SYPHILIS

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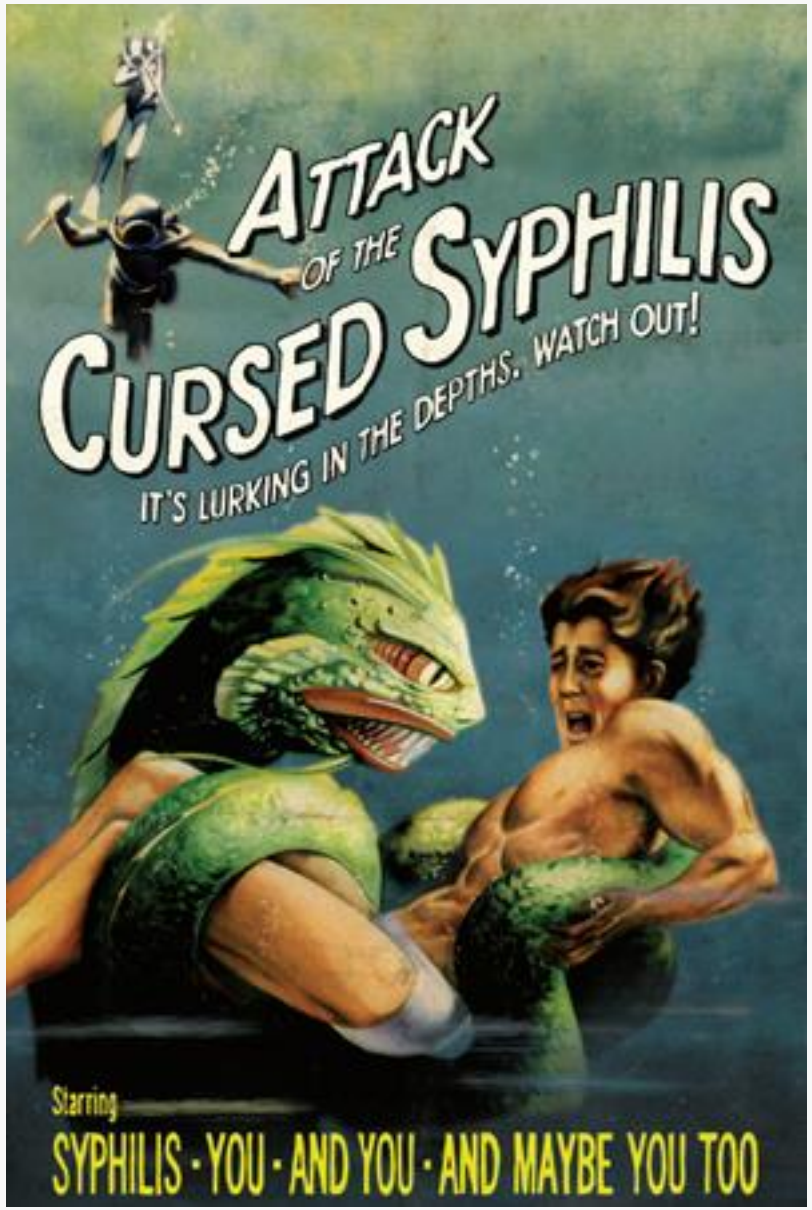
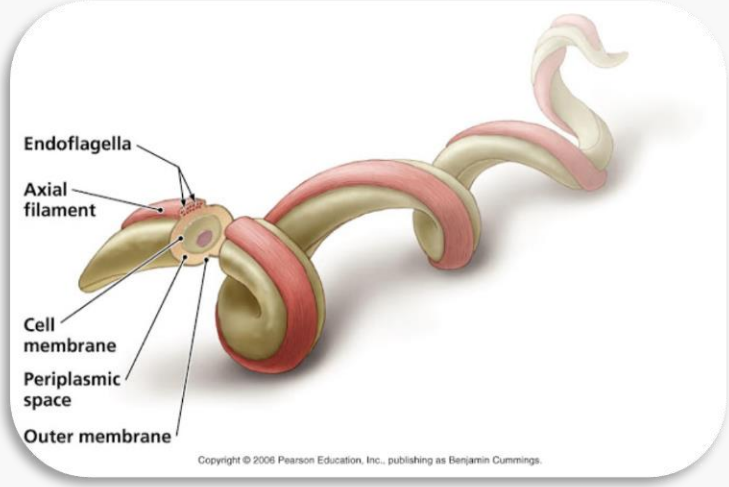
OBJECTIVES

- What/When/Why/Who?
- Natural history of disease
- Tests
- Things to remember
- Treatment
- Considerations
- Monitoring

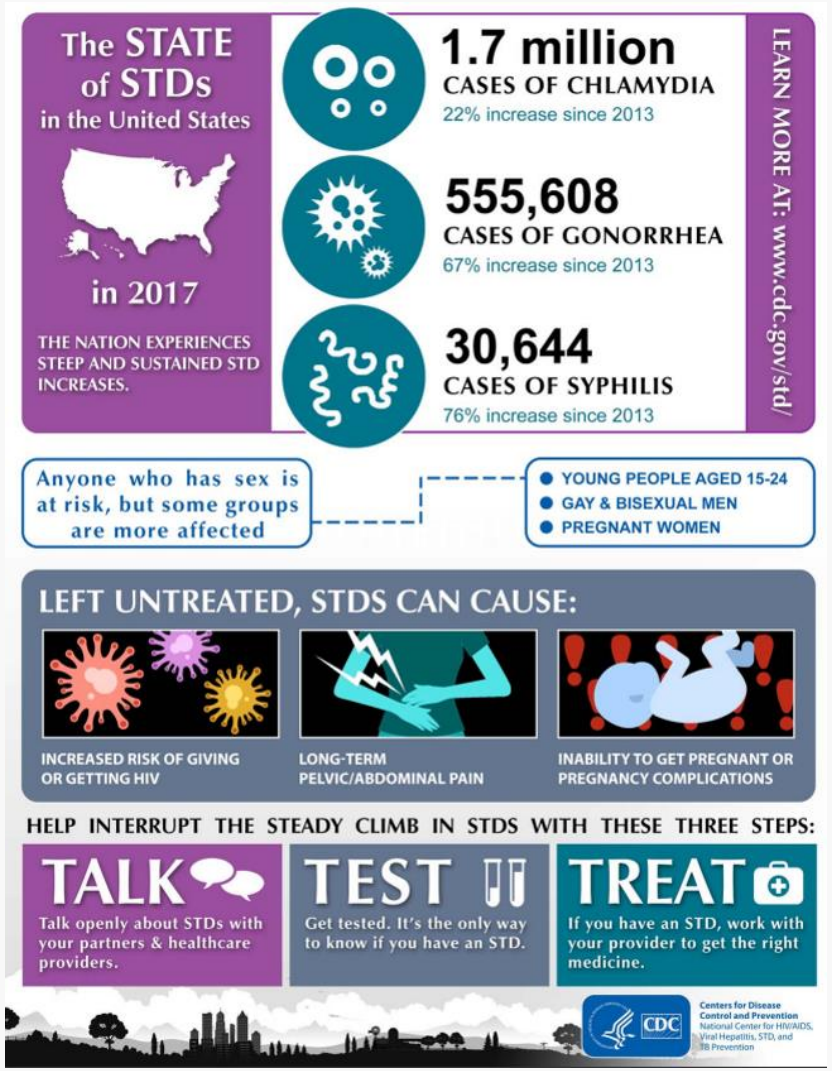


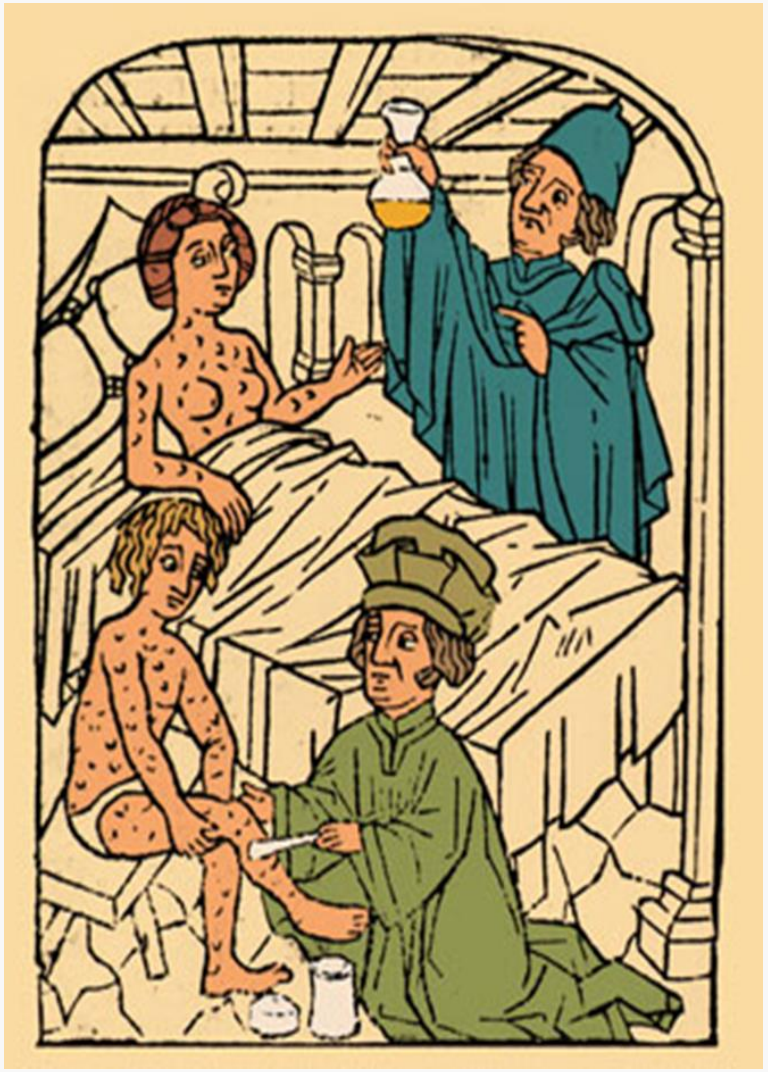
WHAT IS SYPHILIS?

- Syphilis is a systemic, sexually transmitted disease (STD) caused by the *Treponema pallidum* bacterium.
- Two means of syphilis transmission: sexual and vertical
  - Sexual: direct contact with chancres or with mucous membrane lesions
  - Vertical: From infected mother to her unborn baby via the bloodstream.



WHY THIS TALK?





WHY THIS TALK?

- During 2019:
  - There were 129,813 reported new diagnoses of syphilis (all stages), compared to 37,968 new diagnoses of HIV infection in 2018 and 616,392 cases of gonorrhea in 2019.
  - The majority of P&S syphilis cases occurred among gay, bisexual, and MSM.
  - 1,870 cases of congenital syphilis were reported, compared to an estimated 65 cases of perinatal HIV infection during 2018.
    - ~106 cases per 100,000 live births – African Americans
    - ~65 cases per 100,000 live births – Latinos
    - ~22 cases per 100,000 live births – Caucasians

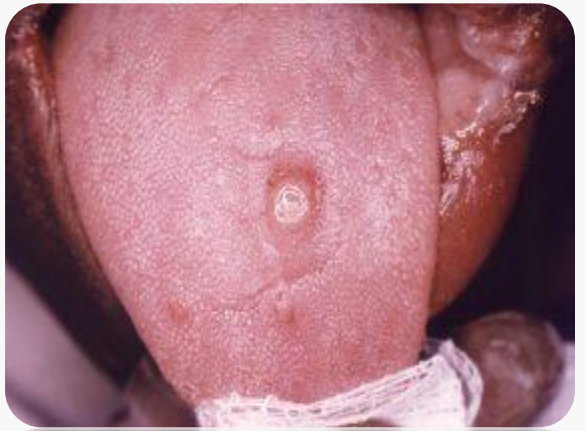
WHO DO WE SCREEN?

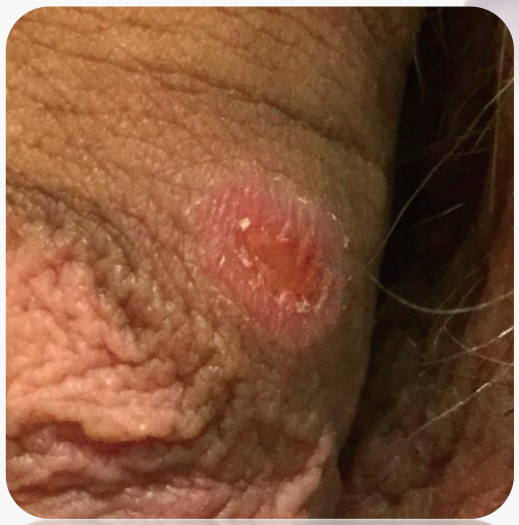
TEST PREGNANT WOMEN:	TEST MSM PATIENTS:
✓ at first prenatal visit	✓ annually if sexually active
✓ at beginning of 3rd trimester and at delivery, if at risk	✓ more frequently if at risk

NATURAL HISTORY

INCUBATION PHASE AND PRIMARY SYPHILIS

- Incubation phase
  - 3 - 90 days
  - Asymptomatic
- Primary
  - Chancre
  - Painless
  - *Usually* at site of exposure
  - Can heal without treatment
  - Highly infectious

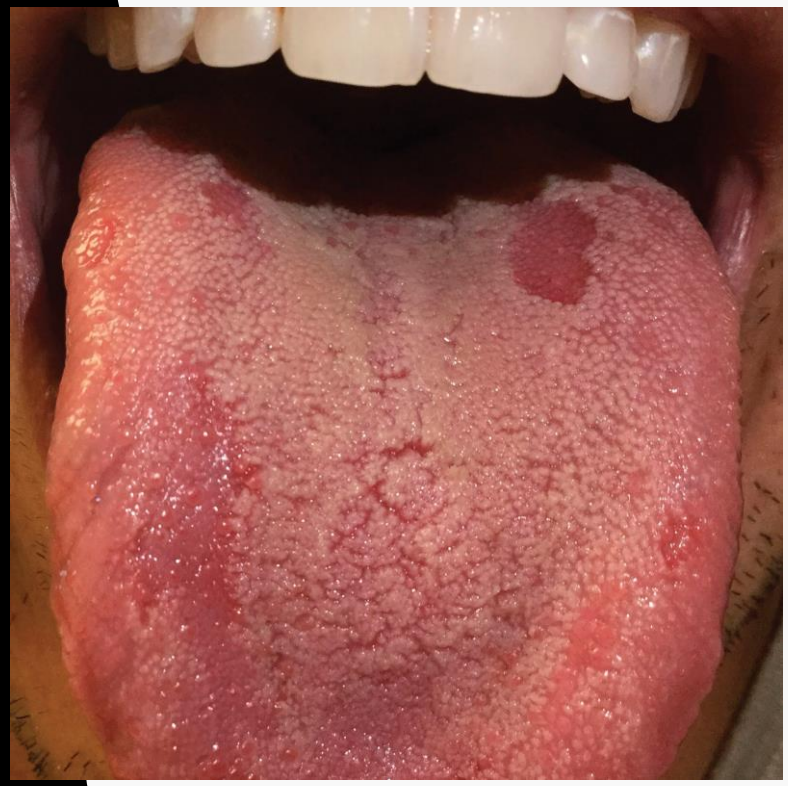


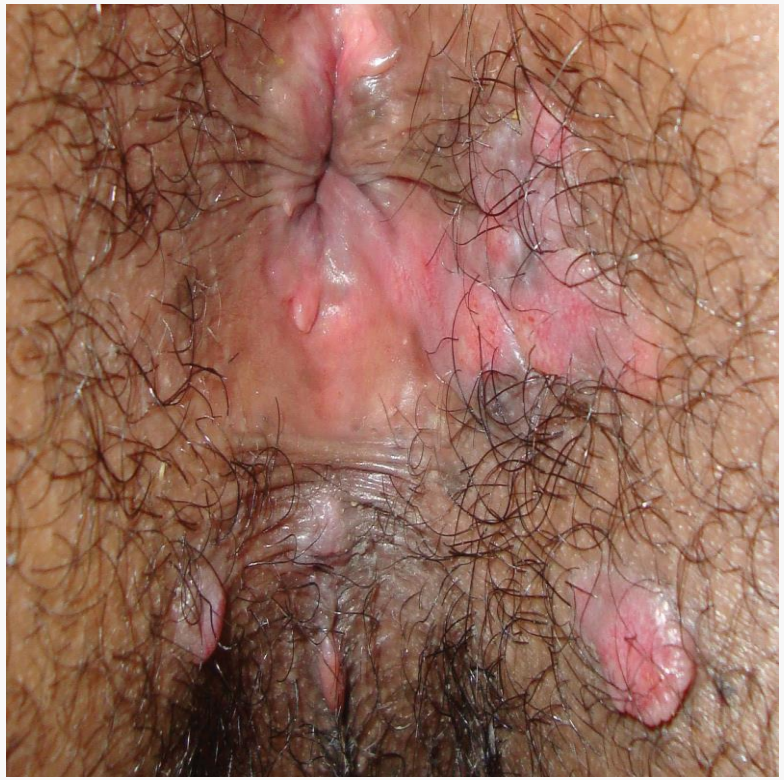


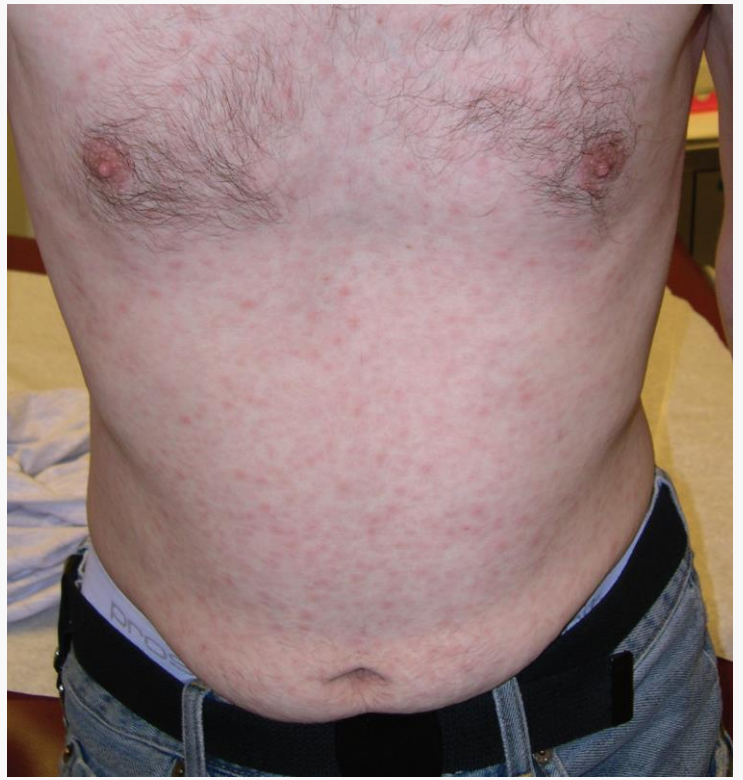
SECONDARY SYPHILIS

- Diffuse maculopapular rash – trunk, extremities, palms and soles
- Start: 3 weeks - 6 months after primary infection
- Duration: 2 weeks to 3 months
- Systemic symptoms
- 25% have: condyloma lata or tongue mucous patches
- Highly infectious

SECONDARY SYPHILIS



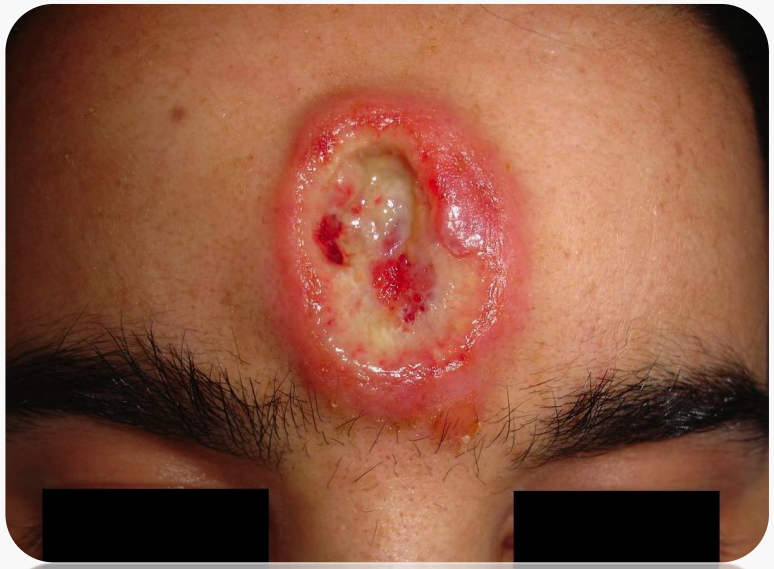




LATENT SYPHILIS

- This stage is characterized by the absence of any signs or symptoms of infection, but associated with positive serologic tests.
- Early
  - Reactive non treponemal and treponemal tests within 1 year of infection
  - P & S symptoms can re-occur → infectious
- Late Latent or Latent of Unknown Duration
  - Reactive non treponemal and treponemal tests more than 1 year after infection
  - Latent: potentially infectious

TERTIARY SYPHILIS = LATE SYPHILIS



- Progressive
- Not infectious
- Classic late presentations:
  - Dementia (general paresis)
  - Tabes dorsalis
- Aortitis and gummatous syphilis (nodular lesions more commonly present in the skin and bones).

NEUROSYPHILIS

- ANY stage
- Early
    - Usually after few years of infection, but can occur during P & S.
    - Manifests as meningitis (CN VI – VIII) or meningovascular syphilis (stroke-like).
- Late
    - Usually 10 – 30 years after onset, at the late latent stage.
    - Symptoms: paresis, dementia, muscle weakness, paralysis or tabes dorsalis.

Table 2 CSF profiles in different neurosyphilis stages

Neurosyphilis stage	Clinical presentation	Signs/symptoms	Onset	CSF leukocytes	CSF protein, mg/dL	Serum RPR	CSF VDRL
Early	Asymptomatic	None	Primary or secondary syphilis	>5	>45	Likely positive[a]	Positive
	Meningitis, ocular (+HIV)	Meningeal symptoms, ocular, involvement of ≥1 cranial nerve	Typically within 1 year	200-400	100-200	Positive	Positive; may be negative in HIV+ patients
Early/late	Meningovascular	Headaches, dizziness, personality changes; stroke-like symptoms[b]	1-7 years (pre-antibiotic era)	10-100	100-200	Positive	Positive (almost always)
Late	General paresis	Progressive dementia leading to death in 2.5 years; dysarthria, facial and limb hypotonia, tremors, abnormal reflexes	10-25 years	25-75	50-100	Positive	Positive
	Tabes dorsalis	Sensory ataxia and lancinating pain; Argyll-Robertson pupil[c]; absent lower extremity reflexes, impaired vibratory and position sense; less common: paresthesias and epigastric pain	20 years	10-50 and occasionally normal	45-75	Typically positive, but not always	Nonreactive up to 25%

Abbreviations: RPR = rapid plasma reagin; VDRL = Venereal Disease Research Laboratory.

[a] Unless recent infection.

[b] Middle cerebral artery most commonly affected.

[c] Pupils respond to accommodation but not to light.

OCULAR SYPHILIS

- ANY stage
- Symptoms: blurry vision, vision loss, pain, redness.
- May present as uveitis, retinitis, and optic neuritis.
- Do not delay treatment while waiting for results due to risk of blindness.

CONGENITAL SYPHILIS

- All pregnant women during 1st trimester
- All HIGH RISK pregnant women during:
  - 1st trimester
  - 28 weeks
  - At delivery
- When diagnosed, need immediate treatment
  - Treatment ≥30 days prior to delivery is likely to prevent cases of congenital syphilis (may not prevent stillbirth or CS in a gravely infected fetus).
- All women who deliver a stillborn (after 20 weeks) should be tested at time of delivery.

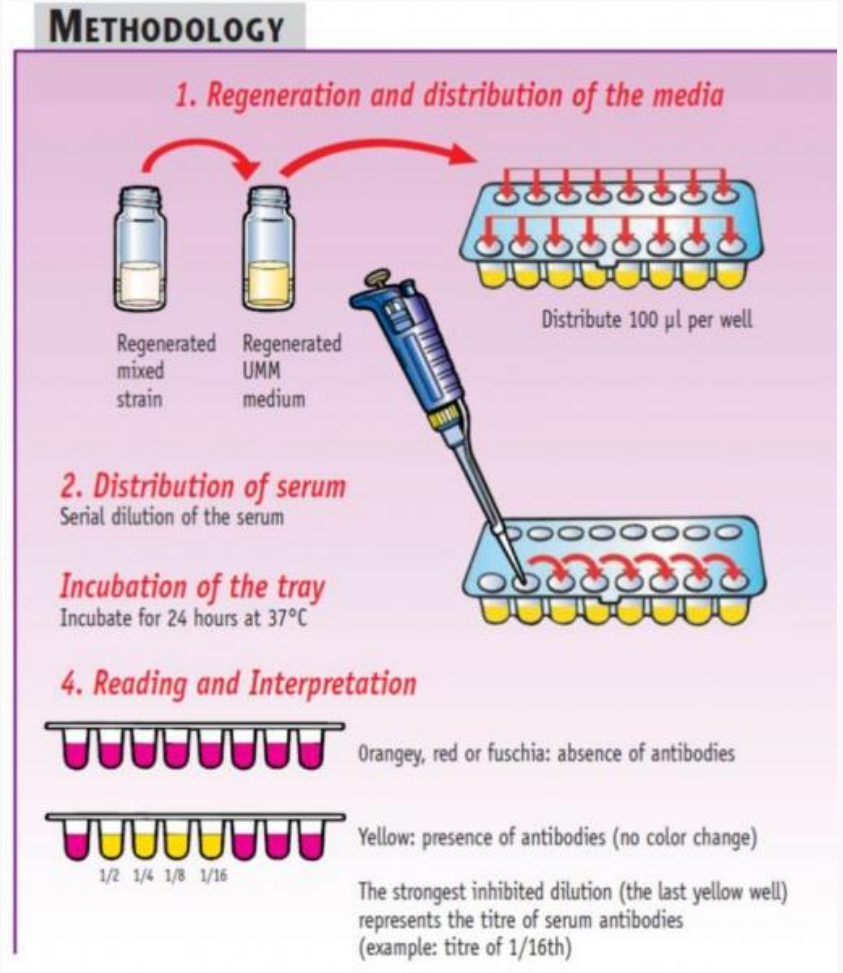
TESTS

DIRECT DETECTION METHODS

- Dark-field microscopy, PCR, and direct fluorescent antibody testing for *T pallidum*.
- In some cases, these tests may allow the diagnosis of syphilis prior to a serologic response.
- Most clinical centers do not have access to these methods and must rely on clinical manifestations and serologic testing.

SEROLOGIC TESTS

- 2 different types based on the type of antigen the antibodies are directed against:
  - Treponemal tests detect antibody to *T pallidum* proteins.
  - Nontreponemal tests detect antibodies directed against lipoidal antigens, damaged host cells, and possibly from treponemes.
- Both tests are used to confirm the infection and determine whether the disease is active.



TREPONEMAL TESTS

- These are:
  - Microhemagglutination assay for *T pallidum*
  - *T pallidum* particle agglutination
  - *T pallidum* hemagglutination assay
  - Fluorescent treponemal antibody absorbed (FTA-ABS) test
  - Chemoluminescence immunoassays
  - Enzyme immunoassays that detect Treponemal antibodies.
- Reported as reactive or nonreactive.
- Reactivity to a treponemal test implies infection, but it does not determine whether the infection is recent or remote or whether it has been treated or not.
- False-positive results with this type of test can occur and may be due to other infections or other inflammatory diseases, such as systemic lupus erythematosus.

NONTREPONEMAL TESTS

- Three types:
  - Rapid plasma reagin (RPR)
  - Venereal Disease Research Laboratory (VDRL) test
  - Toluidine red unheated serum test
- These tests usually react with immunoglobulin M and immunoglobulin G antibodies.
- The results of these tests are semi quantitative.
- Seroconversion occurs around 3 weeks, but can take up to 6 weeks.
  - Consequently, patients can present with primary syphilis and have initially negative serologic tests.
- Titers will normally decline over time, often to undetectable titers after successful treatment.
- False-positive nontreponemal tests have been described in systemic infections such as tuberculosis, rickettsial diseases, and endocarditis, and also during pregnancy.

PARADIGM SHIFT

- Traditionally: a positive nontreponemal was followed by a confirmatory treponemal test.
- However, automated and rapid treponemal testing has allowed the algorithm to be reversed.
- Now: accepted to order a treponemal test as the initial diagnostic tool.
  - Cost effective.
  - Not usually available.

INTERPRETATION OF REACTIVE TESTS

Table 1

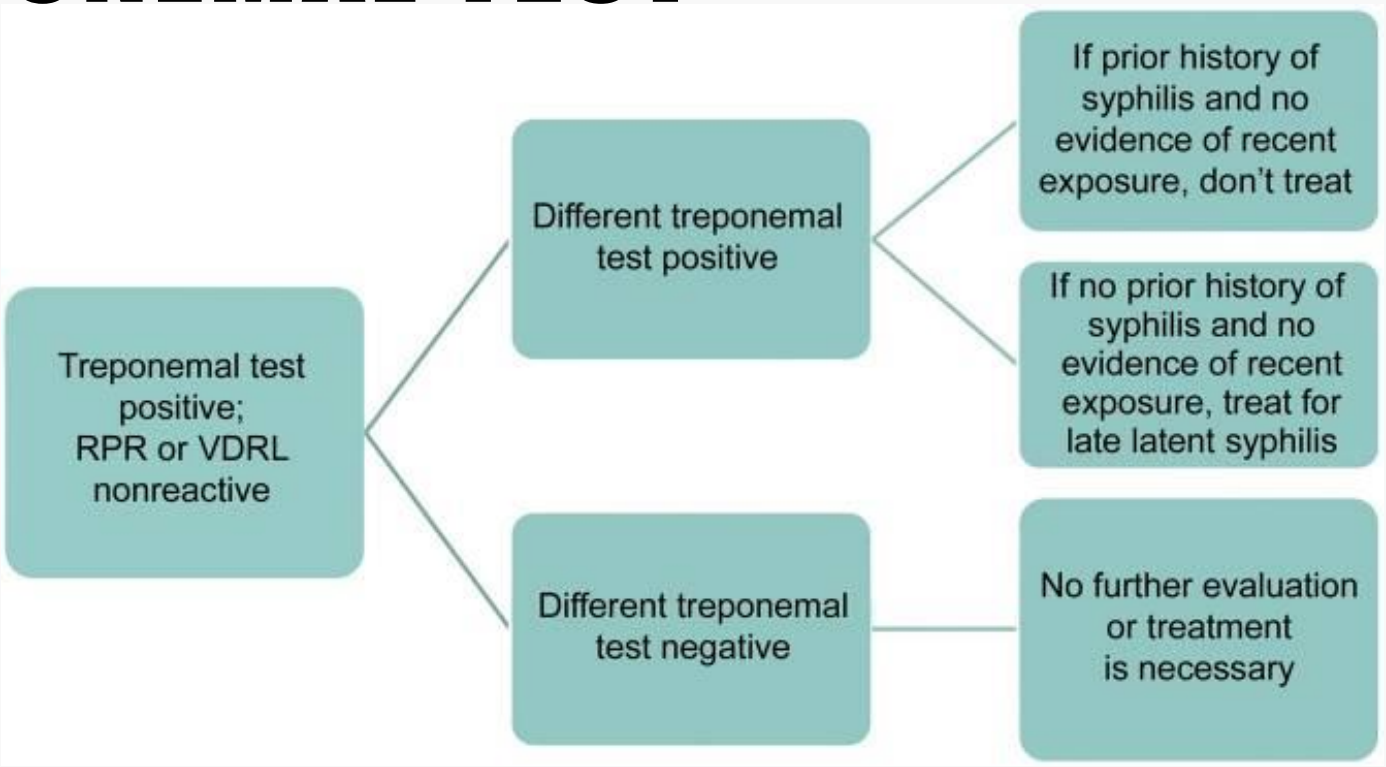
Interpretation of serologic tests in syphilis

Table 1 Interpretation of serologic tests in syphilis

Treponemal test	Nontreponemal test	Possible interpretations
Nonreactive	Nonreactive[a]	1. Absence of syphilis
		2. Very early syphilis before seroconversion
Reactive[b]	Nonreactive	1. Prior treated syphilis
		2. Untreated syphilis
		3. False-positive treponemal test[c]
Reactive	Reactive with or without a measurable titer	1. Active syphilis
		2. Recently treated syphilis with nontreponemal titers that have not yet become nonreactive
		3. Treated syphilis with persistent titers[d]
Nonreactive	Reactive[a]	1. False-positive nontreponemal test

[a] Usually not performed if the initial treponemal test is negative.
[b] By 2 different methods if the nontreponemal test is nonreactive.
[c] Commonly seen among African immigrants with previous exposure to endemic treponematoses.
[d] Successful treatment is usually considered with a fourfold decline in titers (e.g., from 1:32 to 1:8).

CDC ALGORITHM FOR POSITIVE TREPONEMAL TEST AND NEGATIVE NON-TREPONEMAL TEST



CSF EXAMINATION

- When:
  - Sustained (>2 weeks) fourfold increase or greater in titer is observed.
  - Initially high titer (≥1:32) fails to decline at least fourfold within 12–24 months of therapy.
  - Signs or symptoms attributable to (neuro) syphilis develop.

THINGS TO REMEMBER…

- Titers are used to monitor treatment success.
- May have false negative RPR.
- All patients with positive syphilis serologic tests & a presumptive diagnosis of syphilis need staging to determine the treatment regimen.

TREATMENT

- **Primary, Secondary, or Early Latent(<1 year)**
  - Benzathine penicillin G 2.4 million unitsIM in a single dose

- **Late Latent (>1 year), Latent Syphilis of Unknown Duration, or Tertiary Syphilis with Normal CSF Examination**
  - Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals

- **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
  - Additional doses of benzathine penicillin are not indicated in patients with HIV infection.
  - Additional doses of penicillin in pregnant women with early syphilis may be indicted if evidence of fetal syphilis on ultrasound.

TREATMENT ALTERNATIVES

Table 3 List of syphilis treatment options per disease stage

Disease stage	Primary treatment	Alternative treatment
Primary syphilis	Benz PCN 2.4 million units IM × 1 dose	Doxycycline 100 mg PO BID × 14 days
Secondary syphilis	Benz PCN 2.4 million units IM × 1 dose	Doxycycline 100 mg PO BID × 14 days
Early latent syphilis	Benz PCN 2.4 million units IM × 1 dose	Doxycycline 100 mg PO BID × 14 days
Late latent syphilis	Benz PCN 2.4 million units IM weekly × 3 doses	Doxycycline 100 mg PO BID × 28 days
Cardiovascular and gummatous syphilis	Benz PCN 2.4 million units IM weekly × 3 doses	Consult with infectious diseases physician recommended
Neurosyphilis	PCN G 18-24 million units IV daily × 10-14 days	Procaine PCN 2.4 million units IM daily + probenecid 500 mg PO QID for 10-14 days

CONSIDERATIONS

- Jarisch-Herxheimer Reaction
  - Acute febrile reaction with or without headache, myalgia, fever, and other symptoms within the first 24 hours after the initiation of any therapy for syphilis.
  - Most frequent among persons who have early syphilis, presumably because bacterial burdens are higher during these stages.

- Management of Sex Partners
  - Transmission: muco cutaneous syphilitic lesions
  - High risk partners are those who have had sex within:
    - 3 months plus the duration of symptoms for persons who receive a diagnosis of primary syphilis
    - 6 months plus duration of symptoms for those with secondary syphilis
    - 1 year for persons with early latent syphilis.
  - Who do we treat?
    - Within 90 days and negative serologic testing: treat
    - >90 days and:
      - Negative serologic tests: no treatment
      - Positive serologic tests: treat base on staging.

CONSIDERATIONS

- Treatment failure criteria:
  - Persistent signs or symptoms or recurrence.
  - At least a fourfold increase in nontreponemal test titer persisting for >2 weeks.
  - Re-treat, re-test for HIV infection.
  - DDx: re-infection.

CLINICAL AND SEROLOGICAL MONITORING

- P & S
  - At 6 and 12 months after treatment.
  - Retreatment: benzathine penicillin G 2.4 million units IM q week x 3.

- Latent Syphilis
  - At 6, 12, and 24 months after treatment.

- Neurosyphilis
  - If CSF pleocytosis was present initially, a CSF examination should be repeated every 6 months until the cell count is normal.

MONITORING HIV POSITIVE PATIENTS

- Primary and Secondary Syphilis among Persons with HIV Infection
  - Clinical and serological evaluations at: 3, 6, 9, 12, and 24 months after therapy.
  - Treatment failure: management same as HIV-negative.

- Latent Syphilis among Persons with HIV Infection
  - Clinical and serological evaluations at: 6, 12, 18, and 24 months after therapy.
  - Treatment failure: need CSF examination.

- Neurosyphilis among Persons with HIV Infection
  - Same as HIV-negative persons with neurosyphilis.

RESOURCES

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