Yale SCHOOL OF MEDICINE

Syphilis 101
CT STI Clinical Management Series

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Dept of Internal Medicine/Infectious Diseases

May 2, 2024

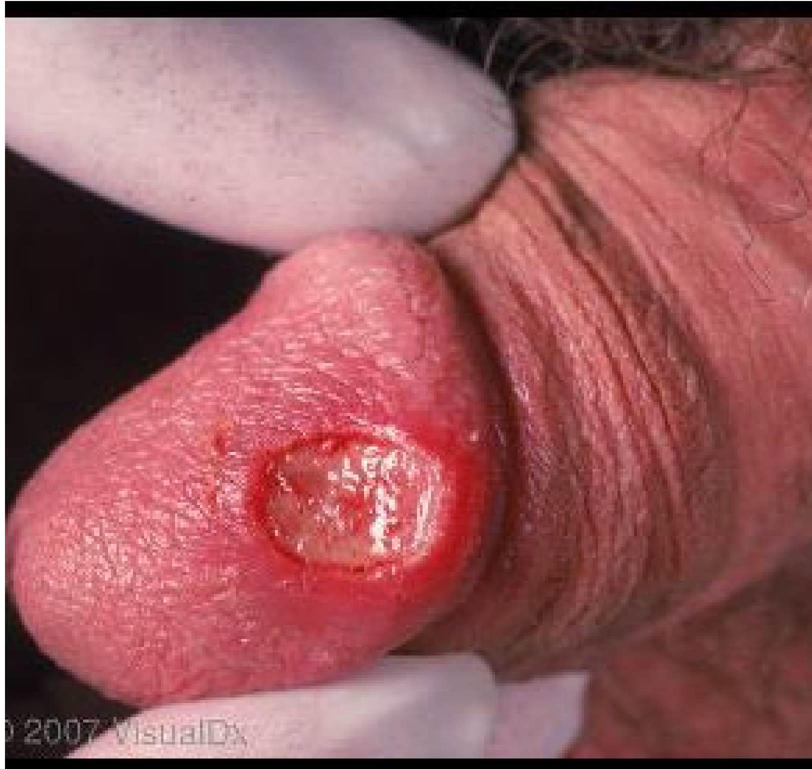
Disclosures

Dana W Dunne, MD, MHS: Nothing to disclose

Learning Objectives

Distinguish	between stages of syphilis based on clinical characteristics
Understand and apply	testing algorithms and interpretation of currently available syphilis tests
Apply	knowledge of syphilis staging to appropriate treatment recommendations

Case-30 year old man presents with 7 days of a painless ulcer on his glans penis.



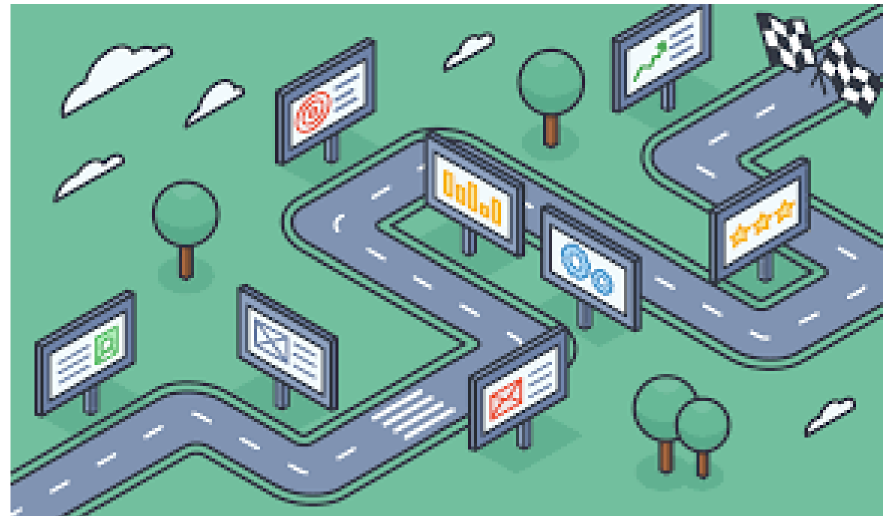
Differential?

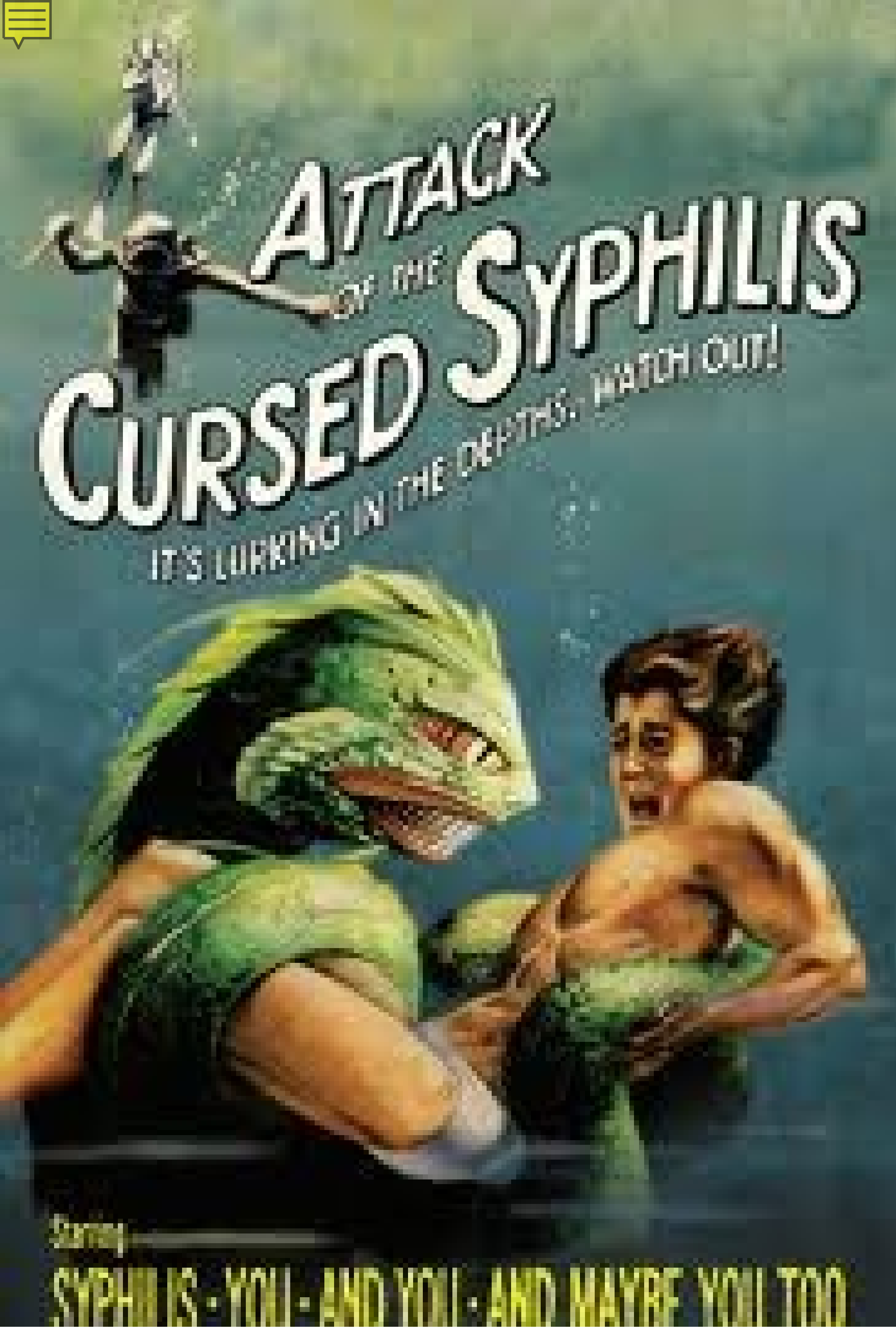
Diagnostics?

Decision to tx?

Roadmap

- General Points
- Clinical
- Diagnosis- Traditional and Reverse algorithms
- Treatment
- Reporting





Transmission and Incubation

- Transmission-
  - Sexual
  - Vertical
  - Kissing
  - Blood transfusion
  - Inoculation
- Infectious= primary, secondary (when lesions/rash present)
- Incubation- 10-90 days; average 21 days.

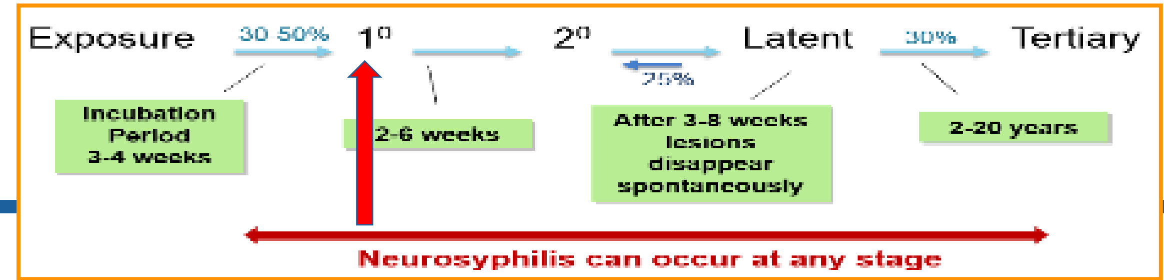
Syphilis- clinical

- **Early** syphilis
  - Primary
  - Secondary
  - Early Latent

- **Late** syphilis
  - Late latent
  - Tertiary syphilis
    - Cardiovascular
    - Neurologic
    - Gummatous

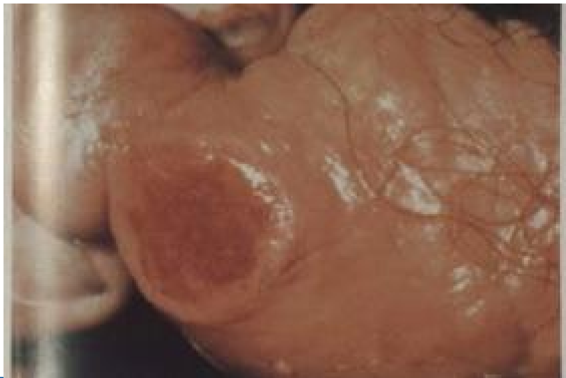
PHOTO ALERT!

Primary Syphilis

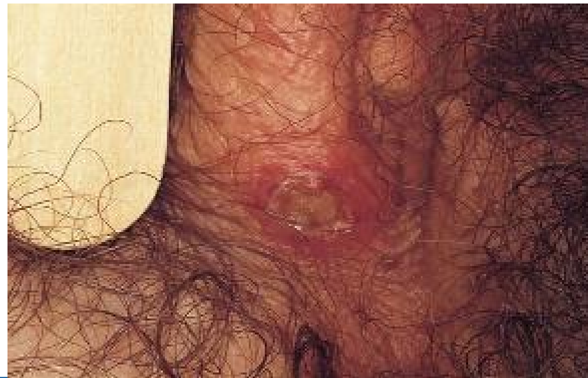


- Incubation- 10-90 days
- Papule at exposed site which ulcerates= **Chancre**
- **Painless** chancre with regional painless lymphadenopathy
- DDx- HSV, chancroid, LGV, donovanosis, trauma, squamous cell cancer, furuncle.

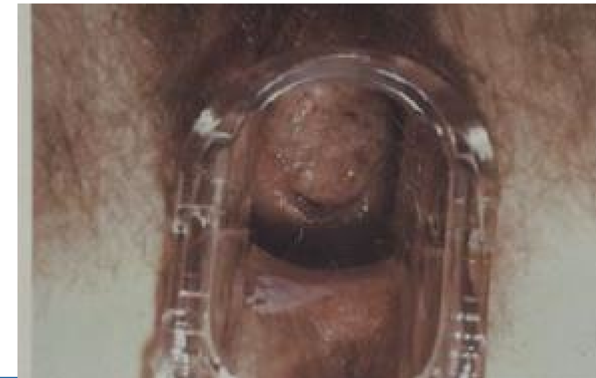
penile

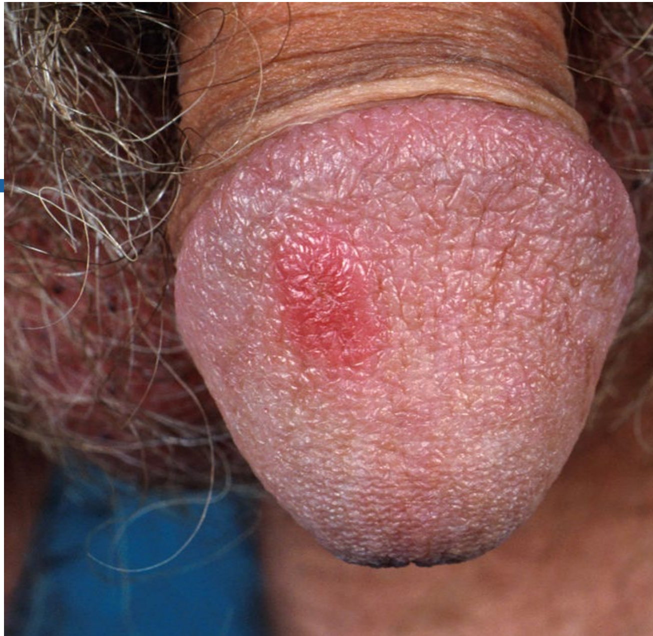
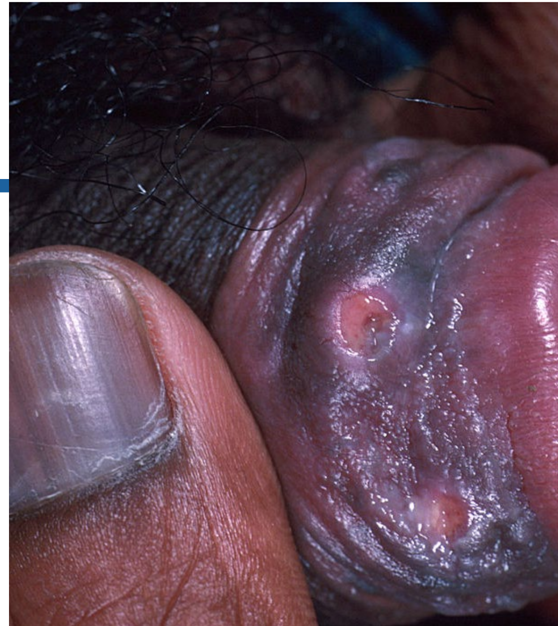
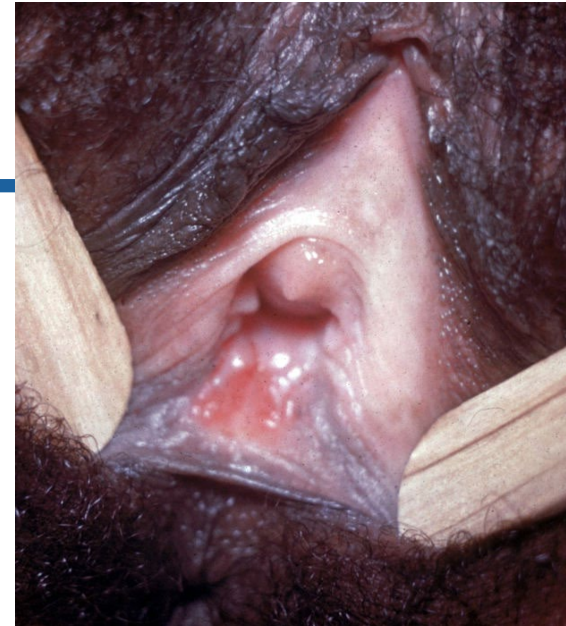
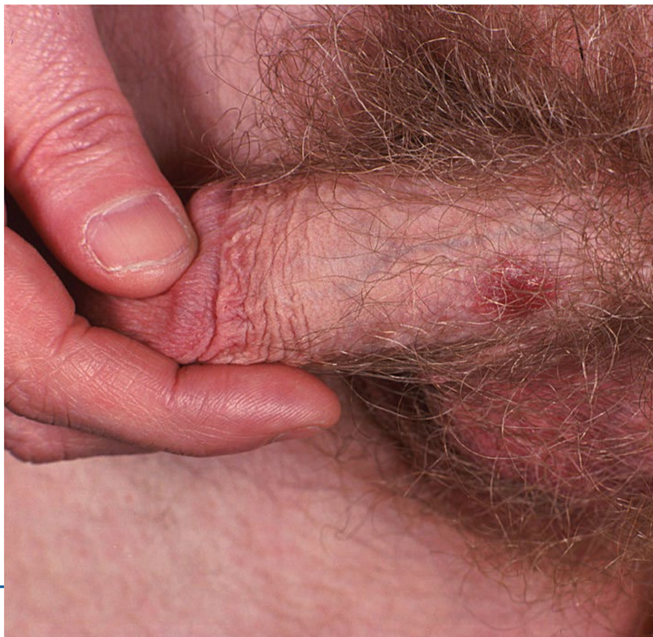


labial



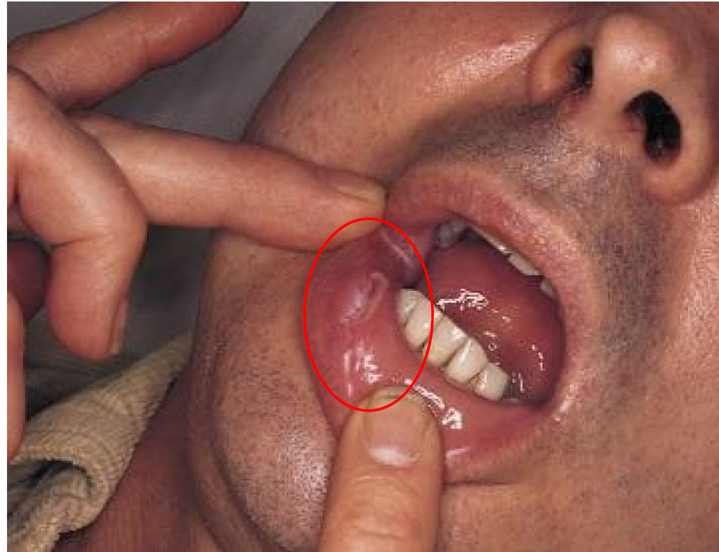
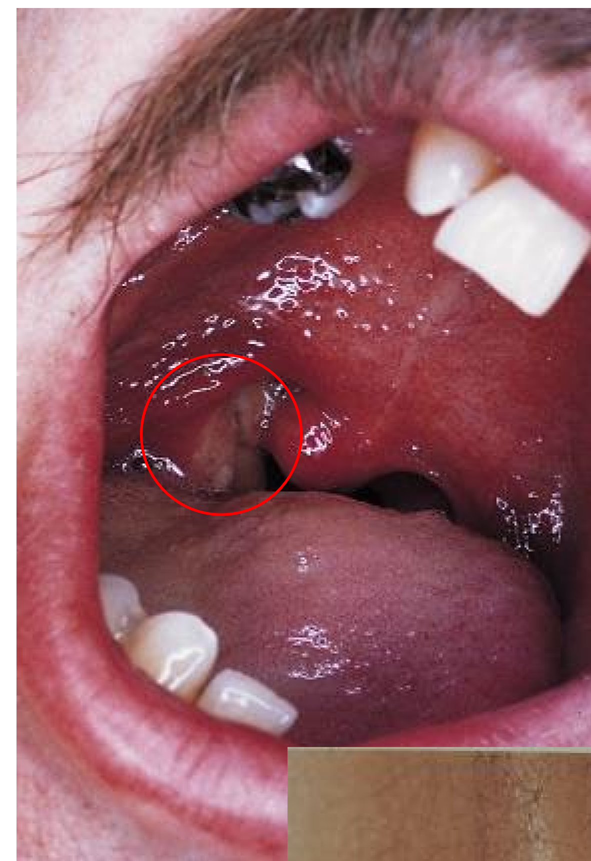
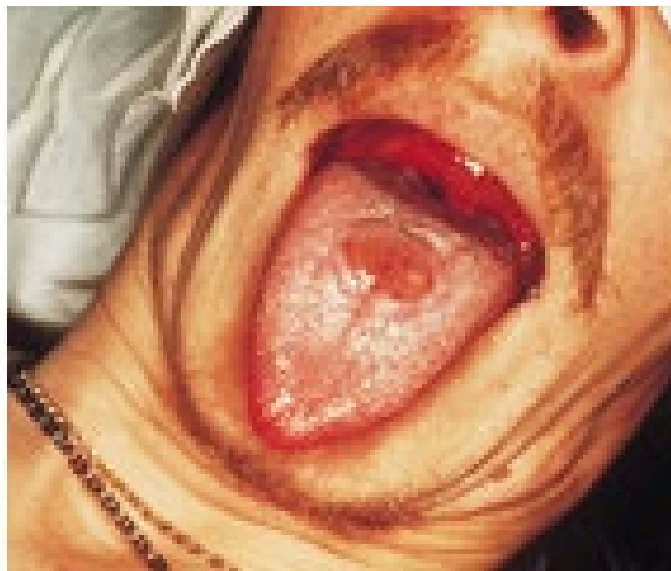
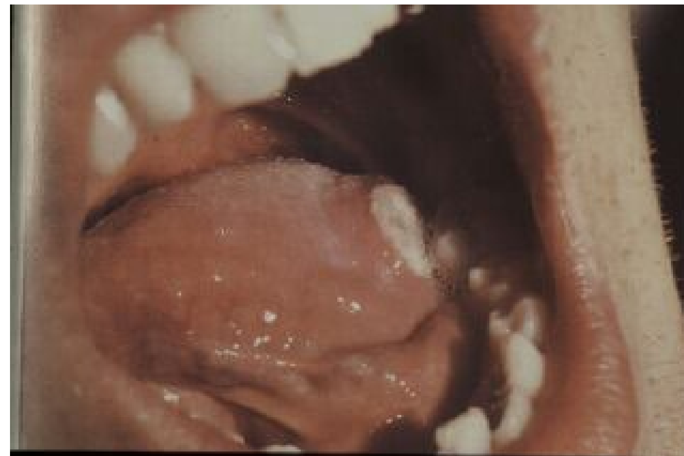
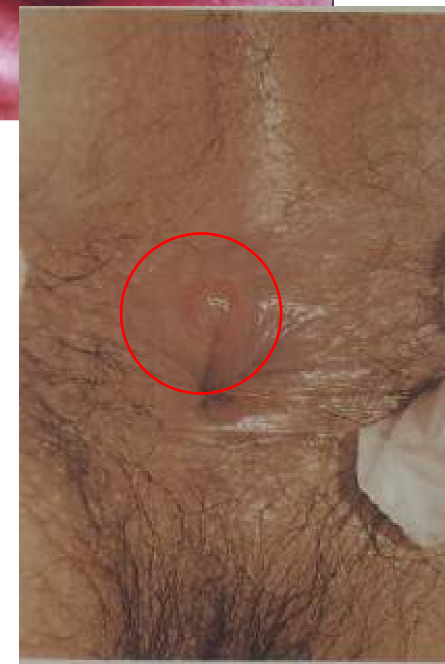
cervical



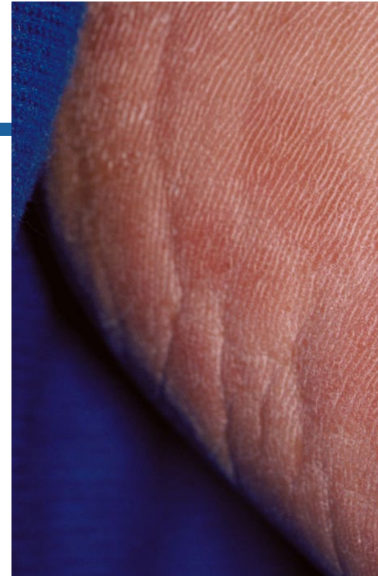
Primary chancres

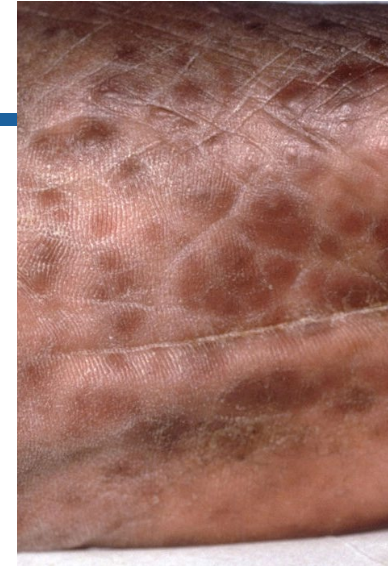
Other chancres

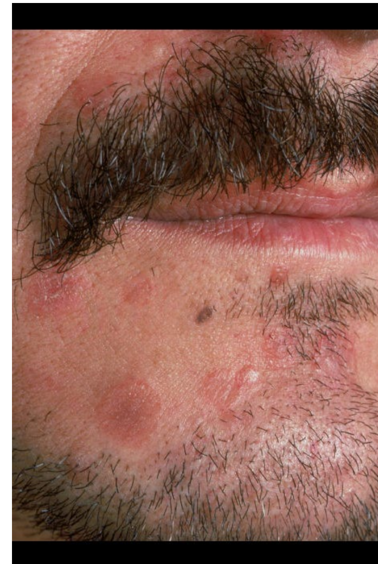






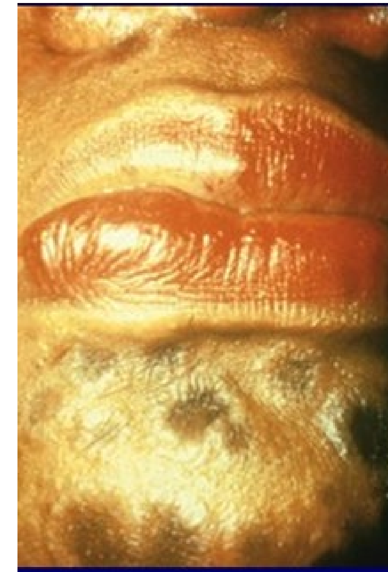
Secondary Syphilis

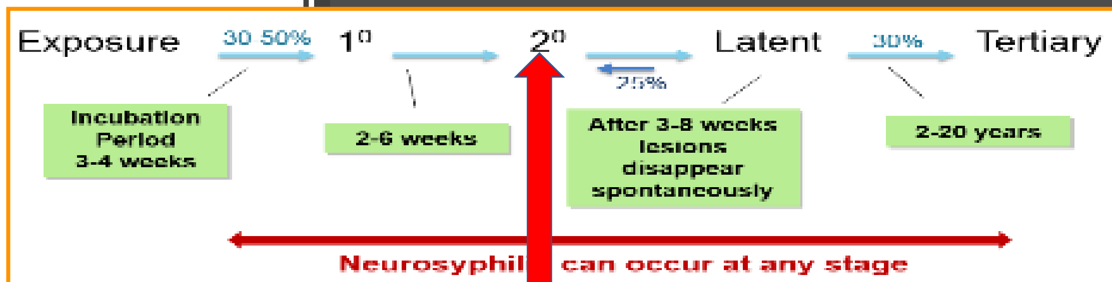
- Skin rash (75-90%)
  - Non-pruritic
  - Palms and soles in 60% of cases
  - ‘nickel and dime’ lesions

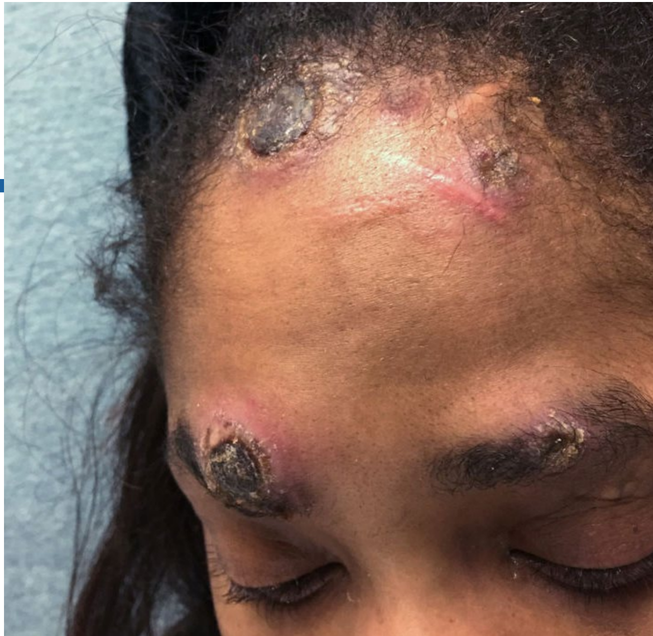
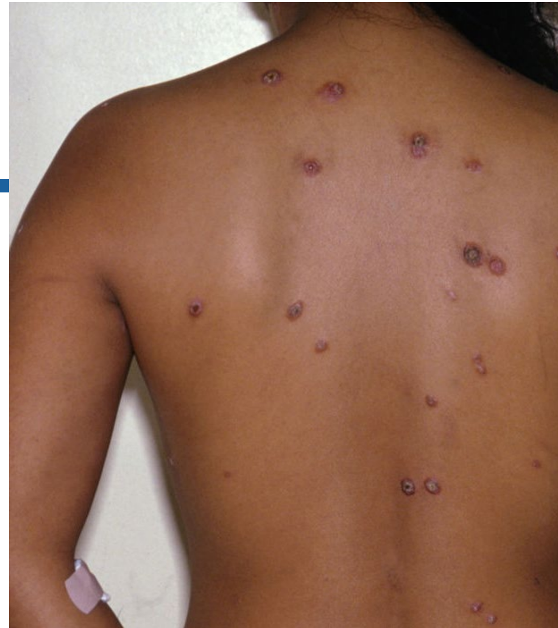
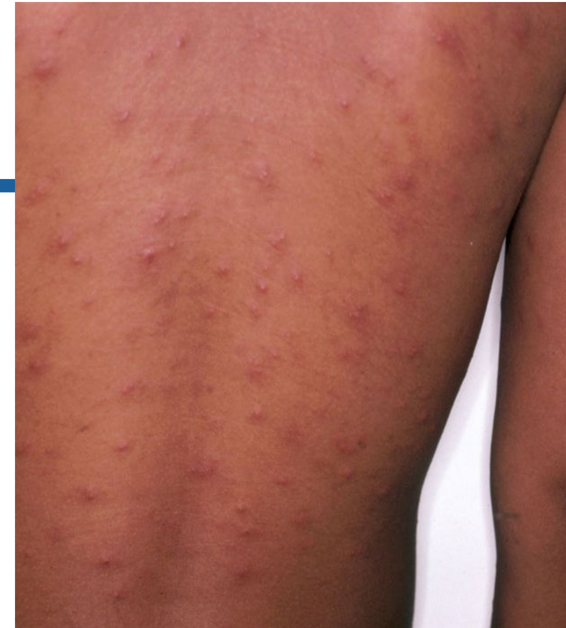
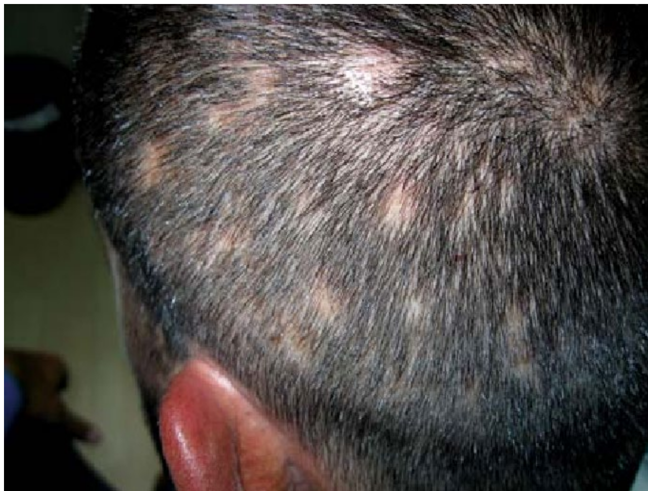










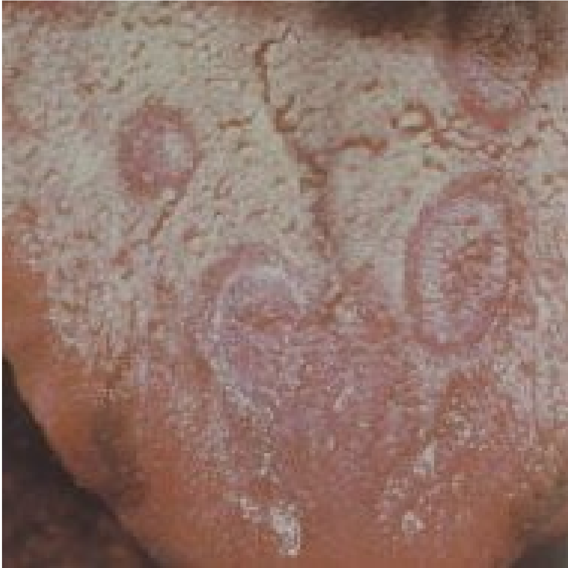





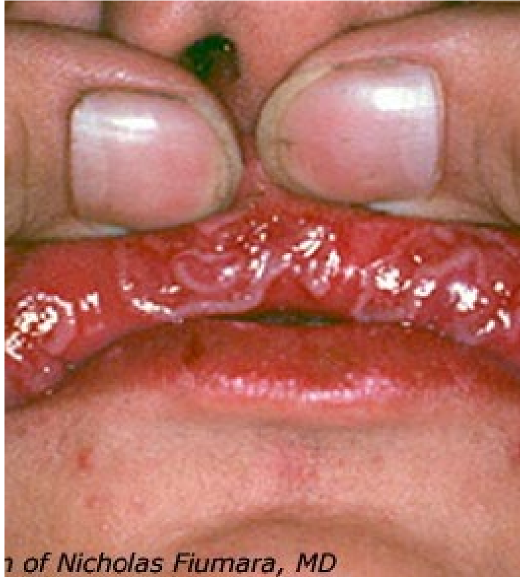
Secondary syphilis

- sore throat, malaise, fever, **generalized lymphadenopathy**, **rash**
- Alopecia areata
- ~~Hepatitis~~
- Renal- nephrotic syndrome
- CNS involvement.

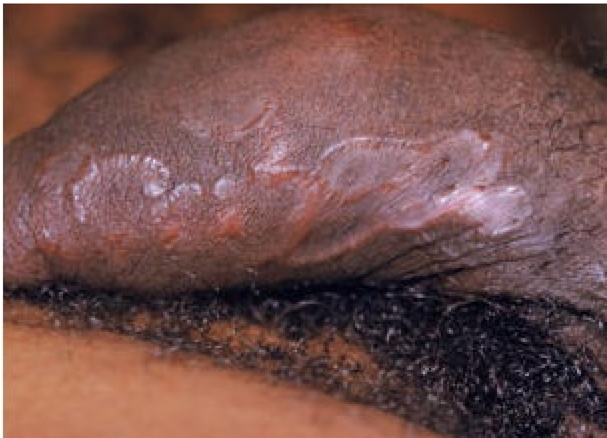
Secondary syphilis: Mucous patches

Oral

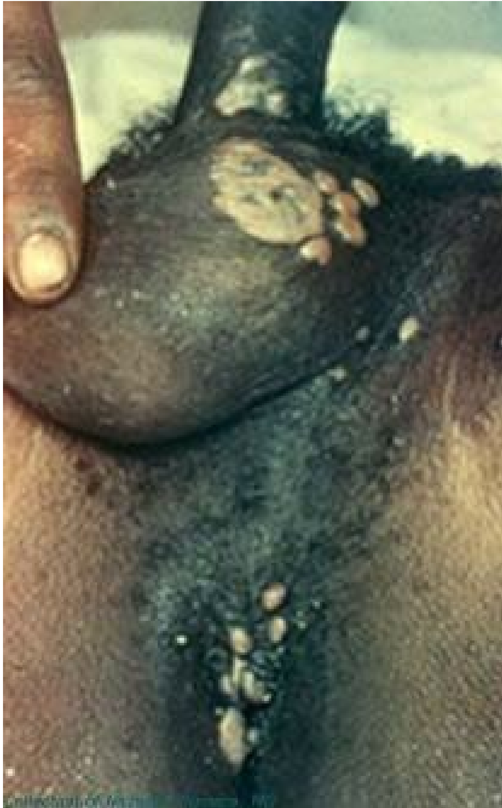


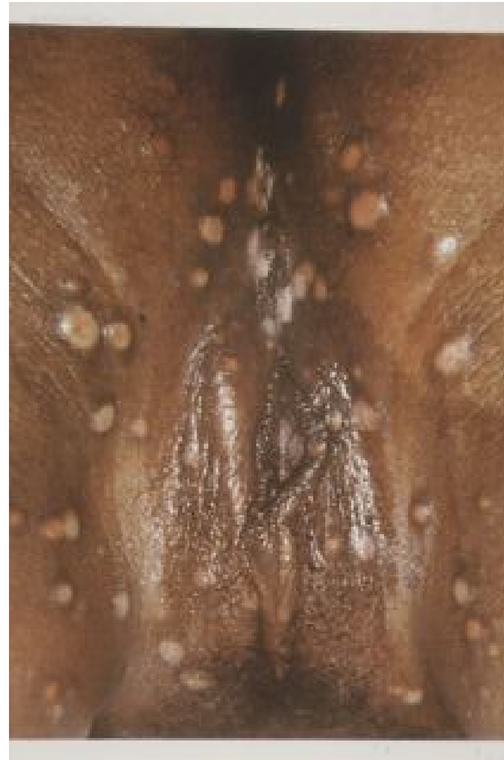


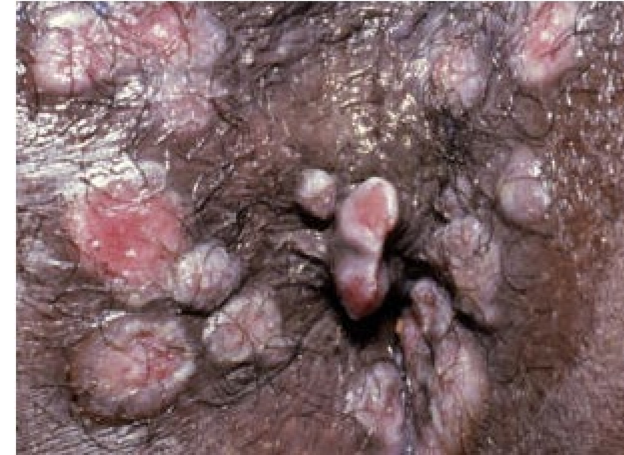
Genital

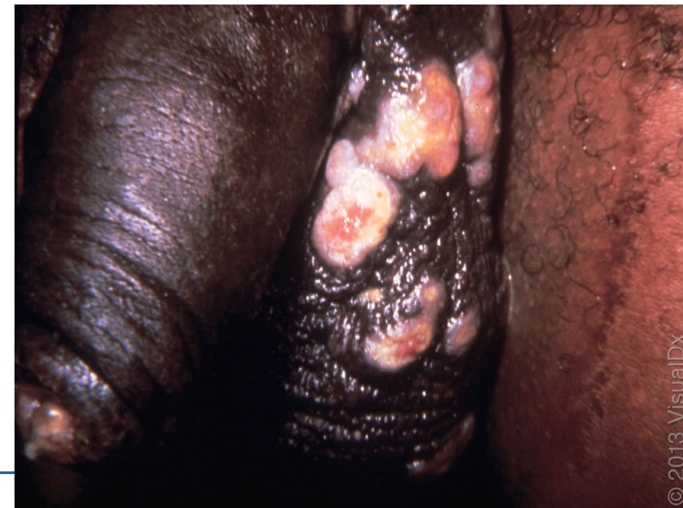


Condylomata lata- (5-25%)-heaped, moist papules in warm areas- gluteal folds, genitals, axillae

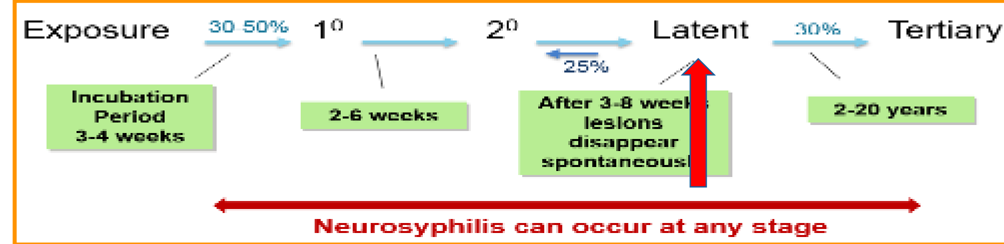








Latent Syphilis



Definition- positive serology in absence of disease

- Early (EL)- <1 year duration
- Late (LL)- >1 year duration

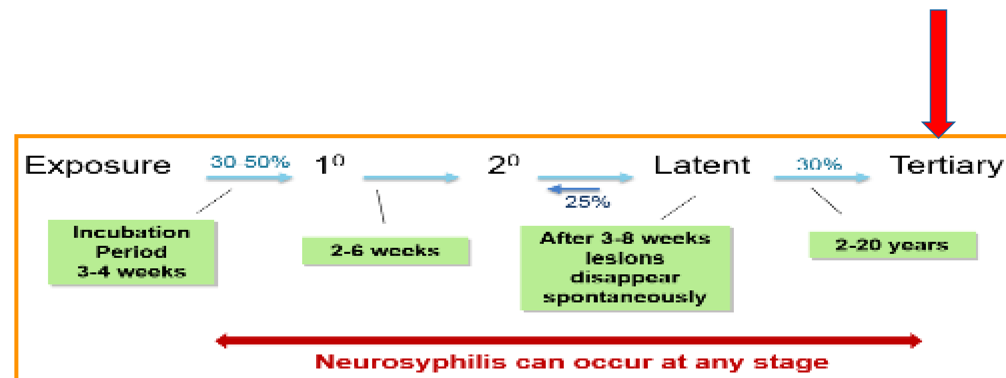
Diagnosis EL if-

- Documented seroconversion in past year
- Unequivocal si/sx of primary or secondary in last year
- Sex partner w/ primary, secondary, EL in last year
- A fourfold increase titer within last 12 months

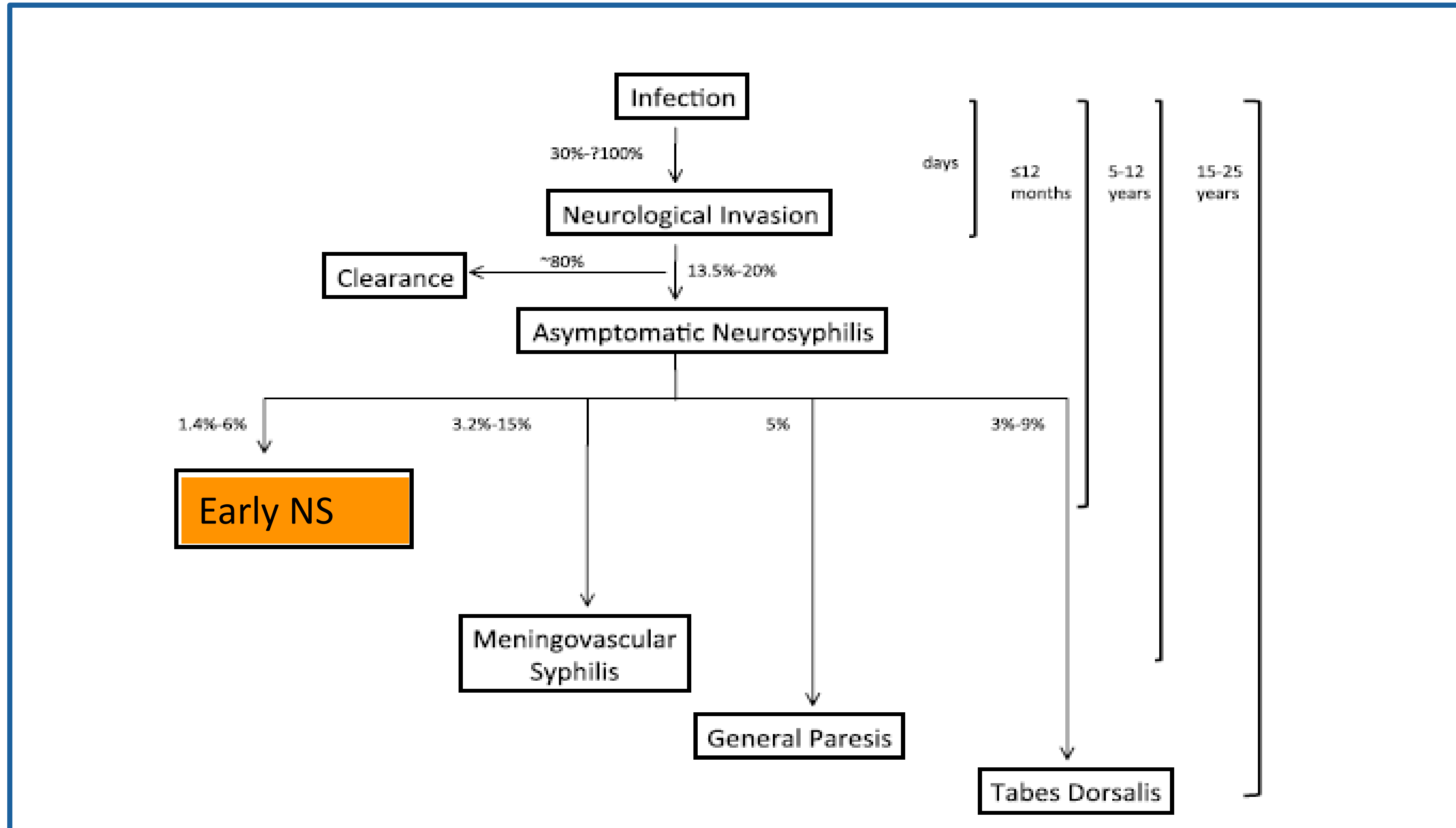
Everyone else should be presumed and treated for LL

Tertiary Syphilis

- Cardiovascular- ascending aortic aneurysm, aortic valvitis, CAD.
- Gummatous- inflammatory lesions in skin, bones, organs.

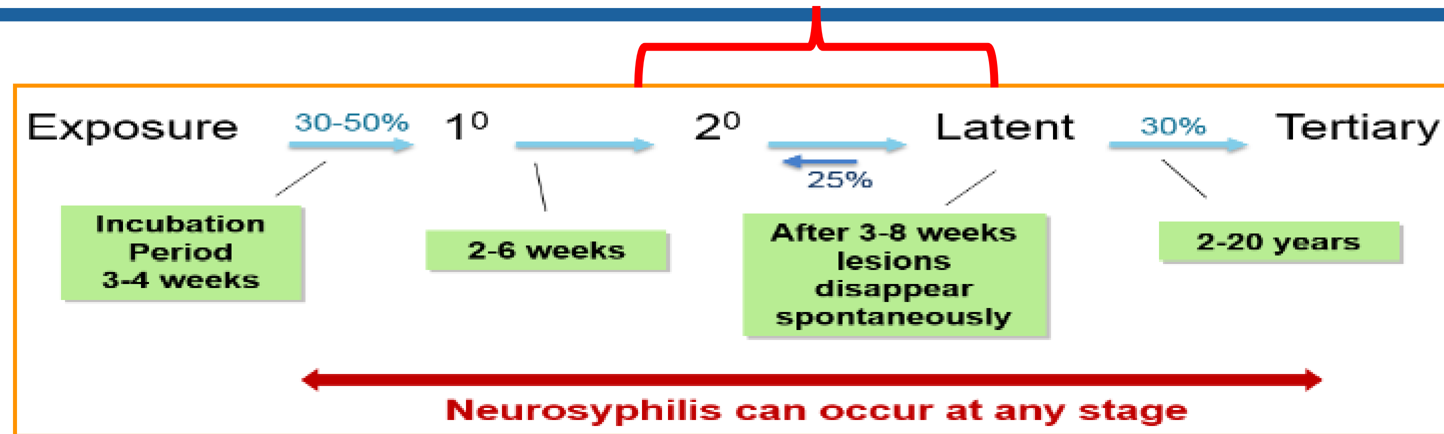


Neurologic involvement with syphilis



Ghanem 2010, CNS Neuroscience and Therapeutics

Syphilis- **Early** Neurologic disease



- Symptoms
  - Visual changes, hearing loss, facial weakness, stuttering stroke symptoms

- Entities- Symptomatic early neurosyphilis (SENS)
  - Ocular- uveitis, chorioretinitis most common
  - Otic- tinnitus, SNHL
  - Cranial Nerve involvement
  - Aseptic meningitis
  - Meningovascular

Syphilis- **Late** (Parenchymatous) Neurologic disease

General "Paresis"

Early	Late
Irritable, personality changes	Lability, impaired memory, confusion, delusions
	Argyll-Robertson Pupils

Tabes Dorsalis

Symptoms	Signs
Ataxic gait Bladder dysfunction Lightening pains Failing vision	Argyll-Robertson Pupils Decreased reflexes Impaired vibration/proprioceptionExample

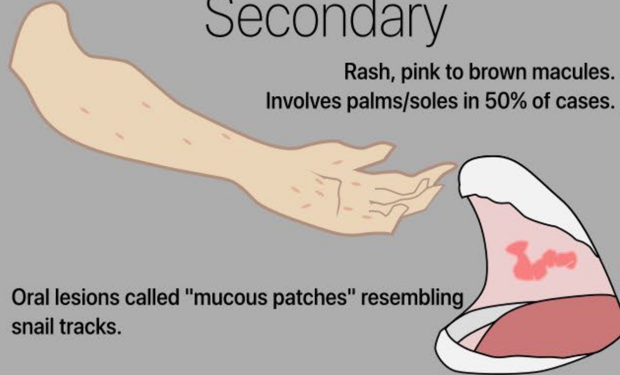
The Stages of Syphilis

Primary

The chancre lesion is the hallmark of primary syphilis. It may appear 10-90 days after exposure. Common sites include penis and labia. Other sites include anus, oral mucosa. Without treatment, chancre disappears in 2-8 weeks.

THE CURB SIDERS INTERNAL MEDICINE

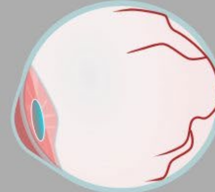
Secondary



Rash, pink to brown macules. Involves palms/soles in 50% of cases.

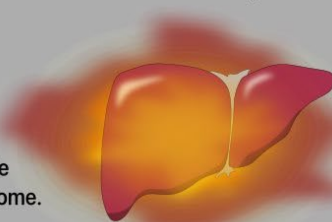
Oral lesions called "mucous patches" resembling snail tracks.

Symptomatic early neurosyphilis, cranial nerve deficits and/or aseptic meningitis presentation.



Ocular syphilis manifestations including anterior or posterior uveitis.

Genito-inguinal rashes, including tinea-mimicker or heaped-up wart-like lesions called condyloma lata.



Less common internal organ manifestations including acute hepatitis and nephrotic syndrome.

Latent

Latent syphilis refers to asymptomatic infection after the period of primary and secondary syphilis (noticed or unnoticed) has passed.

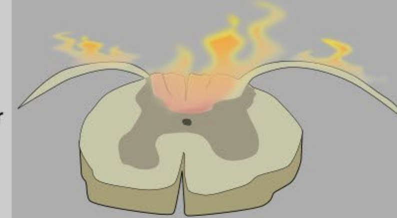
Early Latent

Early latent refers to asymptomaticpatients with positive testing, in whom history can confirm exposure to or symptoms of primary or secondary syphilis within the last year. This is group may receive single-dose penicillin like primary or secondary.

Late Latent

Late latent patients have positive serology but do not meet criteria for early. Thus, multiple doses of penicillin.

Late (Tertiary)



Late Neurosyphilis, including tabes dorsalis, gait impairments, and dementia. Tabes dorsalis damages the dorsal columns and sensory nerve roots, causing a syndrome of pain and sensory deficits similar to those of B12 deficiency.

Gumma are ulcerating granu-lomas on skin, bone, and internal organs.

Cardiovascular effects of late syphilis include aortic aneurysm and coronary arteritis.

Curbsiders Episode # 127!! Graphic by Bryan Brown, MD, MHS

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Testing

Syphilis Diagnosis Overview

Direct

- Darkfield
- Tissue staining

Indirect

Nontreponemal (non specific)
- RPR
- VDLR

Treponemal (specific)
- “Trep Ab” (automated)
- TP-PA (manual)

Syphilis diagnosis- You need BOTH of these:

<u>Lipoidal (non-treponemal)</u>

<u>VDRL, RPR</u>

- detects antibodies to cardiolipin-lethicin-chol
- If used for screening must confirm w treponemal test
- titer generally reflects activity of disease- used for monitoring

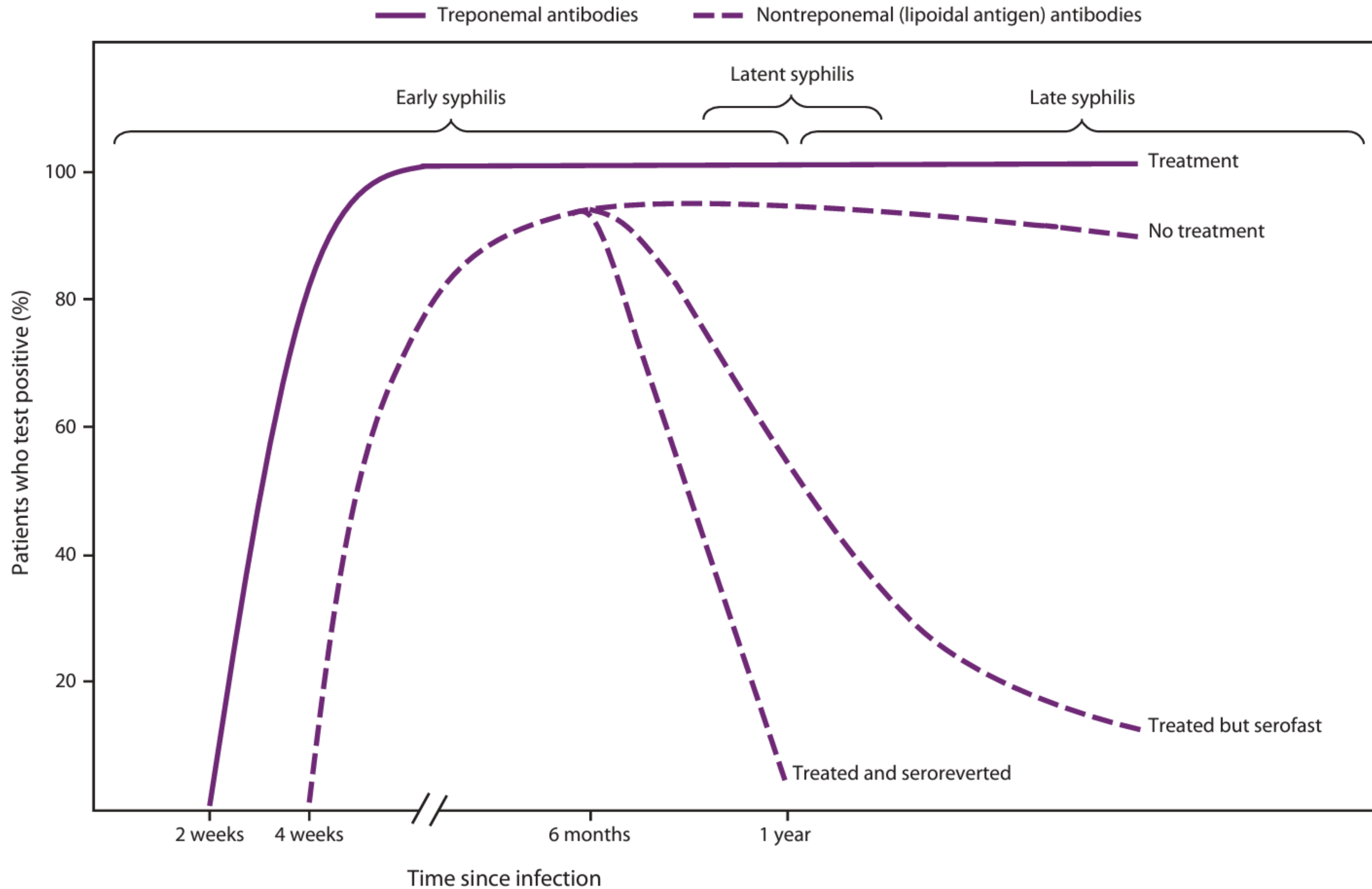
<u>Treponemal specific</u>–

<u>Older</u>-FTA-ABS, TP-PA*

<u>Newer-</u> "Treponemal Ab"- EIA/CIA/MBIA; PoC

- detects antibodies to *T. pallidum*
- may stay positive for life after treatment

FIGURE 1. Serologic response to infection with *Treponema pallidum*, the causative agent of syphilis



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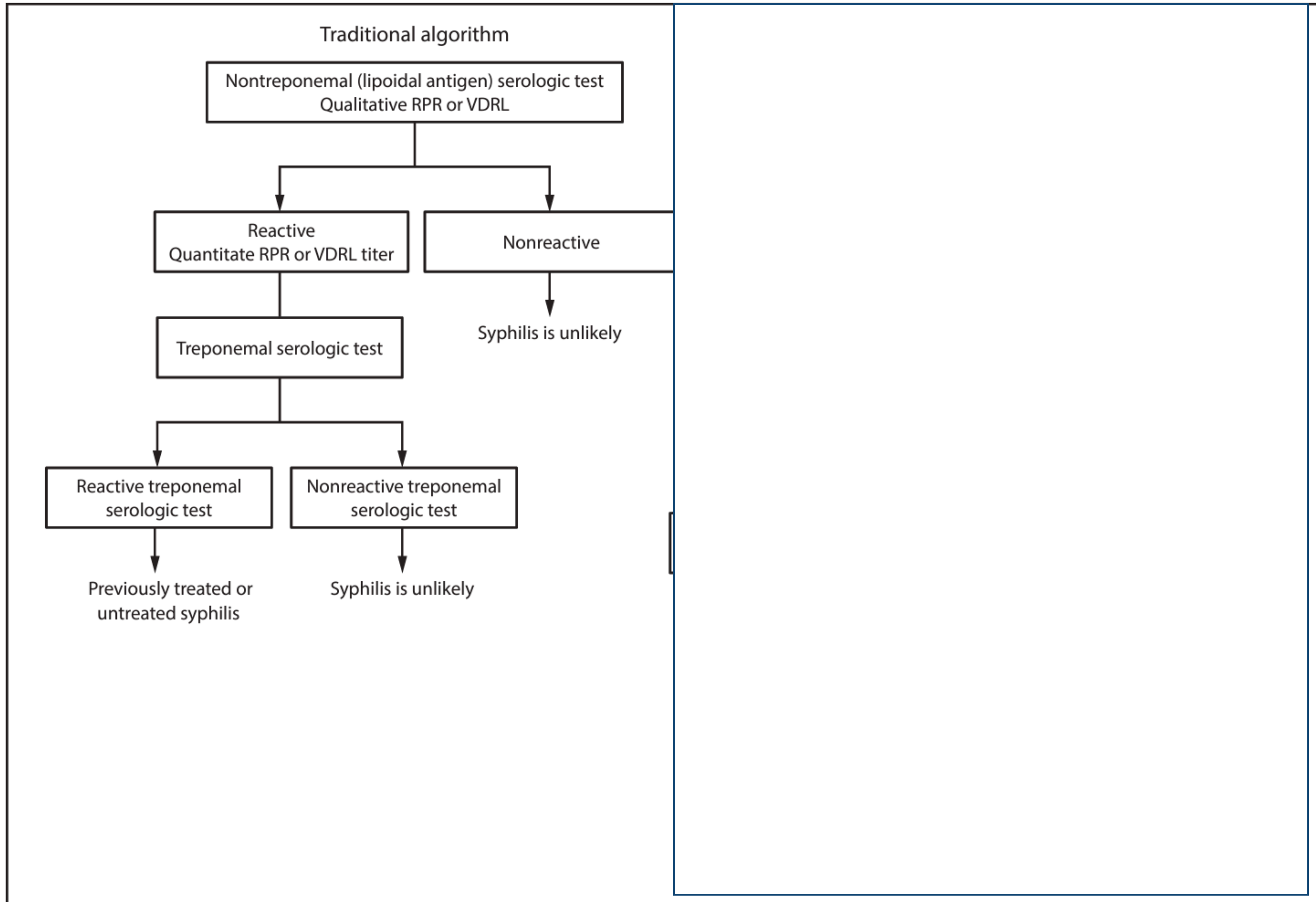
Source: Adapted from Peeling RW, Mabey D, Kamb ML, Chen X-S, Radolf JD, Benzaken AS. Syphilis. Nat Rev Dis Primers 2017;3:17073. Used with permission.

FIGURE 3. Algorithms that can be applied to screening for syphilis with serologic tests — CDC laboratory recommendations for syphilis testing in the United States, 2024



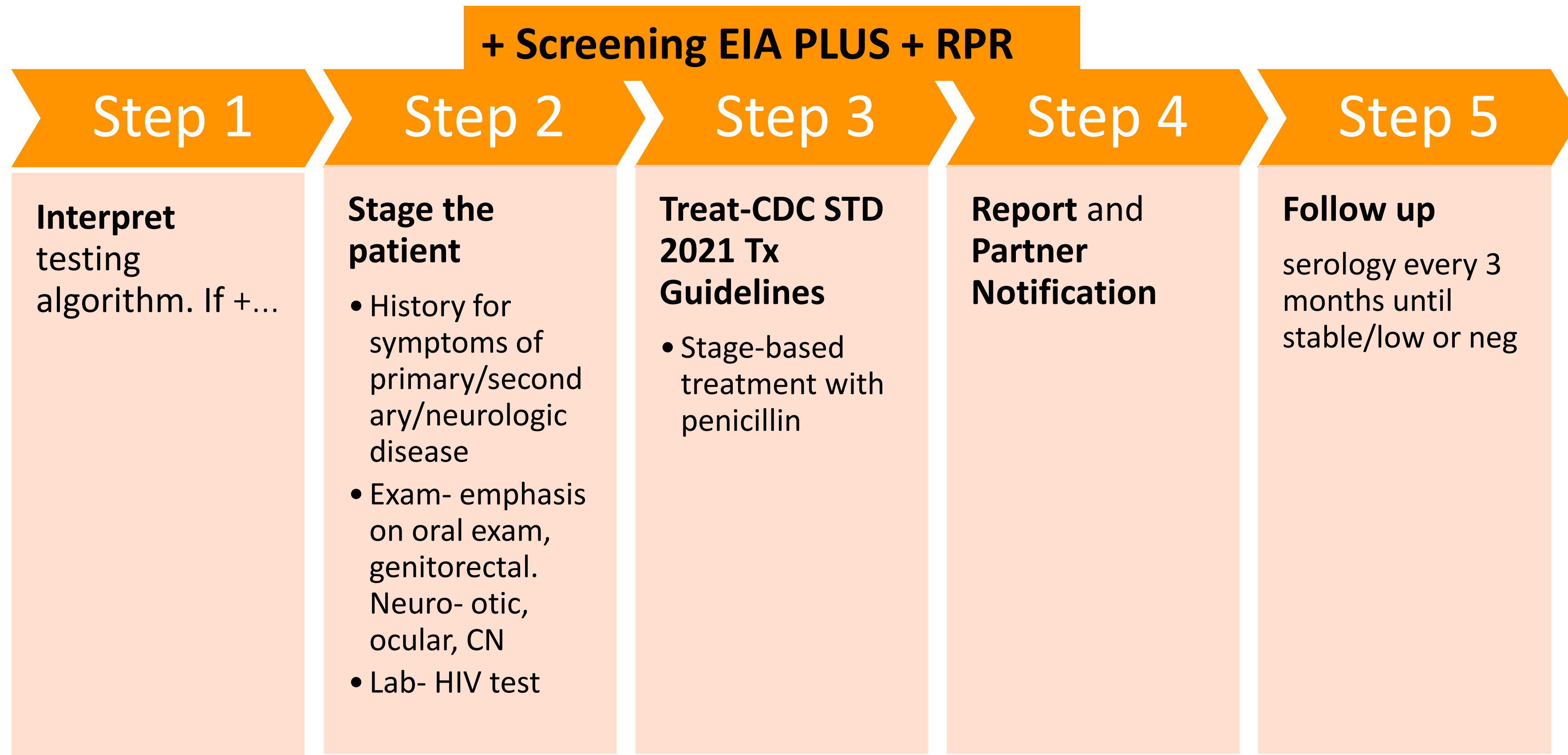
Abbreviations: CIA = chemiluminescence immunoassay; EIA = enzyme immunoassay; RPR = rapid plasma regain; TPPA = *Treponoma pallidum* particle agglutination; VDRL = Venereal Disease Research Laboratory.

CDC Laboratory Recommendations for Syphilis Testing, United States, 2024

Recommendations and Reports / February 8, 2024 / 73(1);1–32

Link to full report

5-step approach to positive serology with confirmation



Staging

History

- Last contact (time, sites)
- Symptoms (of primary, of secondary, includes GI, of neuro)
- Past hx of syphilis; treatment

Physical

- Scalp (alopecia)
- OP- mucous patches, chancres
- Skin- rash, ulcers
- GU- chancre, (genital, anal), condylomata lata, mucous patches
- LAN
- Neuro

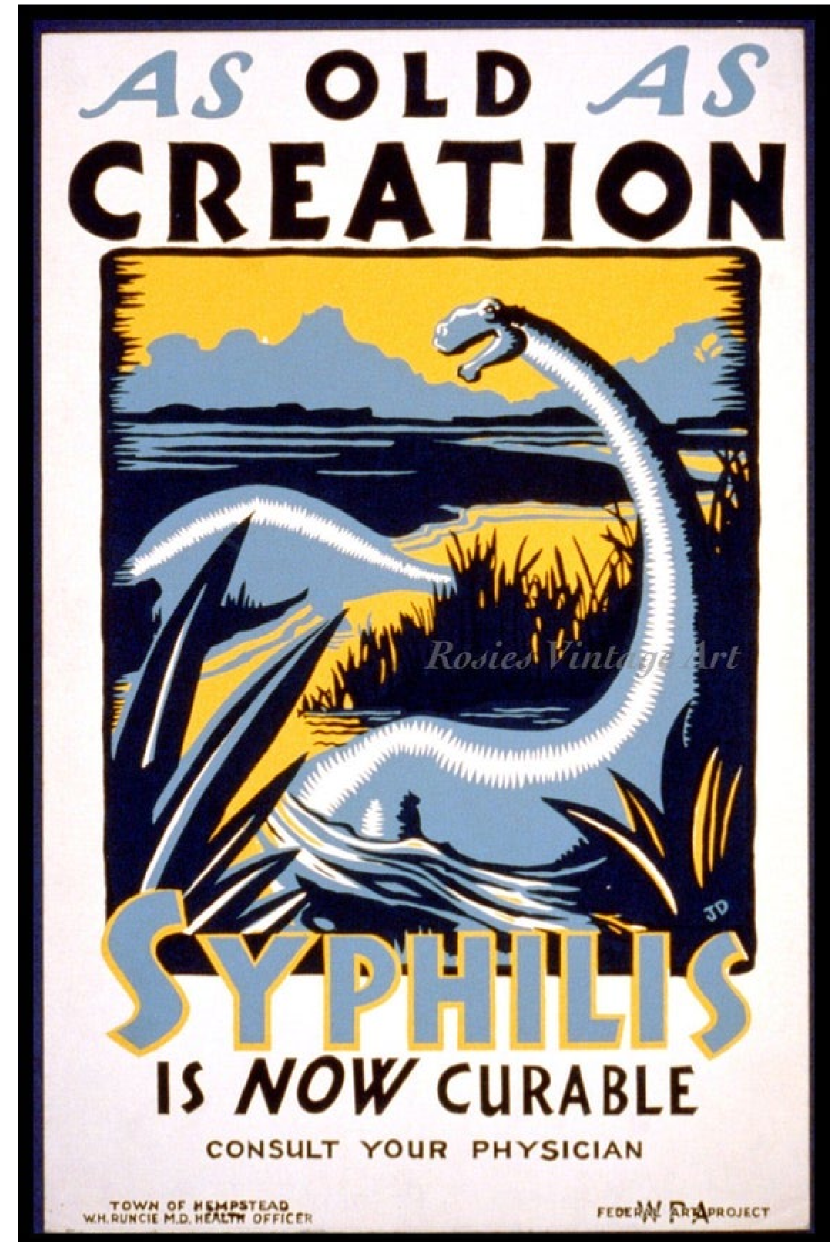
New syphilis dx- Screening questions:

Screening Questions for Neurosyphilis (Including Ocular and Otosyphilis)

Questions	
<u>Symptoms of Otosyphilis</u>	
1) Have you recently had new trouble hearing?	□ Yes – refer to ENT □ No
2) Do you have ringing in your ears?	□ Yes – refer to ENT □ No
<u>Symptoms of Ocular syphilis</u>	
3) Have you recently had a change in vision?	□ Yes – refer to ophthalmology □ No
4) Do you see flashing lights?	□ Yes – refer to ophthalmology □ No
5) Do you see spots that move or float by in your vision?	□ Yes – refer to ophthalmology □ No
6) Have you had any blurring of your vision?	□ Yes – refer to ophthalmology □ No
<u>Symptoms of neurosyphilis</u>	
7) Are you having headaches?	□ Yes □ No
8) Have you recently been confused?	□ Yes □ No
9) Has your memory recently gotten worse?	□ Yes □ No
10) Do you have trouble concentrating?	□ Yes □ No
11) Do you feel that your personality has recently changed?	□ Yes □ No
12) Are you having a new problem walking?	□ Yes □ No
13) Do you have weakness or numbness in your legs?	□ Yes □ No

Medical providers should consider evaluation and treatment for neurosyphilis in persons with new persistent headaches rated as moderate or greater; new change in vision, including loss, blurring, seeing spots or flashing lights; new change in hearing, including loss, muffling or tinnitus; new and persistent change in personality, memory or judgment; new numbness in both legs; or new gait incoordination.

Treatment



Syphilis Treatment- (any HIV status)

- Early syphilis (primary/secondary/EL)

Benzathine PCN 2.4 million units IM x 1
Or
Doxycycline 100 mg po bid x 14 d*

- Late syphilis (LL or non neuro tertiary)

Benzathine PCN 2.4 million units IM q week x 3
Or
Doxycycline 100 mg po bid x 28 d*

2021 CDC STD Treatment Guidelines
*if pcn allergic (except pregnancy)

Syphilis Treatment- (any HIV status)

- Neuro and Ocular

Aqueous penicillin G 3-4 MU iv q 4hours x 10-14 d

- Tertiary (non neuro)

Benzathine PCN 2.4 million units IM q week x 3
Or
Doxycycline 100 mg po bid x 28 d*

2021 CDC STD Treatment Guidelines

*if pcn allergic (except pregnancy)

Sexually Transmitted Disease Confidential Case Report Form STD-23 (rev. 10/13/2020)

STATE OF CONNECTICUT
DEPARTMENT OF PUBLIC HEALTH
STD CONTROL PROGRAM
410 Capitol Avenue, MS#11STD
PO Box 340308
Hartford, CT 06134-0308

☐ **Note**: Check this box to request forms

PATIENT INFORMATION

Name (Last) (First) (MI) | Date of Birth | Home Phone Number | Other Phone Number

Address (Number and Street) (City or Town) (State) (Zip Code)

Sex ☐ Male ☐ Female ☐ Unknown | Pregnant ☐ Yes ☐ No ☐ Unknown | Marital Status ☐ Married ☐ Single ☐ Unknown

Race ☐ White ☐ Black/African American ☐ Asian ☐ American Indian/Alaska Native ☐ Native Hawaiian/Other Pacific Islander ☐ Other, specify: ____________________ ☐ Unknown

Ethnicity ☐ Hispanic/Latino ☐ Non-Hispanic/Latino ☐ Unknown

Sex of Partners ☐ Men ☐ Women ☐ Both ☐ Unknown | Insurance Status ☐ Private ☐ Medicaid ☐ None ☐ Other

DISEASE INFORMATION

☐ **Gonorrhea** **OR** ☐ **Chlamydia**

☐ Symptomatic Uncomplicated
☐ Asymptomatic
☐ Pelvic Inflammatory Disease
☐ Other, specify:______________________

☐ **Syphilis**

☐ Primary (Chancre Present)
☐ Secondary (Rash, Lesions, etc.)
☐ Early Latent – No SX (Duration < 1 Year)
☐ Late Latent – No SX (Duration > 1 Year)
☐ Late – With SX
☐ Congenital

☐ **Other STDs**

☐ Neonatal Herpes ($\leq$ 60 days of age)
☐ Chancroid

PARTNER NOTIFICATION SERVICES

Providers treating STDs are expected to counsel patients in prevention and identify and refer partners to medical care for examination and treatment.

☐ Partners referred for exam and treatment by provider.
☐ Expedited Partner Therapy provided.
☐ Provider requesting assistance with partner notification from state health department. Please inform patient of this notification.

TREATMENT INFORMATION

Treatment Date: ____________

☐ Not Treated

Specify Antibiotic and Dosage:
____
____
____

DIAGNOSTIC INFORMATION

Test Date: ____________

☐ Laboratory Confirmed
☐ Clinical Diagnosis-No Lab. Confirmation

Reporting Laboratory: ____________________

Results or attach lab report: ____________________

ATTENDING PHYSICIAN INFORMATION

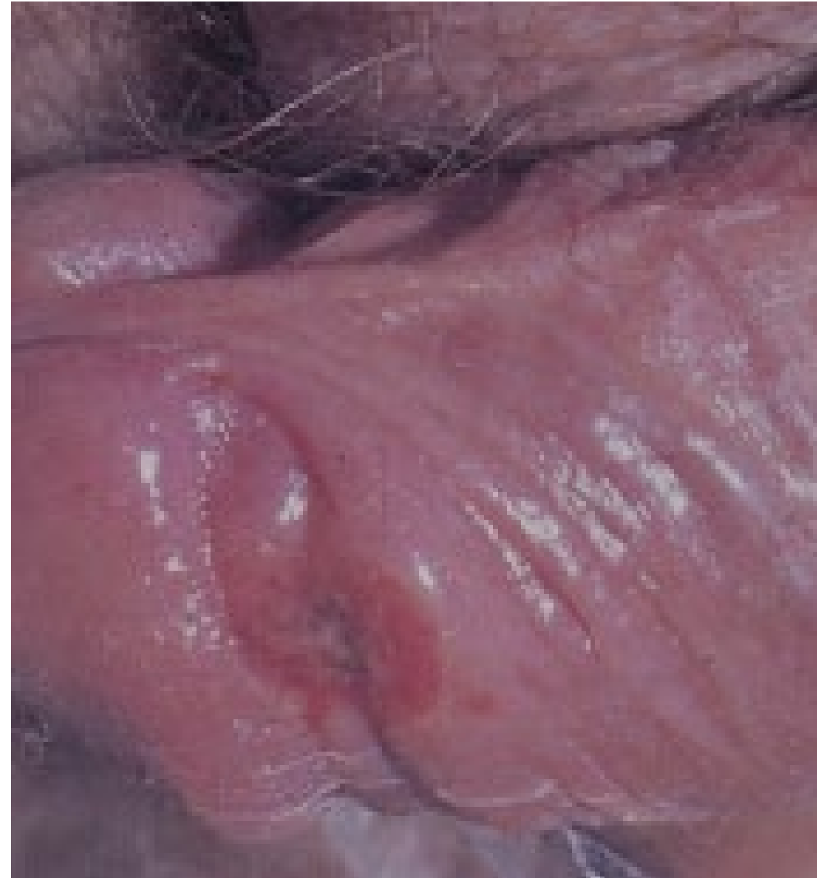
Name:____________________ Address:____________________ Phone Number:______________ Date Reported:____________

If reporting from a Hospital or Facility, please complete the following: Name of person reporting (if different than above) ____________________

Name of Hospital or Facility:__________________ ☐ Inpatient ☐ ER/Urgent Care ☐ Outpatient Clinic ☐ OB/GYN ☐ Family Planning

Case #1

- **Painless Ulcer – dx and management questions**
  - Work up/DDX
  - Empiric treatment or no?
  - With what
  - What else?



Genital Ulcer- approach

Take a (sex) history

- Time since last sexual contact
- Any RF for syphilis (MSM)
- Painful or painless
- Associated lymphadenopathy (and painful or not?)
- Travel

Examine

- Rubbery, indurated feel vs shallow
- Associated LN? Where?
- Other- rash/skin, OP

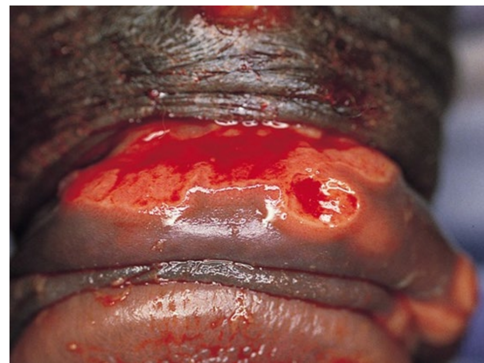
Diagnostic Testing

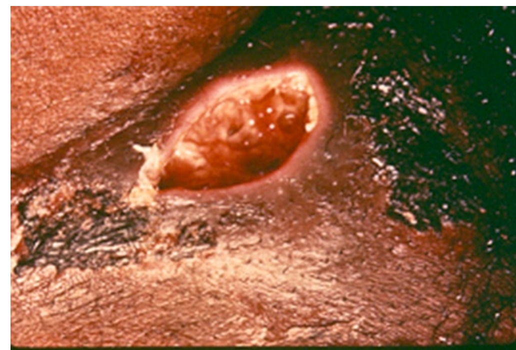
Genital ulcer diagnostic work-up

- HSV- PCR for HSV 1 and 2 (or viral culture if no PCR available) *AND*

- Syphilis testing
  - Darkfield
  - Serology

- *Hemophilus ducryei*- culture if suspicious (painful and purulent, likely travel)





Treatment

- Empiric
  - **Treat the most likely diagnosis**
  - If serology negative and ulcer there <7 days:
    - Treat if still epidemiologically and clinically likely
    - Don’t treat if unlikely but return in one week and **repeat serology** (and review HSV pcr results)

- What regimen?
  - A doxycycline 100 mg po bid x 7 d?
  - B ceftriaxone 125 mg IM x 1 ?
  - C azithromycin 2 gm po x 1 ?
  - D penicillin 2.4 MU IM x 1?
  - E pencillin 2.4 MU IM q week x 3?

What else?

1. Test for other STI including HIV
2. Recommend abstinence for 7 days
3. Partner referral
4. PrEP referral or prescription

CT STD Partner Notification Line

1-860-509-7920 !!

Take home points

Always take a sexual history

Know the current epidemiology to guide screening

Ulcers- always check for HSV and syphilis, serology can be negative early. Empiric tx if high risk

Always test for HIV

Use penicillin whenever possible

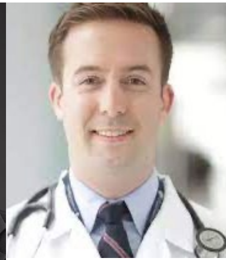
LP if symptoms but that means you have to ask questions

Report, report, report

STD Clinical Consultation Network (STDCCN)

- Provides STI/STD clinical consultation services within 1-5 business days, depending on urgency, to clinicians nationally
- Consultation request is linked to your regional PTC's STI/STD expert faculty
- Just a click away: www.STDCCN.org
- Also embedded in Treatment Guidelines App!

Dr. Amit Achhra
ID, Yale


Dr. Kevin L. Ard
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Dr. Philip A. Chan
ID, Brown

Dr. Erica Hardy
OB-Gyn/ID, Brown

Dr. Katherine K. Hsu
Pedi ID, Boston Med Ctr/MDPH

Dr. Devika Singh
ID, U of Vermont

Dr. Zoon Wangu
Pedi ID, UMass/MDPH

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Follow Up

Serology

HIV-: Repeat RPR or VDRL at 6 and 12 months

HIV+: Repeat RPR or VDRL at 3,6,9,12, months.

CSF- if had been abnormal at initial LP, following peripheral serologies acceptable (NEW 2021)

Tx failure:

1. Ongoing si/sx lasting longer than 2 weeks from tx

2. Rise in NT 4x from treatment titer

→ ***Recheck HIV, LP, retreat w 3 shots benzPCN***

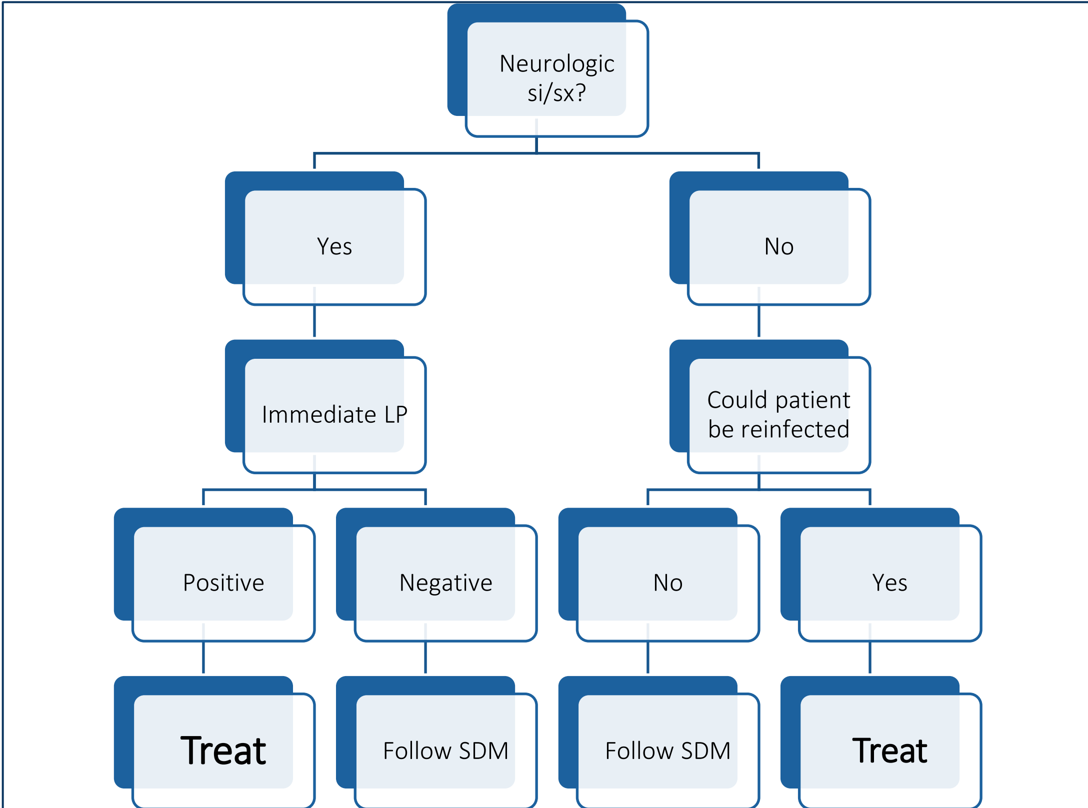
3. Failure to decrease 4x 6-12 months after early syphilis tx

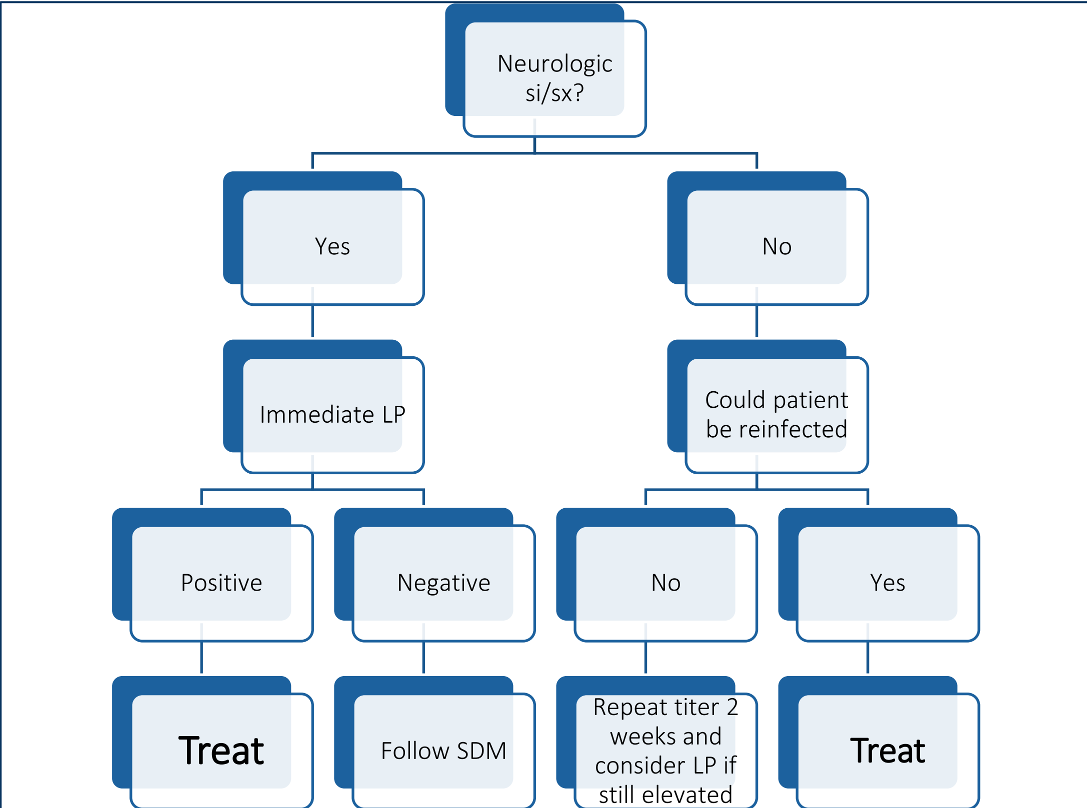
→ ***Recheck HIV, LP?, retreat w 3 shots benzPCN?***

What to do if titers don't respond appropriately?

Lack of a fourfold decline in titers after waiting a **full 12m** (EL) and a **full 24m (LS)**:

A **four-fold increase i**n titers after appropriate therapy:





When to do an LP (HIV pos or neg)?

1. Si/sx of NS-
   1. Evidence of cranial nerve dysfunction
   2. ~~Auditory or ophthalmologic abnormalities~~ (NEW 2021)
   3. Meningitis
   4. Stroke
   5. Acute or chronic alteration in mental status
   6. Loss of vibration sense
2. Diagnosis of Tertiary syphilis
3. Not serologically responding to treatment

- Si/sx and Pos CSF-VDRL= diagnostic of neurosyphilis
- Si/sx with abn CSF (prot >40, WBC >5) with NEG CSF-VDRL = consider neurosyphilis. Negative CSF-TPPA *virtually* excludes neurosyphilis

CDC STD Tx Guidelines 2021