Syphilis 101

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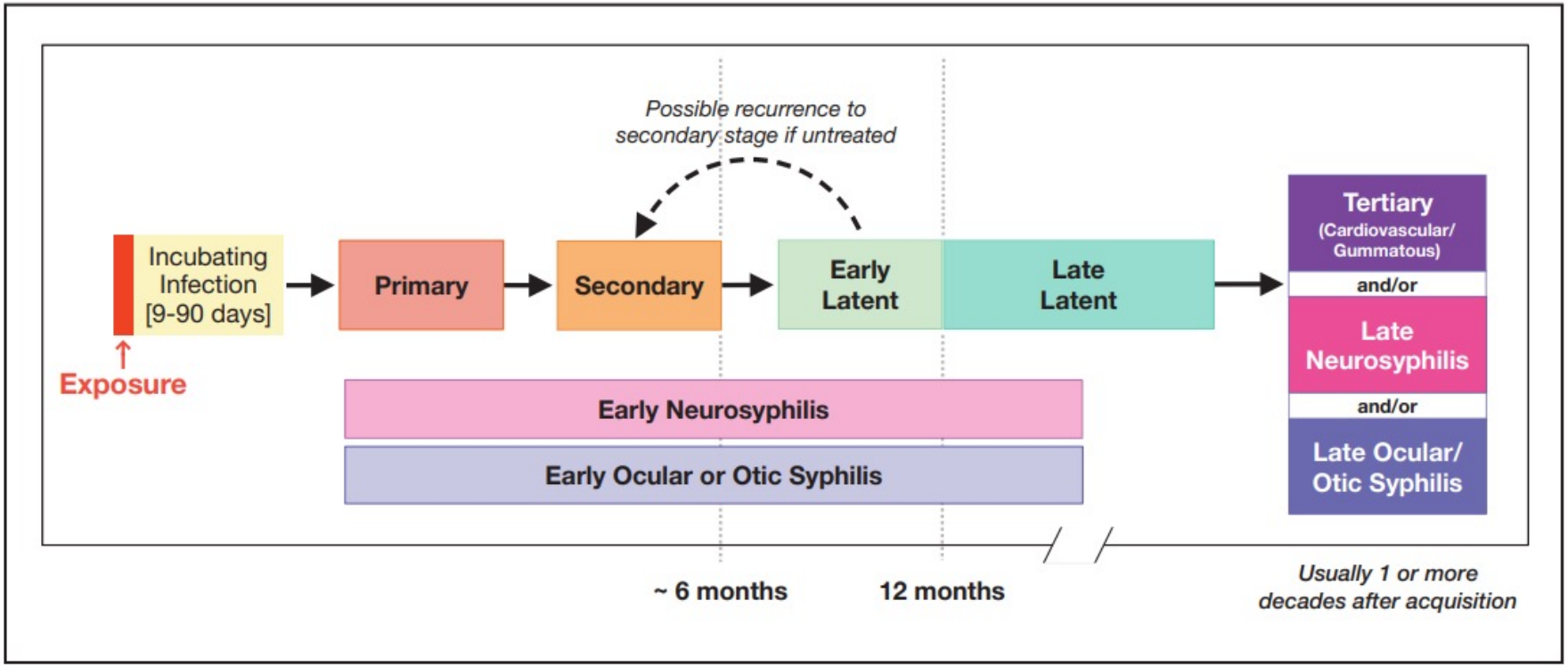
Syphilis

- **Sexual** (horizontal) and vertical transmission
- Average incubation period is **21 days** (can range from 10-90 days)
- **Four stages**
  - Primary
  - Secondary
  - Early (non-primary, non-secondary)
  - Unknown duration or late

The Natural History of Untreated Syphilis



Primary Syphilis

- **A single chancre** marks the onset of primary syphilis (can be multiple)
- **Usually firm, round, and painless** Located where syphilis enters the body
- Can appear in **difficult to notice** locations (anus, vagina)
- **Lasts 3 to 6 weeks** and heals regardless of whether a person receives treatment
- **Will progress** if untreated to secondary stage

In 40 % of the Cases the lesions may be multiple and painful

The Diagnosis, Management and Prevention of Syphilis (nycptc.org)

Secondary Syphilis

- **Skin rashes** and/or mucous membrane lesions (in the mouth, vagina or anus)
  - Usually does not itch, may appear as rough, red, brown spots
- **May be accompanied** by fever, swollen lymph nodes, sore throat, hair loss, aches and pains
- **Resolves** regardless of whether a person receives treatment
- **Will progress** if untreated to the latent and possible tertiary stage

The Diagnosis, Management and Prevention of Syphilis (nycptc.org)

Latent Syphilis

Latent (hidden) stage of syphilis

- When there are no visible signs or symptoms of syphilis

Early latent syphilis

- Where infection occurs **within the past 12 months**

Late latent syphilis

- **Is** where infection occurs **more than 12 months ago**

Latent syphilis of unknown duration

- When there is **not enough evidence** to confirm if initial infection was within the previous 12 months

Tertiary Syphilis

- Rare, develops in a subset of untreated syphilis infections
- Appears 10-30 years after infection, can be fatal
- Can affect multiple organ systems including brain, nerves, heart, blood vessels, eyes, liver, bones, joints

https://www.cdc.gov/std/statistics/2019/case-definitions.htm)

https://phil.cdc.gov/Details.aspx?pid=17837

Neurologic Manifestations of Syphilis

- **Can occur at any stage**

Neurosyphilis (Nervous System)	**Ocular Syphilis** (Visual System)	**Otosyphilis** (Auditory/Vestibular System)
- Severe headache - Trouble with muscle movements - Paralysis - Numbness - Altered mental status	- Eye pain or redness - Floating spots in field of vision - Sensitivity to light - Can lead to permanent blindness	- Ringing in ears (tinnitus) - Balance difficulties - Vertigo - Can lead to permanent hearing loss

Congenital Syphilis Transmission

How	• Transplacental during maternal spirochetemia • Direct contact with an infectious lesion during birth • Not transferred into breast milk
When during gestation?	• At any time during gestation with increasing frequency as gestation advances.
Transmission according to syphilis stage:	• Primary or secondary syphilis: **60% to 90%** • Early latent: **40%** • Late latent syphilis: **10%**

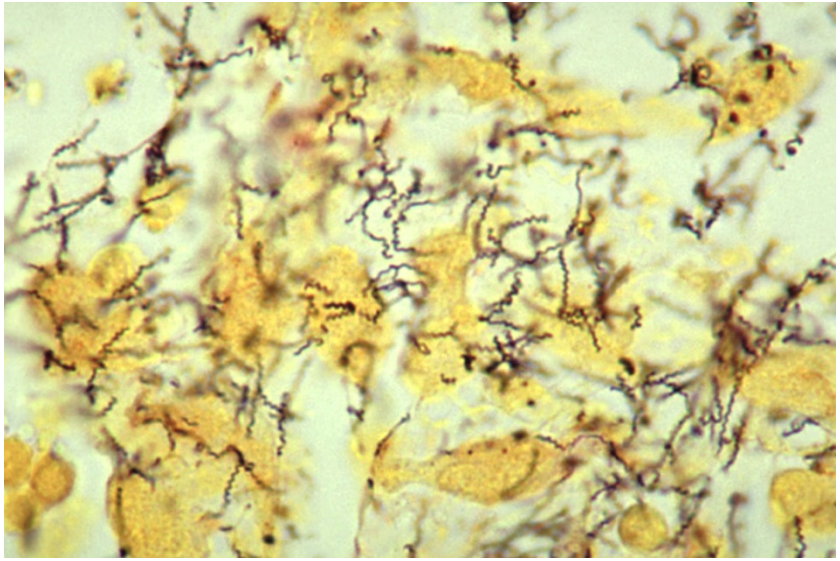
N Engl J Med. 1952;247(2):48.

Clinical Manifestations of Congenital Syphilis (CS)

https://www.cdc.gov/ncbddd/birthdefects/surveillancemanual/quick-reference-handbook/congenital-syphilis.html

The Beginning of Laboratory Diagnosis of Syphilis: Direct Detection of Organisms using Microscopy

1905 T. pallidum, was first observed in diseased tissues by German zoologist Fritz Schaudinn



1906 Karl Landsteiner, used dark-field microscopy to detect syphilitic treponemes in infected specimens

https://asm.org/articles/2019/june/revisiting-the-great-imitator,-part-i-the-origin-a

Non-Treponemal Testing

In 1906 the Wassermann, Neisser and Bruck

- Developed the first serologic test for the diagnosis of syphilis
- Complement Fixation

In 1907 Landsteiner dilucidated the antibodies

- "Reagins" were directed against a cardiolipin found tissue

In 1922 a flocculation test was developed

- Led to development of RPR and VDRL

In 2018 A study found that *T. pallidum* contained a cardiolipin

- The increase in the anti cardiolipin antibody production are the combined effects of both the *T. pallidum* cardiolipin antigen and the damaged host-cell cardiolipin antigen during syphilis infection.

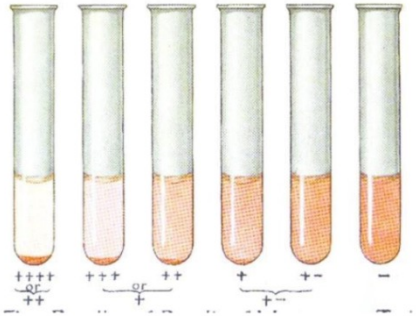
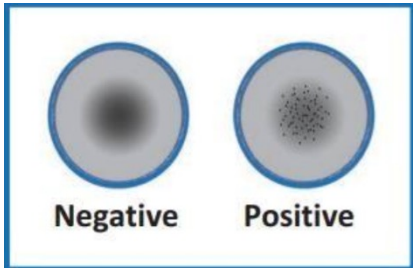


Figure 5. Wasserman test [19]



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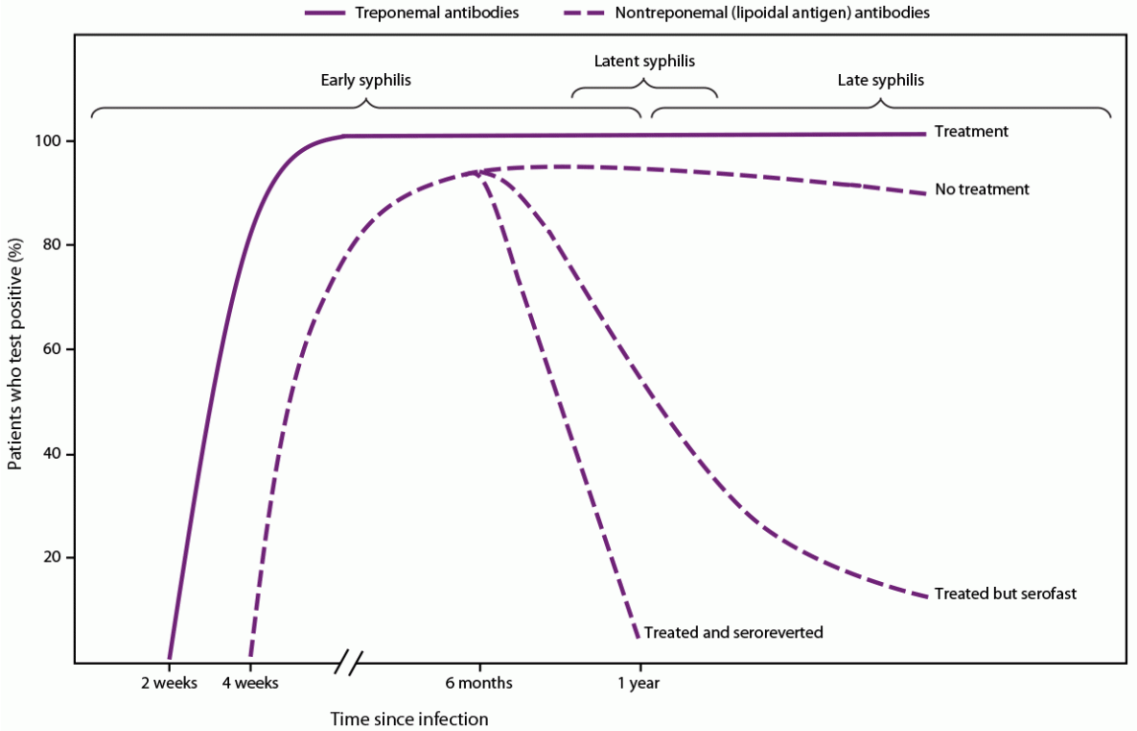
Serologic Tests for Syphilis

Nontreponemal	Treponemal
VDRL, RPR	CIE, EIA, FTA-ABS, TP-PA, rapid tests
Measure IgG and IgM to cardiolipin-cholesterol-lecithin antigen	Measure IgG and IgM to Treponemal antigens
Qualitative or quantitative	Qualitative
Used as a screening test	More specific
Titer used to follow response to therapy	Generally, remain reactive for life

CIE: Chemiluminescent assay, Enzyme Immunoassay, FTA-ABS, Treponema Pallidum Particle-Agglutination Essay

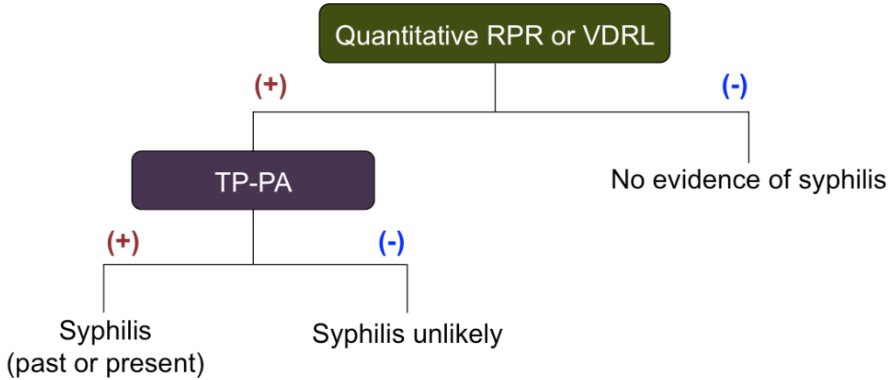
Serologic response to infection with *Treponema pallidum*, the causative agent of syphilis



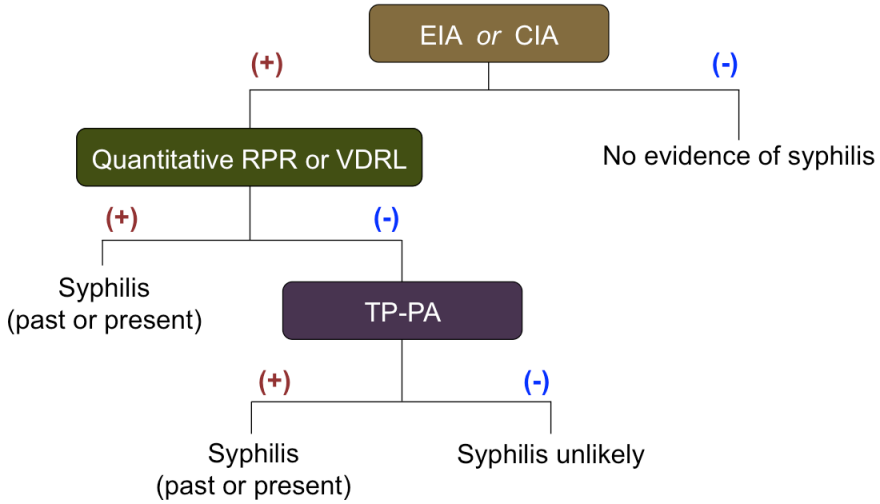
CDC Laboratory Recommendations for Syphilis Testing, United States, 2024

Syphilis testing algorithms

Traditional Sequence



Reverse Sequence

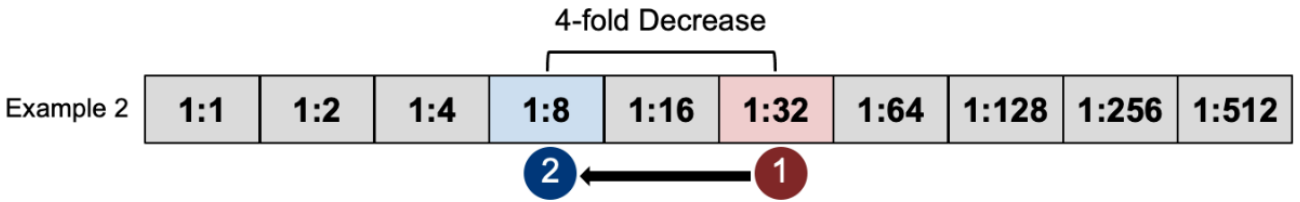


Treatment

STAGE		
Primary & Secondary, Early non-primary, non secondary	**Late Latent/or Unknown Duration**	**Neurosyphilis, ocular and otosyphilis**
Benzathine penicillin 2.4 million units IM in **a single dose** Doxycycline 100mg BID **for 14 days**	Benzathine penicillin 2.4 million units total administered as **3 doses** of 2.4 million units IM each **at 1-week intervals** Doxycycline 100mg BID **for 28 days**	Aqueous crystalline penicillin G 18-24 million units per day, administered as 3-4 million units by IV **every 4 hours or continuous infusion for 10-14 days** Alternative: procaine penicillin G 2.4 million units IM 1x/day PLUS probenecid 500 mg orally 4x/day, **both for 10-14 days**

Follow-up testing

- **Adequate serologic response to treatment: ≥4-fold decline in nontreponemal titer**
  - Early Syphilis Primary/secondary/early latent: **within 12 months**
  - Late Syphilis: Late Latent, tertiary: **within 24 months**
  - Persons with HIV: **within 24 months**
- **Serofast** (lack of seroreversion):
  - Persistent nontreponemal titer after treatment



"Always Obtain RPR close or on the day of treatment"

IHS Screening Recommendations for Syphilis

1. **Offer annual syphilis testing for persons ages 13 and older**.
2. **Prescribe and administer Penicillin G Benzathine for every age and every stage of syphilis** infection in the absence of contraindications to therapy.
3. **Turn on the annual Electronic Health Record reminder at all sites**
    1. To facilitate testing for two years or until incidence rates decrease locally to baseline.
4. **Provide three-point syphilis testing for all pregnant people**
    1. At the first prenatal visit, the beginning of the third trimester, and delivery.
5. **Adoption of an HIV/Viral Hepatitis/STI testing bundle** at all sites

IHS Screening Recommendations for Syphilis

6. Adopt and provide Express STI testing services at all sites

7. Provide field testing outside hospitals and clinics

8. Provide field treatment for syphilis whenever necessary for adults diagnosed with syphilis and their partners.

9. Provide presumptive treatment of syphilis for anyone having signs or symptoms of syphilis or with known exposure to syphilis.

10. Offer and provide DoxyPEP to appropriate populations to prevent bacterial STIs, including syphilis.

Management of sex partners

- Partner A is diagnosed with primary, secondary, or early latent syphilis. If partner B had sexual contact with partner A:
  - < 90 days before the diagnosis of syphilis, then partner B **should be treated presumptively for early syphilis**, **even if serologic tests are negative**.
  - > 90 days before the diagnosis of syphilis, then partner B should be treated for early syphilis only if serologic tests are not available or follow-up is uncertain. If serologic tests are negative, no treatment is needed.

Case #1

A 34-year-old woman is screened for syphilis and has a positive Treponema pallidum-specific-EIA. RPR is nonreactive. Tests for HIV, Neisseria gonorrhoeae, and Chlamydia trachomatis are negative. She has no medical problems, takes no medications, and does not use illicit drugs. She has been sexually active with the same male partner for the past 3 years. She has no prior history of any STI, and has never been tested or treated for syphilis. She is asymptomatic and the physical examination is normal. **What is the most appropriate next step?**

A) Repeat both the EIA and the RPR

B) Send an alternative nontreponemal test

C) Send an alternative treponemal test

D) No further workup at this time

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Case #2

A 47-year-old gender nonbinary individual is clinically diagnosed with secondary syphilis and treated with benzathine penicillin G 2.4 million units intramuscular (IM) in a single dose. Their lab test results return with a positive syphilis enzyme immunoassay (EIA) and a positive Rapid Plasma Reagin (RPR) at a titer of 1:256. Their HIV-1/2 antigen-antibody test is negative. At a follow-up visit in 6 months, no new symptoms have developed and RPR testing reveals a titer of 1:32.

What would you recommend as the next course of action regarding management of syphilis for this individual?

A) Treat with a single dose of intramuscular benzathine penicillin G 2.4 million units

B) Treat with 3 weekly doses of benzathine penicillin 2.4 million units

C) Perform a lumbar puncture and cerebrospinal fluid analysis

D) No further treatment is necessary at this time, but continue monitoring

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References

- CDC STD 2021 Treatment Guideline: https://www.cdc.gov/std/treatment-guidelines/default.htm
- STD Prevention Training Centers: https://www.cdc.gov/std/projects/nnptc.htm
- STD online self-study: https://www.std.uw.edu/
- CDC self-study: http://www.cdc.gov/std/training/std101/home.htm
- USPS Task Force: https://www.uspreventiveservicestaskforce.org/uspstf/

Resources

- National Clinician Consultation Center http://nccc.ucsf.edu/
  - HIV Management
  - Perinatal HIV
  - HIV PrEP
  - HIV PEP line
  - HCV Management
  - Substance Use Management
- Present on ECHO
- https://hsc.unm.edu/scaetc/programs-services/echo.html
- AETC National HIV Curriculum https://aidsetc.org/nhc
- AETC National Coordinating Resource Center https://targethiv.org/library/aetc-national-coordinating-resource-center-0
- HIVMA Resource Directory https://www.hivma.org/globalassets/ektron-import/hivma/hivma-resource-directory.pdf
- Additional trainings scaetcecho@salud.unm.edu
- www.scaetc.org

IHS/Tribal Resources

- Sexually Transmitted Infections (STI) Initiative: STI Toolkit.https://www.ihs.gov/sites/nptc/themes/responsive2017/display_objects/documents/sti/Express-STI-Guide.pdf

- https://www.indiancountryecho.org/resource-hubs/syphilis-resources/ The STOP SYPHILIS campaign offers free materials, including print materials, social media posts, and short educational videos.

- Go to www.stopsyphilis.org For questions about field testing and treatment policies and procedures, contact Tina Tah, Public Health Nursing Consultant, by e-mail at tina.tah@ihs.gov