for public health practice?

CDC continues to recommend traditional screening using a nontreponemal test followed by testing of reactive sera with a treponemal test. When reverse sequence screening is used, CDC recommends reflexively testing all sera that produce reactive EIA/CIA results with a quantitative nontreponemal test and reflexively testing sera with discordant results (i.e., reactive EIA/CIA and nonreactive RPR/VDRL test) with a confirmatory Treponema pallidum particle agglutination assay (TP-PA); all test results should be reported promptly and concurrently to the clinician and public health department.

Data from two laboratories that tested 1407 sera specimens with reverse sequence syphilis screening indicated that, among patients with reactive EIA/CIA results, 64.7% had reactive nontreponemal test results and among those discordant sera, 12.2%–80% were nonreactive with a second treponemal test, suggesting they were false positive results.

Your best friend in the interpretation of serologic tests for syphilis to determine management and treatment is your local HEALTH DEPARTMENT

Syphilis: Treatment
Therapy for Syphilis

- Parenteral penicillin G is drug of choice for all stages of syphilis
- It is the ONLY therapy with documented efficacy for neurosyphilis or for syphilis during pregnancy

Primary and Secondary Syphilis: Therapy

- Benzathine penicillin G, 2.4 million units IM in a single dose

Penicillin Allergic Nonpregnant Patients

- Doxycycline 100 mg PO BID for 2 weeks

Treatment Recommendations Primary, Secondary, Early Latent

- Penicillin treatment of choice +/- HIV
  - Benzathine penicillin 2.4 mu IM x 1
- No benefit of additional therapy
  - Enhanced treatment (IM + oral)
- Penicillin alternatives
  - Doxycycline, ceftriaxone
  - Azithromycin 2 gm (resistance/treatment failure)
    - Use only when penicillin or doxycycline not feasible
    - Do not use in MSM or pregnancy
Azithromycin

- Macrolide resistance associated with A2058G mutation in 23S rRNA gene
  - Canada, Ireland, Czech Republic, China
  - Prevalence of mutation US
    - A2058G found in 9/11 US sites (Su, ESTDOR 2009)
    - MSM->MSW, no association with US region, race
- Treatment failure
  - US, Czech Republic, China

Follow-up

- Re-examine patients clinically and serologically at 6 months and 12 months after treatment
  - Rolfs study states that 15% of patients with early syphilis will not achieve a two dilution decline in nontreponemal titer at 1 year

What are the serological criteria for treatment failure?

- Failure: recurrence, persistence or progression of symptoms or by rising titer
- For latent syphilis, titers may decline 4-fold by 12-24 months, but data conflict

HIV-Infected Patients

- Primary and Secondary Syphilis
  - 2.4 million units IM benzathine penicillin G
- Follow-up: 3,6,9,12, and 24 months
- Treatment failure within 6-12 months: CSF examination
- Retreat with 7.2 million units penicillin if CSF if normal
Latent Syphilis

- Early latent Syphilis
  - Benzathine penicillin G 2.4 million units IM in a single dose
- Late Latent Syphilis or Syphilis of Unknown Duration
  - Benzathine penicillin G 7.2 million units total, given as three doses of 2.4 million units IM each at 1-week intervals

What if they miss a week?

- Pharmacology data suggest that an interval of 10-14 days between doses might be acceptable before starting over.
- If the patient is pregnant, adhere strictly to the weekly dose regimen. If she misses a week, start over.

Follow-up

- Repeat nontreponemal titer at 6, 12 and 24 months.
- If failure, consider LP
- Patients with a normal CSF exam, re-treat if:
  - Titors increase 4-fold
  - A high titer (>1:32) fails to decline at least 4-fold
  - Signs or symptoms attributable to syphilis develop
- Some patients remain serofast with negative CSF exam. Unclear what to do.

Jarisch-Herxheimer reaction

- Self-limited reaction to anti-treponemal therapy, seen more commonly with treatment of early stages
- Characterized by fever, malaise, nasea/vomiting, sometimes with chills and exacerbation of rash
- Occurs within 24 hours after therapy and resolves within 24 hours
- Warn patient that it is NOT ALLERGIC reaction
- Can be treated with symptomatic support
- Antipyretics may be recommended but no proven methods prevent reaction
Diagnosis of Neurosyphilis

- No single test can be used
- Dx can be made with any combination of:
  - abnormal CSF cell count (>5 WBC)
  - abnormal CSF protein
  - Reactive CSF-VDRL with or without symptoms
- CSF-FTA yields more false positives, but is very sensitive; some believe a neg CSF-FTA excludes neurosyphilis

Treatment

- Aqueous crystalline penicillin G 18-24 million units a day, given as 3-4 million units IV every 4 hours or continuous infusion for 10 to 14 days
  
  OR

- Procaine penicillin 2.4 million units IM a day, PLUS probenecid 500 mg orally four times a day, both for 10-14 days
Other treatment

- Ceftriaxone 2 grams daily IV or IM for 10-14 days
- Other regimens have not been adequately evaluated for treatment of neurosyphilis

AND...

- Some experts administer benzathine penicillin, 2.4 million units IM after completion of neurosyphilis treatment to provide a comparable total duration of therapy for late latent disease

Syphilis in Pregnancy

- All women should be screened serologically for syphilis during the early stages of pregnancy
- In population where prenatal care is suboptimal, RPR-card test screening and treatment should be done at time pregnancy is diagnosed
- In high risk population, screen early, at 28 weeks and at delivery

Syphilis in Pregnancy

- Any woman who delivers a stillborn after 20 weeks gestation should be tested for syphilis
- No infant should leave the hospital without the maternal serologic status having been determined at least once during pregnancy or at the time of delivery
Syphilis in Pregnancy

- 2.4 million units benzathine penicillin G is effective therapy for 1\textsuperscript{st}, 2\textsuperscript{nd}, and early latent antepartum syphilis
- 98% success with carefully defined congenital syphilis
- Fetal treatment failures are more frequent when moms are treated after the 20th week of gestation and with secondary syphilis

Syphilis in Pregnancy

- 4.8 million units of benzathine penicillin G over 2 weeks is effective for antepartum syphilis BUT
- One U.S. retrospective case-control study found no improvement in prevention of CS in high-risk setting of secondary syphilis
- African retrospective study found no treatment better than a single 2.4 million unit dose of benzathine penicillin in preventing preterm birth, still birth, and CS

Syphilis in Pregnancy

- Are there alternatives to penicillin?
  - NO
- No clinical trial with other medicines
- Fetal azithromycin serum, amniotic fluid levels are low

Jarisch-Herxheimer Reaction

- Acute febrile reaction often accompanied by headaches, myalgia, and other symptoms
- Often occurs within the first 24 hours after any syphilis treatment
- More common with early syphilis
- Patients should be advised of this
- Pregnant women should be aware that it may precipitate early labor and to notify obstetrician or go to ER if problems occur
Syphilis in Pregnancy

- Women treated during the second half of pregnancy are at risk for premature labor and/or fetal distress if therapy precipitates the Jarisch-Herxheimer reaction
- Advise the women to seek obstetric attention if they notice any contractions or decrease in fetal movements
- Stillbirth is a rare complication of treatment and should not delay it

Syphilis in Pregnancy Follow-UP

- Serologic titers should be repeated in the third trimester and at delivery
- Monthly checks are not necessary but may be checked in women at high risk for reinfection or in high geographic prevalence areas
- The clinical and antibody response should be appropriate for the stage of the disease
- Most women will deliver before their serologic response to treatment can be definitively assessed