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Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

HOW CAN YOU RECOGNIZE AND DIAGNOSE NEUROSYPHILIS?

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UW Psychiatry & Behavioral Sciences

project ECHO

SPEAKER DISCLOSURES

✓ None

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QUESTION 1: SYPHILIS IS NO LONGER AN ACTIVE PROBLEM IN THE UNITED STATES.

- True

Or

- False

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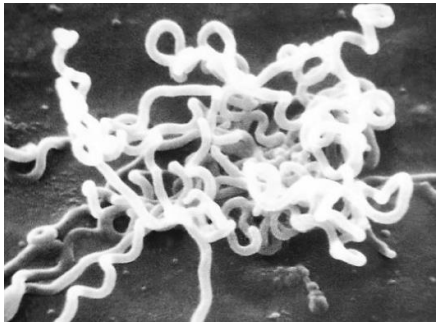
NEUROSYPHILIS OBJECTIVES

1. Recognize that syphilis IS still an active public health concern and name the highest risk demographic

2. List some of the signs/symptoms concerning for neurosyphilis



3. Know how to diagnose a pt with syphilis

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CASE

- 46yo man with HIV (CD4 215, VL undetectable) who presents with vision changes.
  - December severe retro-orbital headaches that progressed to holocephalic
  - January headaches resolved but “floaters” in right eye
  - 4 days PTA (March) “millions” of floaters and sense of looking through tissue paper; R eye injection/red
  - **ROS**: hx of penile lesion in September, did not seek medical attention or testing
- **Medications**: dolutegravir, emtricitabine/tenofovir

IS THIS NEUROSYPHILIS? WHAT MORE WOULD YOU WANT TO KNOW? HOW WILL YOU TELL?

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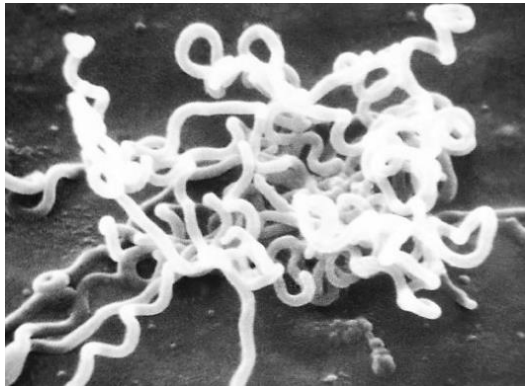
NEUROSYPHILIS

- Epidemiology of syphilis
- Syphilis clinical review
- Neurosyphilis
  - Early
  - Late
- Diagnosis
- Treatment



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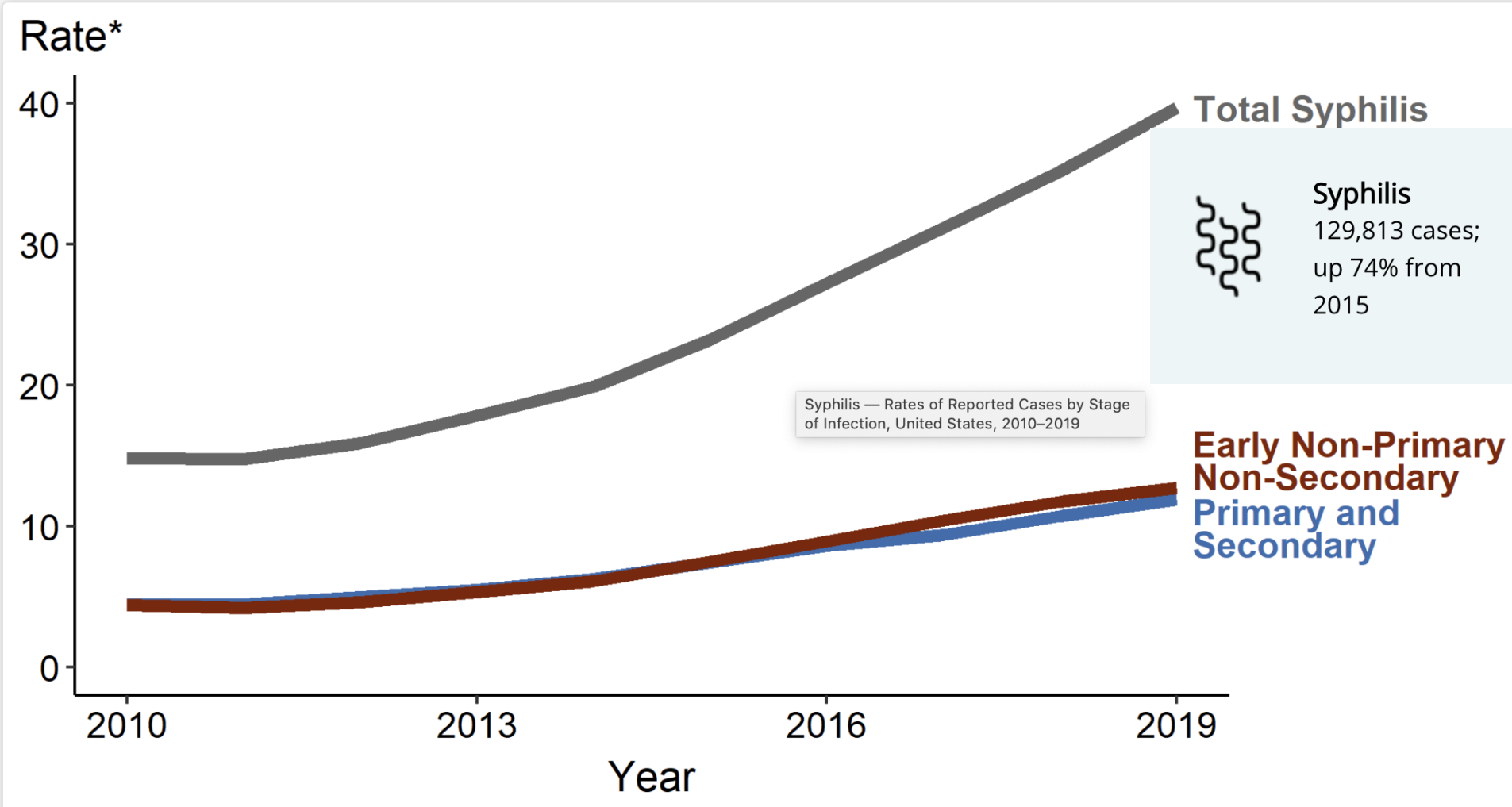
Albrecht Dürer

"Pray to God for my protection, particularly from the French disease; I know of nothing of which I am more badly afraid of right now. Nearly everybody has it, and many people are quite eaten up by it so that they die."

Genitourin Med 1990; 66: 33-40.

SYPHILIS: CLIMBING RATES OF INFECTION



https://www.cdc.gov/std/statistics/2019/figures/SYPH-1.htm

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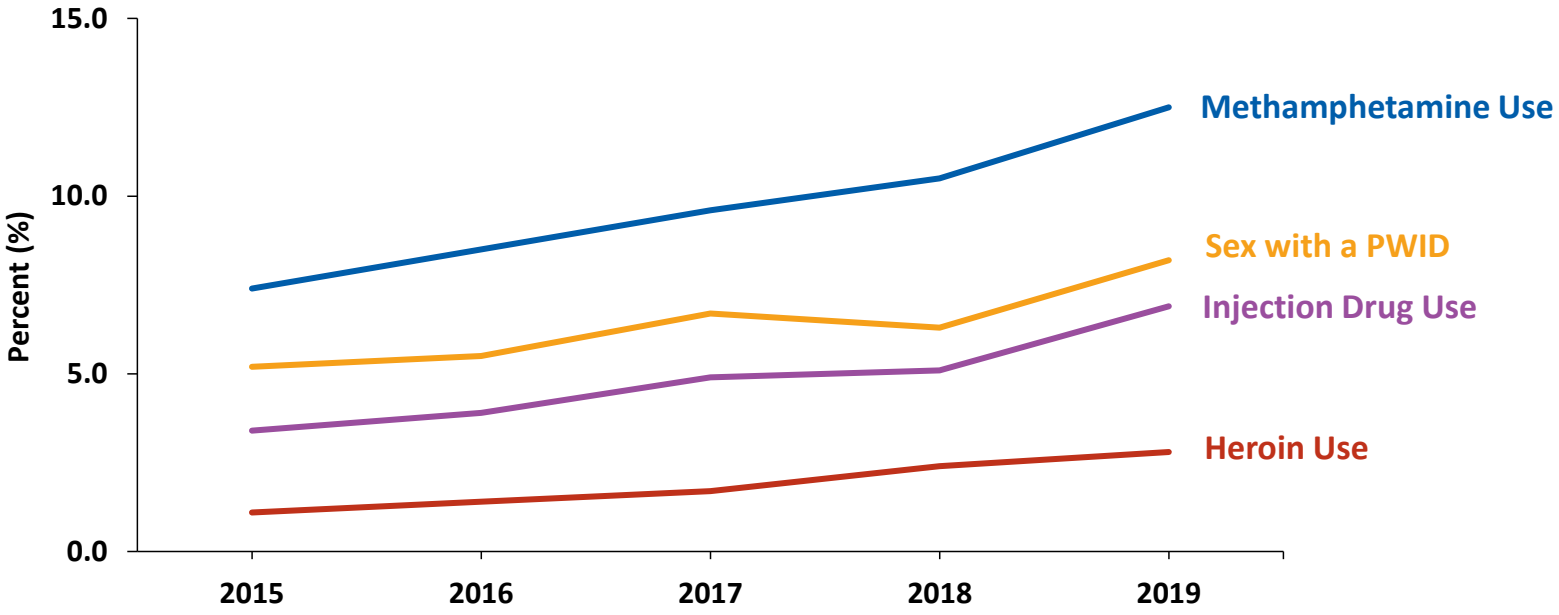
REPORTED* INJECTION DRUG USE, METHAMPHETAMINE USE, HEROIN USE, AND SEX WITH A PWID AMONG PRIMARY AND SECONDARY SYPHILIS CASES, UNITED STATES, 2015–2019



* Proportion reporting injection drug use, methamphetamine use, heroin use, or sex with a PWID within the last 12 months calculated among cases with known data (cases with missing or unknown responses were excluded from the denominator).
Abbreviations: PWID = person who injects drugs

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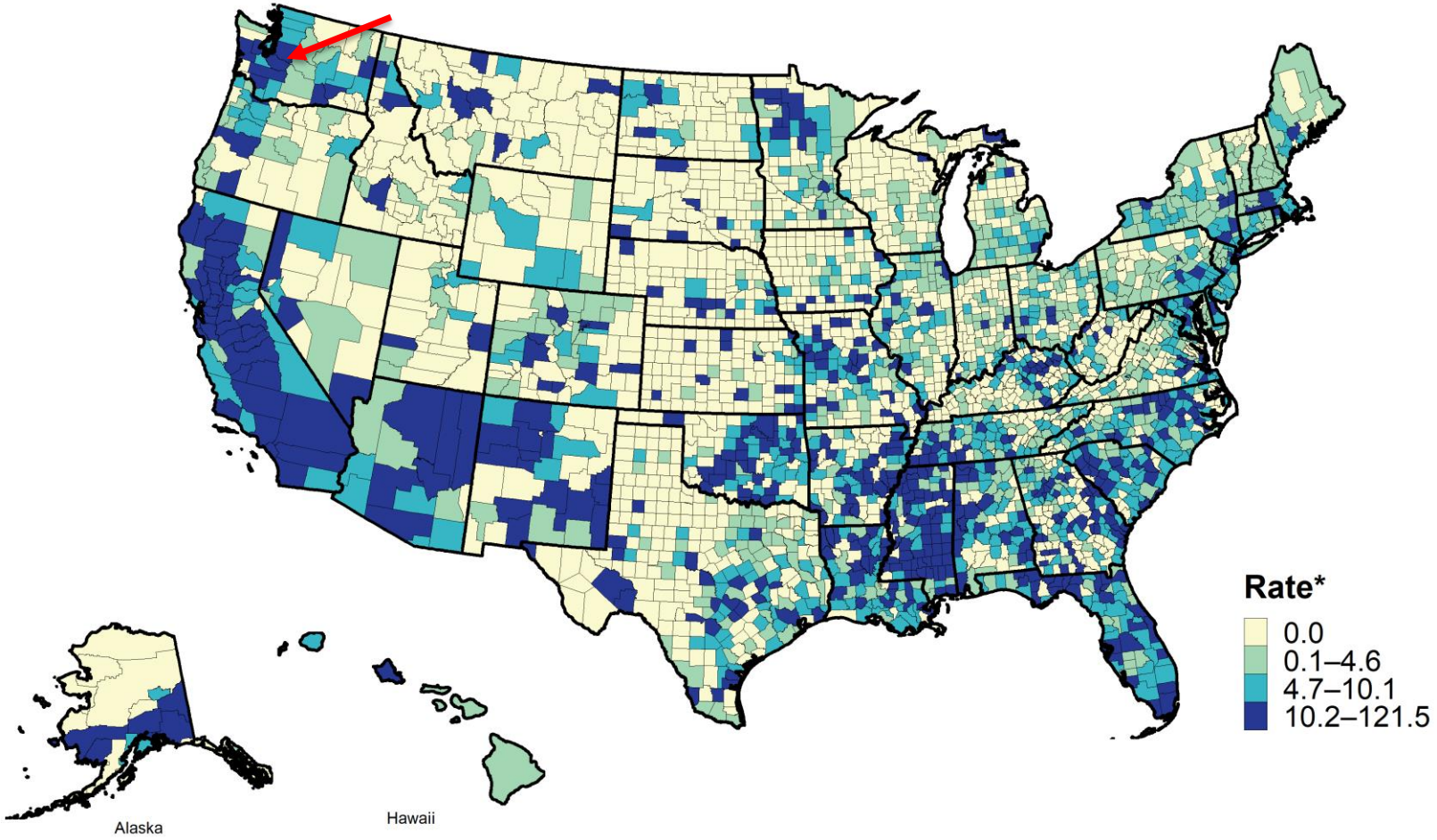
WHAT, SYPHILIS HERE?

PRIMARY AND SECONDARY SYPHILIS — RATES OF REPORTED CASES BY COUNTY, UNITED STATES, 2019 *PER 100,000



https://www.cdc.gov/std/statistics/2019/figures.htm

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QUESTION 2: WHICH GROUP IS AT HIGHEST RISK FOR CONTRACTING SYPHILIS (IN THE US)

A. WSW (women who have sex with women
B. MSM (men who have sex with men)
C. MSW (men who have sex with women)
D. WSM (women who have sex with men)

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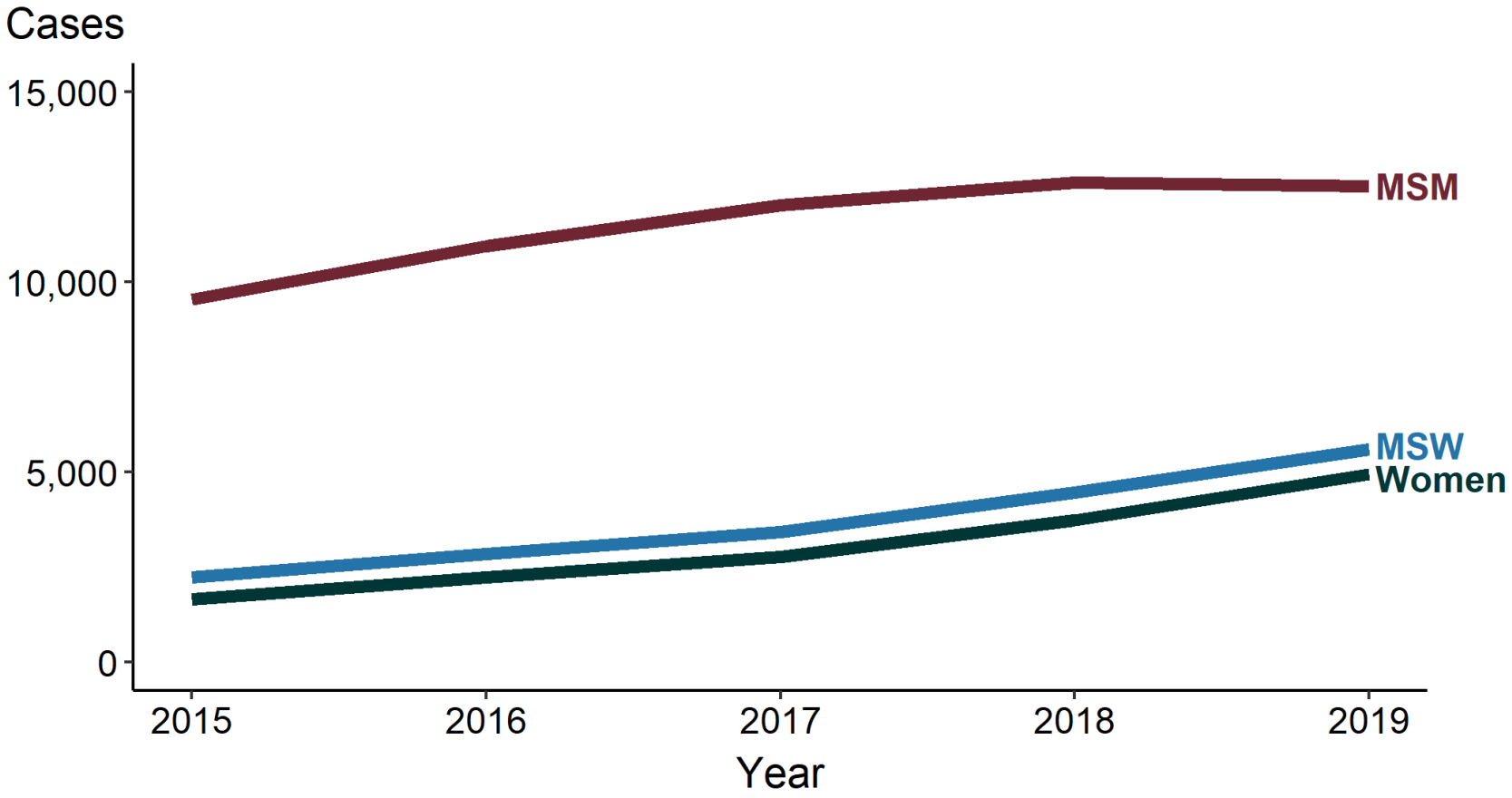
HIGHEST RISK DEMOGRAPHIC GROUP?



*31 states were able to classify ≥70% of reported cases of primary and secondary syphilis among males as either MSM or MSW for each year during 2015–2019.

ACRONYMS: MSM = Gay, bisexual, and other men who have sex with men; MSW = Men who have sex with women only

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TAKE-HOME POINT

- Syphilis IS still an active problem
- Highest risk demographic = MSM (men who have sex with men)

NEUROSYPHILIS

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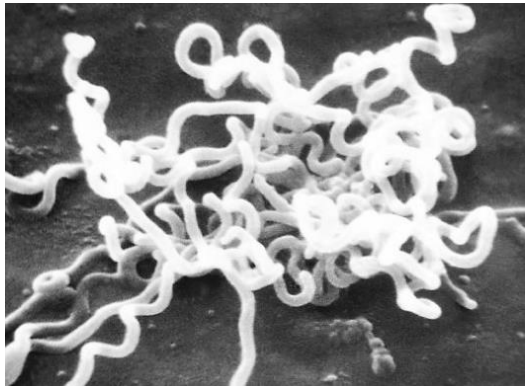
- Syphilis clinical review
- Neurosyphilis
  - Early
  - Late
- Diagnosis
- Treatment



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QUESTION 3: NEUROLOGIC INVOLVEMENT IN SYPHILIS IS SEEN ONLY IN LATE LATENT OR TERTIARY SYPHILIS.

- True

Or

- False

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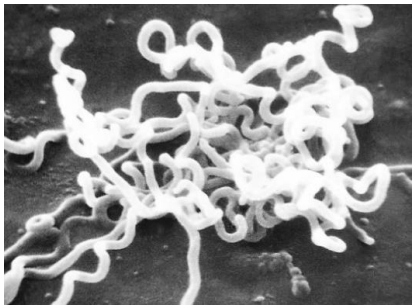
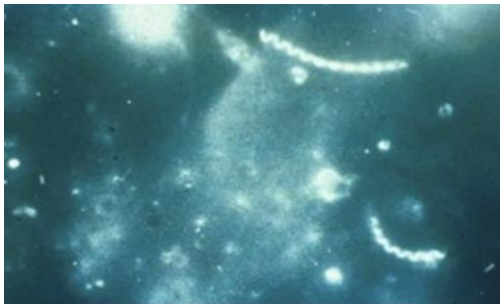
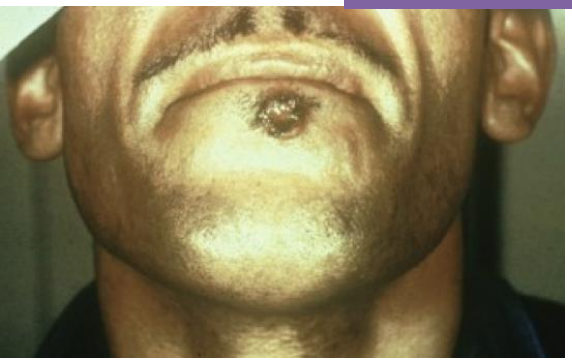


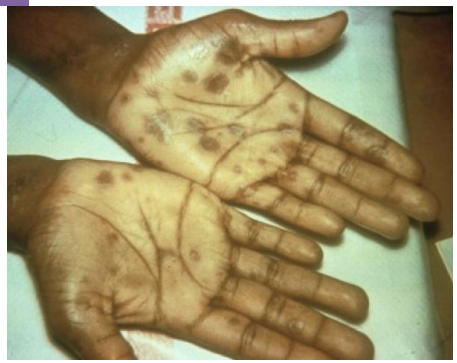
SYPHILIS REVIEW

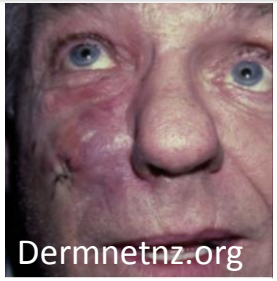


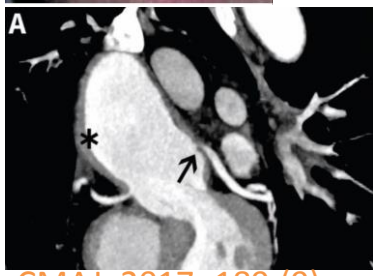
Primary Secondary Latent Tertiary

Neurosyphilis

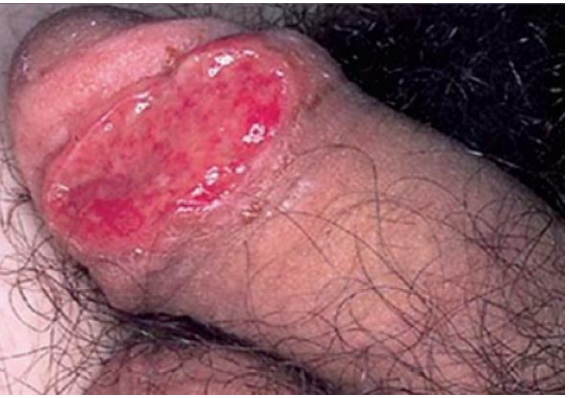






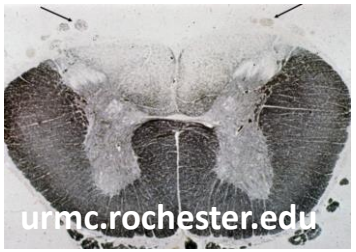


CMAJ. 2017; 189 (9).



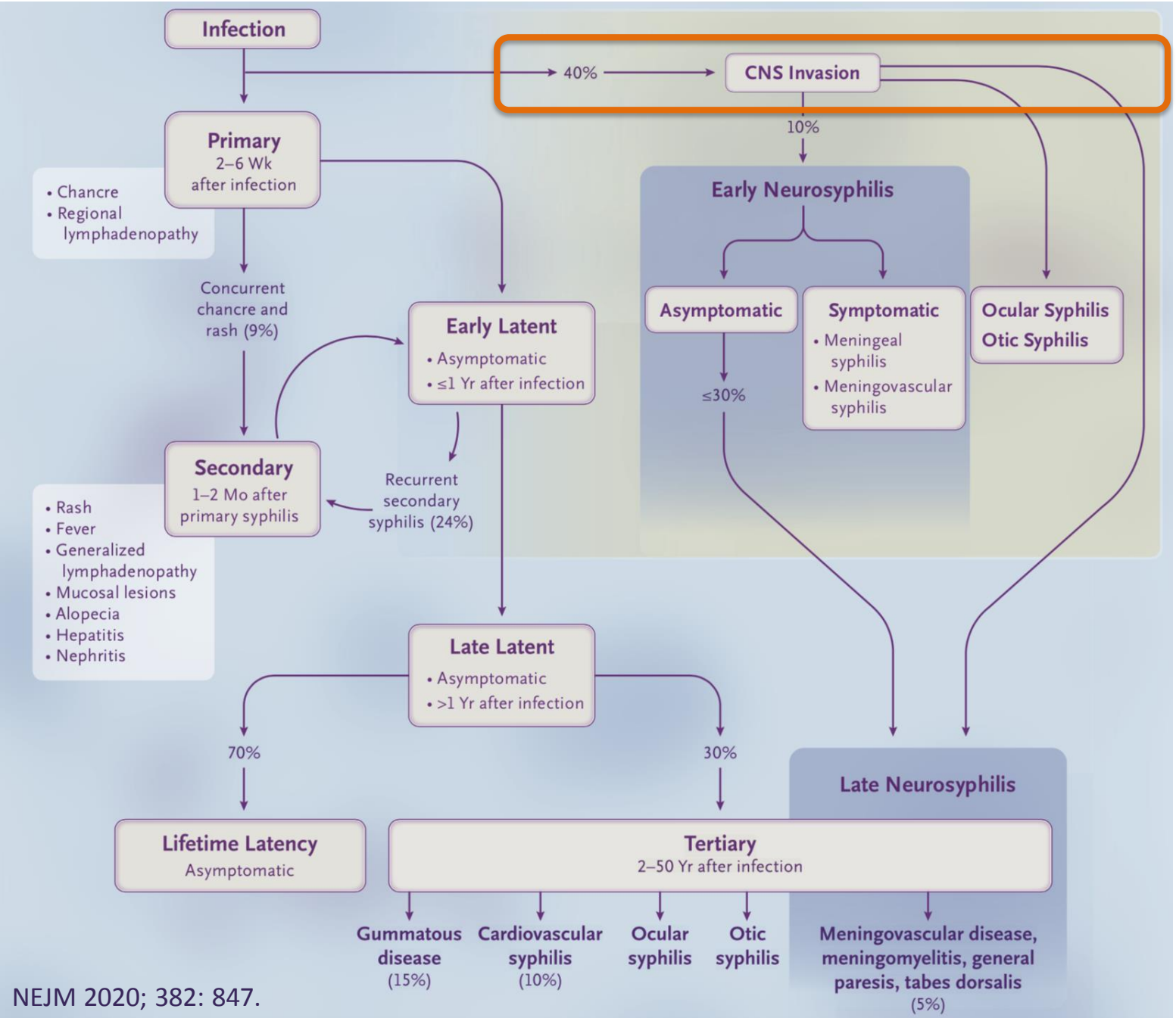
NEJM 2020; 382: 845-54.

https://www.cdc.gov/std/syphilis/images.htm



General paresis

NEUROSYPHILIS CAN DEVELOP AT ANY STAGE



NEJM 2020; 382: 847.

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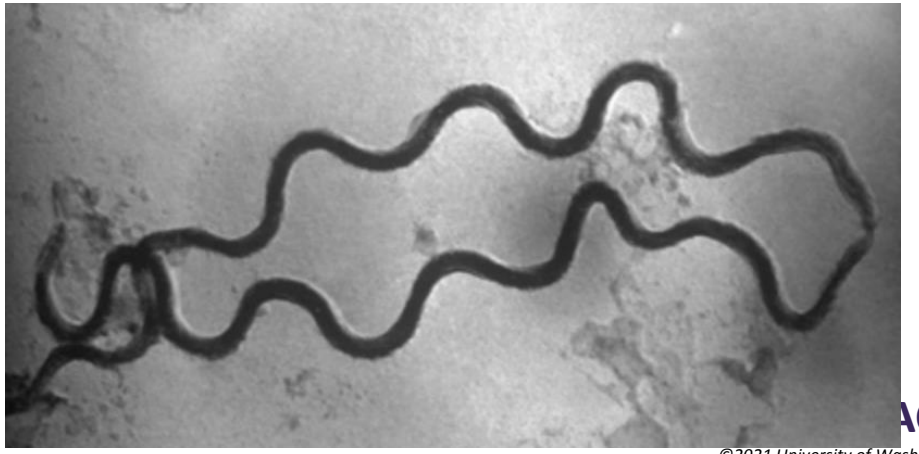
TAKE-HOME POINT

- Neurosyphilis can occur at ANY STAGE of syphilis



NEUROSYPHILIS

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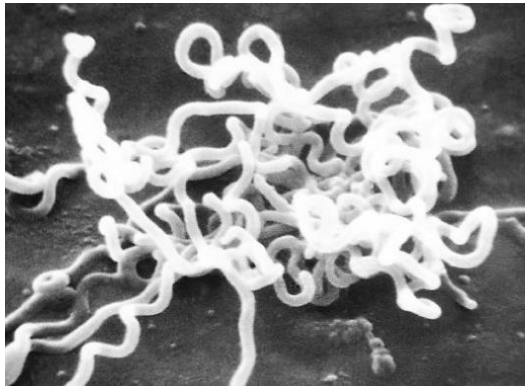

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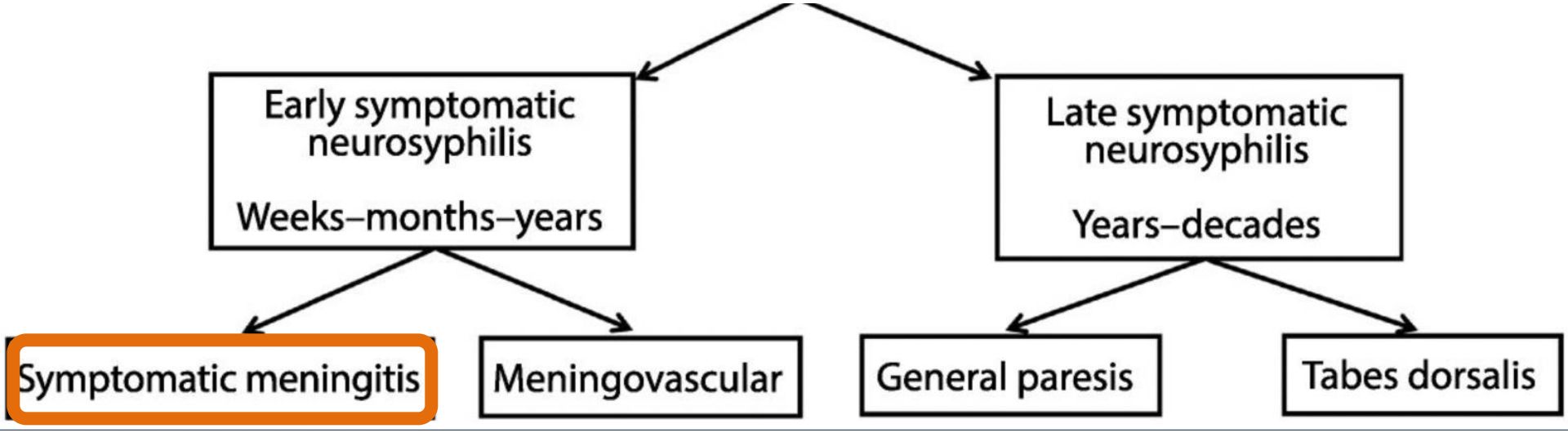
HOW TO RECOGNIZE NS: EARLY



- Headache, photophobia, neck stiffness, confusion/encephalopathy
- Cranial neuropathies (CN II, VII, VIII)

NEJM 2020; 382: 847. Continuum 2015; 21(6): 1714-1728. Continuum 2021; 27(4): 1018-1039.

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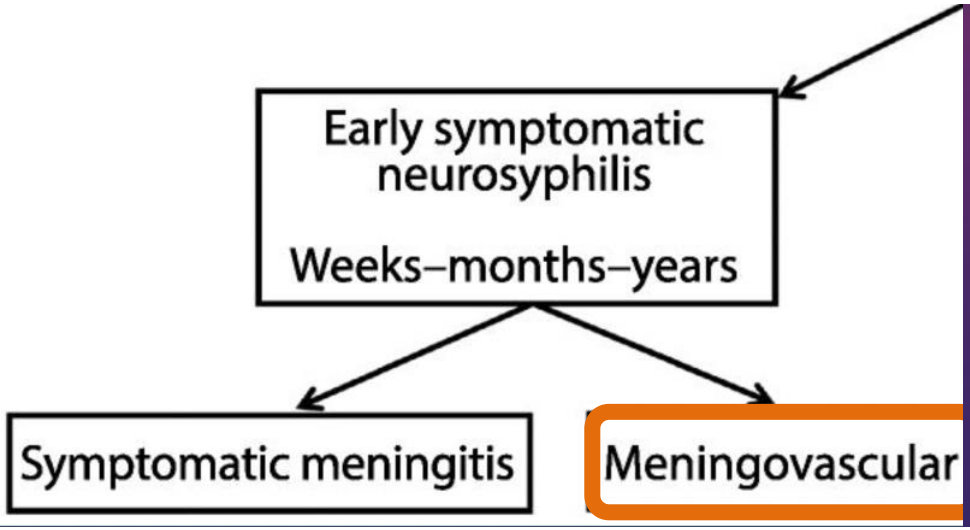
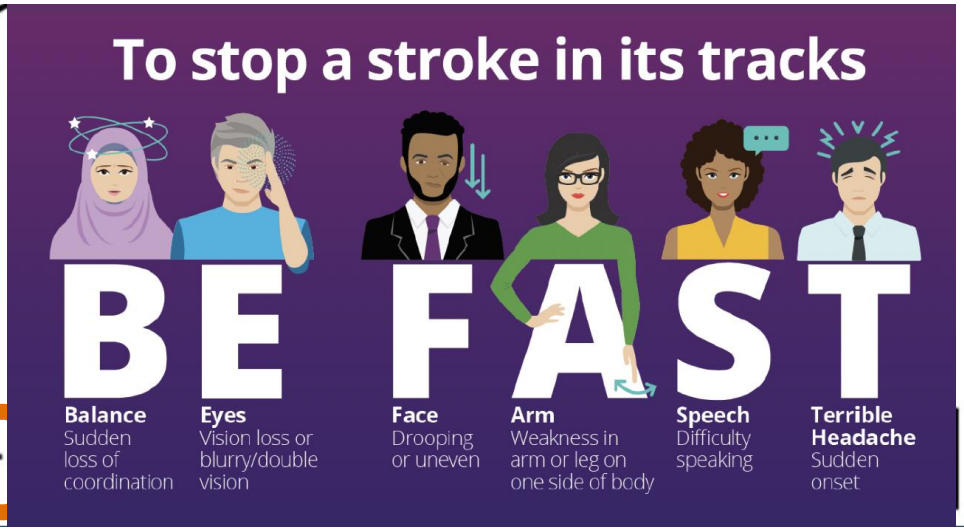
HOW TO RECOGNIZE NS: EARLY





- Acute stroke with focal neurologic deficits
  - Clues to make you suspicious:
    - Prodromal meningitis symptoms (headache, neck stiffness, etc…)
    - Sexual history suggests risk
    - Lack of traditional vascular risk factors (HTN, HLD, DM, Afib…)

NEJM 2020; 382: 847. Continuum 2015; 21(6): 1714-1728. Continuum 2021; 27(4): 1018-1039.

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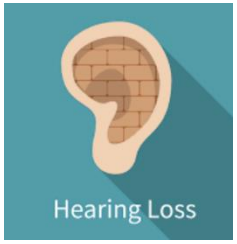
HOW TO RECOGNIZE NS: EARLY

Ocular

- Can involve any structure of the eye!
  - Posterior uveitis
  - Panuveitis
- Symptoms may include:
  - Decreased visual acuity/vision loss
  - Redness
  - Sensitivity to light
  - +/- Pain



Otic

- Sensorineural hearing loss
- +/- Tinnitus
- +/- Vertigo

Even if no other neurologic symptoms, ocular/otic syphilis= neurosyphilis!

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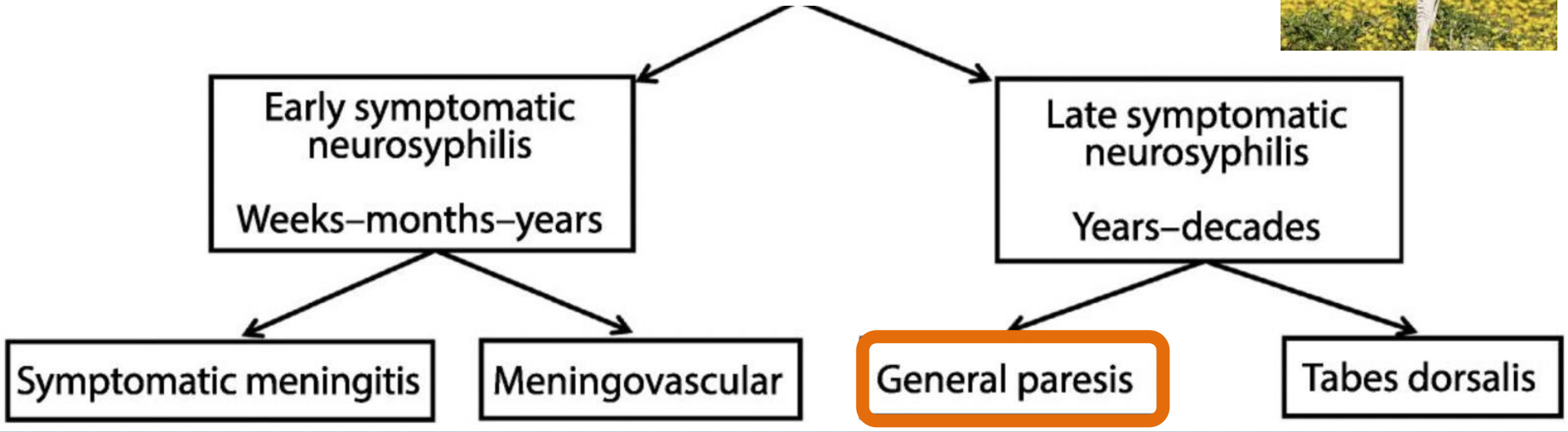
HOW TO RECOGNIZE NS: LATE



- Personality/behavioral changes, psychiatric symptoms
- Cognitive impairment
- Seizures

NEJM 2020; 382: 847. Continuum 2015; 21(6): 1714-1728. Continuum 2021; 27(4): 1018-1039.

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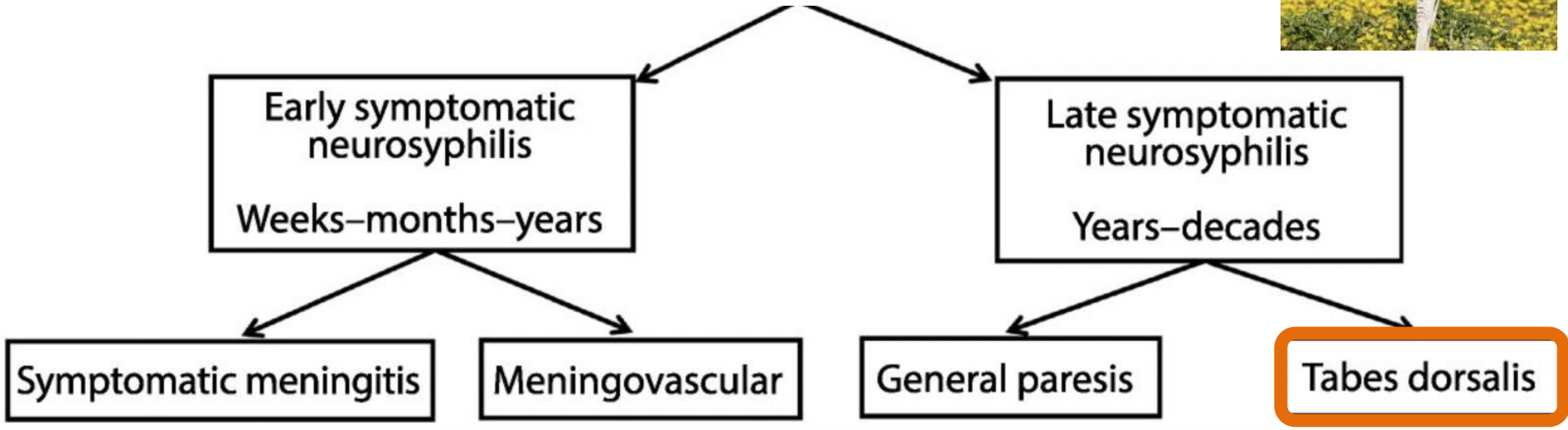
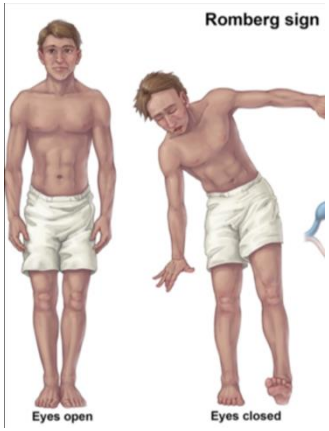
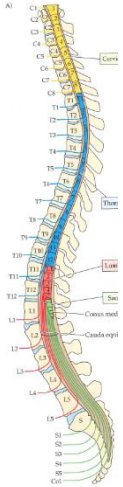
HOW TO RECOGNIZE NS: LATE



- Sensory gait ataxia, impaired proprioception, lancinating pain in trunk and legs
- Lower extremity areflexia





[NEJM Tabes Dorsalis 2016; 375:e40]

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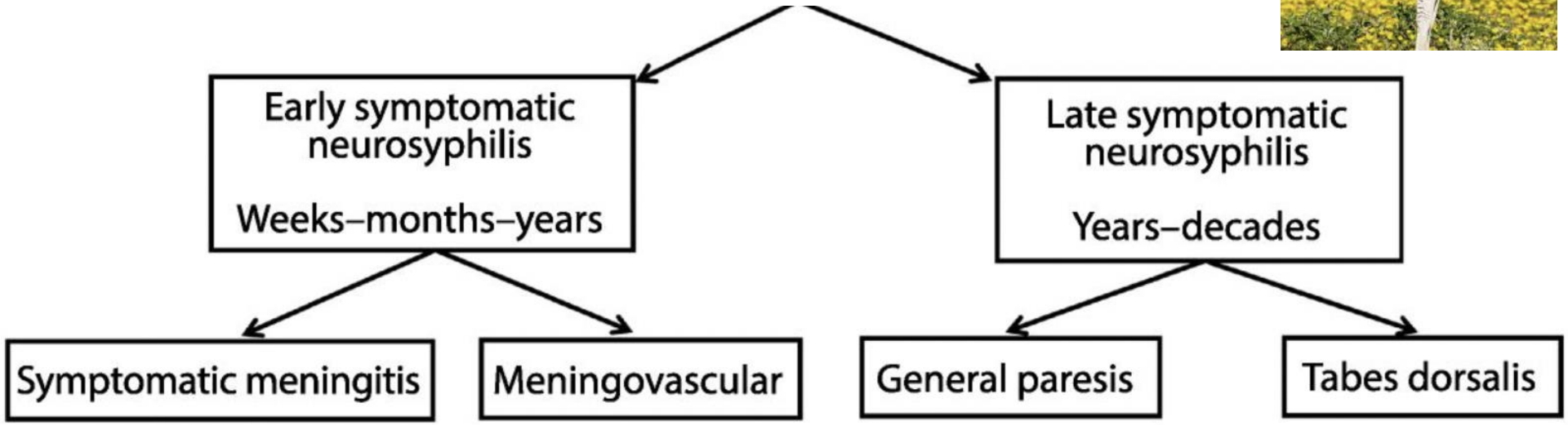
NEJM 2020; 382: 847. Continuum 2015; 21(6): 1714-1728. Continuum 2021; 27(4): 1018-1039.

HOW TO RECOGNIZE NS: LATE



Syphilitic Gummas

- Proliferative granulomatous lesions that can affect brain or spinal cord
  - Can be mistaken for tumors on imaging
  - Presenting symptoms: headache, seizure, focal weakness (depending on location of lesion)

NEJM 2020; 382: 847. Continuum 2015; 21(6): 1714-1728. Continuum 2021; 27(4): 1018-1039.

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HOW TO IDENTIFY NEURO SYMPTOMS? ASK!

Table 2. Frequency of Self-reported Symptoms in Interviewed Early Syphilis Cases Self-reporting ≥ 1 Neurologic or Ocular Symptom—STD Surveillance Network[a], October 2016–November 2017 (n = 151)

Self-reported Symptoms	No. (%)
Ocular symptoms in past 60 d[b]	
Blurry vision	46 (30)
Vision changes	33 (22)
Floaters	22 (15)
Vision loss	14 (9)
Red eye	15 (10)
Eye pain	12 (8)
Flashing lights	15 (10)
Other (eg, photophobia)	23 (15)
Neurologic symptoms in past 60 d[b]	
Headaches	58 (39)
Tinnitus (ringing in ears)	32 (21)
Hearing change	26 (17)
Hearing loss	11 (7)
Altered mental status	7 (5)
Other (eg, unsteadiness, dizziness, decreased memory)	23 (15)
Stroke-like symptoms	4 (3)

[a]Five STD Surveillance Network jurisdictions participated in the enhanced surveillance project.

[b]Symptoms are not mutually exclusive.

CID 2021; 72(6): 961-7.

Have you experienced a change in hearing in the past 60 days?

Have you experienced hearing loss in the past 60 days?

Have you experienced ringing or buzzing in your ears (tinnitus) in the past 60 days?

Have you experienced headaches in the past 60 days?

Have you experienced an altered mental status in the past 60 days?

Have you experienced stroke-like symptoms in the past 60 days?

https://www.cdc.gov/std/funding/ssun/strategyc_ocular_neurosyphilis_surveillance_protocol_march-2019.pdf

Have you experienced dizziness or balance troubles in the past 60 days?

Have you experienced a stiff neck in the past 60 days?

Have you experienced eye pain in the past 60 days?

Have you experienced blurry vision in the past 60 days?

Have you experienced red eye in the past 60 days?

Have you experienced vision changes in the past 60 days?

Have you experienced any flashing lights in the past 60 days?

Have you experienced any floaters in the past 60 days?

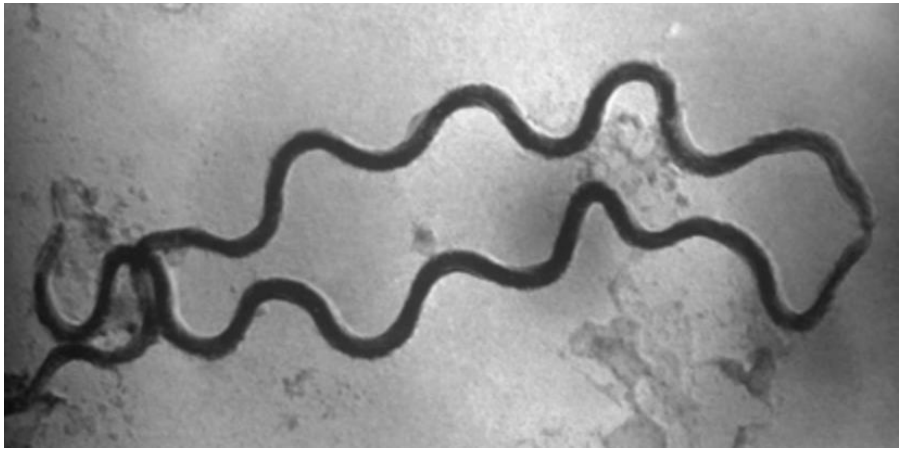
Have you experienced vision loss in the past 60 days?

Have you experienced photophobia or light sensitivity in the past 60 days?

Have you experienced double vision in the past 60 days?

Have you experienced any other neurologic, otologic, or ocular symptoms in the past 60 days?

ARE CERTAIN NEUROLOGIC SYMPTOMS MORE PREDICTIVE OF NEUROSYPHILIS (NS) THAN OTHERS?



CID 2018; 66(3): 363-367.

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ASSOCIATIONS BETWEEN SYMPTOMS AND NEUROSYPHILIS (REACTIVE CSF-VDRL)

Symptom	Odds Ratios (95% CI)	
	HIV-	HIV+
≥Mild photophobia	0.5	2.0 (1.1-3.8)*
≥Mild gait incoordination	1.3	2.4 (1.3-4.4)**
≥Mild vision loss	1.6	2.3 (1.3-4.1)**
≥Moderate vision loss	2.3	6.7 (3.5-12.9)***
≥Moderate hearing loss	0.6	3.1 (1.3-7.5)*

*P<0.05, **P<0.01, ***P<0.001

CID 2018; 66(3): 363-367.

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TAKE HOME POINT

- Symptomatic Neurosyphilis has a number of potential clinical symptoms, clues to the diagnosis…
  - Meningitis symptoms? Meningovascular symptoms?
  - Ocular or otic symptoms?
  - Parenchymal forms (less common) general paresis, tabes dorsalis, syphilitic gummas
  - Specific symptoms might raise suspicion (in those who are HIV+)…

CASE: 46

- 46yo mal
  vision ch
  prior pen
- **Exam**:

Base Eye Exam

Visual Acuity (Snellen - Linear)

	Right	Left
Dist sc	CF	
Near sc	CF	20/30
Near cc	CF	20/20

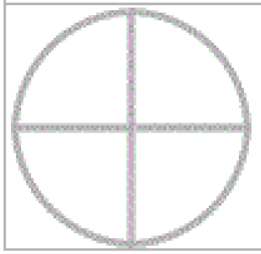
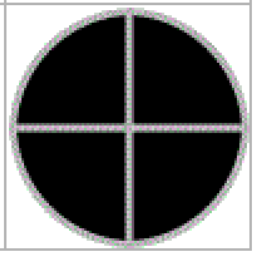
Tonometry (Tonopen, 6:43 PM)

	Right	Left
Pressure	11	13

Pupils

	Dark	Light	Shape	React	APD
Right	3	2	Round	Brisk	None
Left	3	2	Round	Brisk	None

Visual Fields

Left	Right
Full	
	

Extraocular Movement

Right	Left
Full, Ortho	Full, Ortho

Dilation

Both eyes: 1.0% Mydriacyl, 2.5% Phenylephrine @ 6:43 PM

Edited by: Van Brummen, Alexandra, MD

Additional Tests

Color

	Right	Left
Ishihara	0/11	11/11

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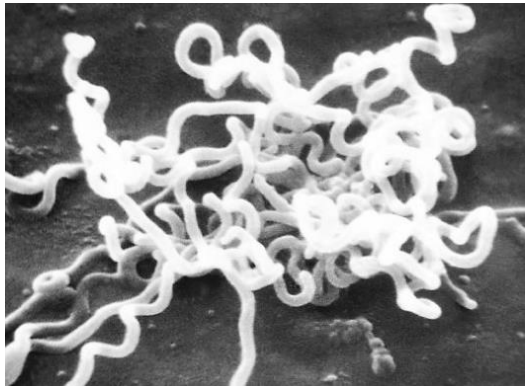

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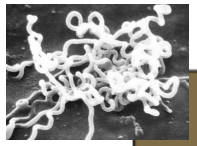
INTERPRETING SYPHILIS LABS…



EIA *or* CIA

(+)

(-)

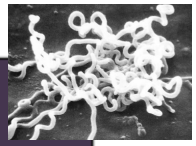
No evidence of syphilis

Quantitative RPR or VDRL

(+)

(-)

Syphilis
(past or present)



TP-PA

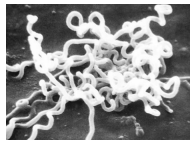
(+)

(-)

Syphilis
(past or present)

Syphilis unlikely

After successful treatment, antibody titers usually decline in most people



Treponemal tests are often positive for life

https://www.std.uw.edu/go/pathogen-based/syphilis/

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INTERPRETING SYPHILIS LABS CAN BE MURKY (SOMETIMES)

Serum treponemal test (eg, TPPA, FTA-ABS, treponemal immunoassays)	Serum nontreponemal test (eg, RPR): +	Serum nontreponemal test (eg, RPR): −
+[a]	**True positive:** untreated syphilis **True positive:** treated syphilis with inappropriate decline in nontreponemal titer or serofast nontreponemal titer	**True positive:** treated syphilis with appropriate decline in nontreponemal titer to nonreactive **True positive:** untreated late syphilis with decline in nontreponemal titer over time **False negative:** false negative nontreponemal test in setting of early (ie, primary) syphilis before seroconversion of nontreponemal test, prozone reaction, or HIV infection **False positive:** false positive treponemal test in various settings,[62,63] including yaws, pinta, or another endemic treponemal infection; other infections (eg, malaria, leprosy); pregnancy; and autoimmune disease
−	**False positive:** false positive nontreponemal test in various settings, including pregnancy, injection drug use, autoimmune disease, older age, and other infections such as tuberculosis, rickettsial infection, and malaria	**True negative:** no evidence of syphilis infection **False negative:** early (ie, primary) syphilis before seroconversion of nontreponemal and treponemal tests

Continuum 2021; 27(4): 1018-1039.

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CASE: 46YO W/ VISION CHANGES, A DIAGNOSTIC TEST RETURNED…

- T. Pallidum IgG/IgM Reactive
- RPR Reactive, 1:512
- TP-PA Reactive

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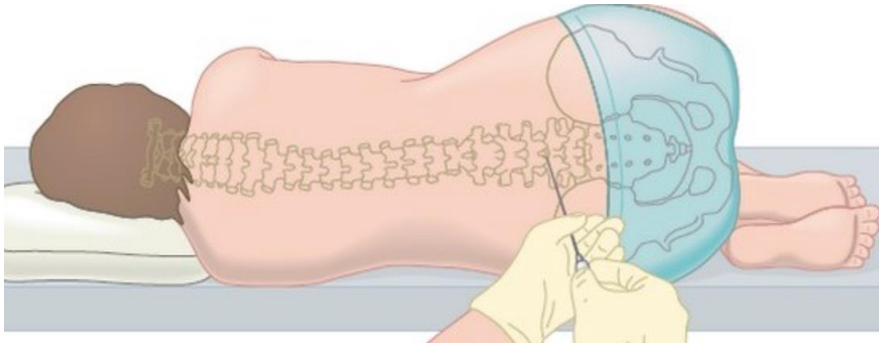
QUESTION 4: WOULD YOU DO A LUMBAR PUNCTURE? (46YO MAN WITH VISION LOSS AND LABS SUGGESTIVE OF SYPHILIS)

- Yes
- No

TO DIAGNOSE NEUROSYPHILIS, WE NEED A LUMBAR PUNCTURE (LP)!

Per CDC guidelines, LP should be done in syphilis patients with:

- Cranial nerve dysfunction
- Meningitis
- Stroke
- Altered mental status
- Loss of vibration sense
- Vision loss
- Hearing loss

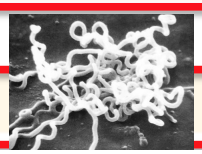


Workowski KA, Bolan GA, Centers for Disease C, Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep 2015;64:1-137.

NEUROSYPHILIS LABS

Table 2. Sensitivity and Specificity of Laboratory Tests for Neurosyphilis.*

Test	Sensitivity		Specificity
	Early Neurosyphilis	Late, Symptomatic Neurosyphilis	Late, Symptomatic Neurosyphilis
		percent	
CSF content			
White-cell count >5–10/mm^3¶	100	95	Approximately 97
Protein >45 mg/dl‖	90	95	<50
Serologic tests			
Serum VDRL and RPR†	100‡	50–75	90
CSF VDRL	75§	30–70	100 (if not contaminated with blood)
Serum FTA-ABS, TPHA	100‡	Approximately 96	Approximately 60
CSF FTA-ABS	100	Approximately 99	Approximately 50–70



NEJM 2019; 381: 1358-63.

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CASE: 46YO W/ VISION CHANGES (CONT…)

- Lumbar puncture opening pressure was normal at 19.5 cm H20
  - CSF WBC 10 (78%L, 16%N, 6% M)
  - CSF RBC 10
  - CSF protein 39
  - CSF glucose 57
  - CSF VDRL + 1:1

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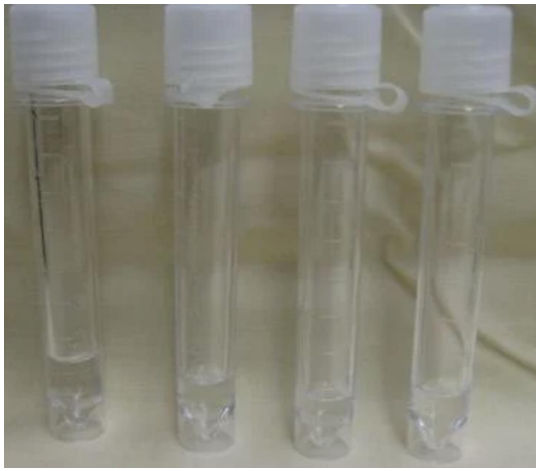
TIPS FOR RECOGNIZING NEUROSYPHILIS BY CSF

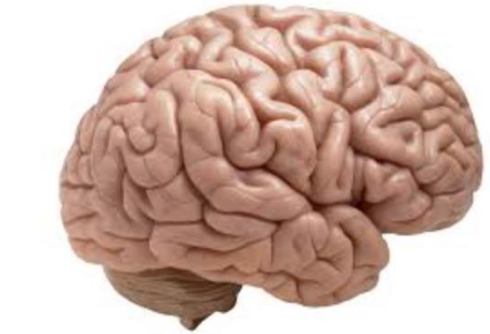
- Likely consistent w/ NS
  - Reactive CSF-VDRL (specific > sensitive)
  - CSF WBCs pleocytosis
    - HIV uninfected, WBC > 5
    - HIV infected
      - **If CD4 < 200 + plasma VL undetectable and on ARV: WBC >5**
      - **If CD4 >200 OR plasma VL detectable OR not taking ARV: WBC >20**
- Less consistent w/ NS
  - Non-reactive CSF-FTA ABS (sensitive > specific)

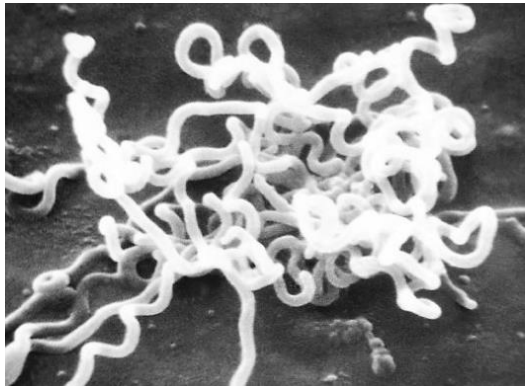


BMC Infect Dis 2007; 7: 37. Continuum 2015; 21(6): 1724. JID 2004; 189: 369-76.

NEUROSYPHILIS

- Epidemiology of syphilis
- Syphilis clinical review
- Neurosyphilis
  - Early
  - Late
- Diagnosis
- Treatment





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WHY DO WE NEED TO DIAGNOSE NEUROSYPHILIS?

- Treatment is different for NS

Table 2. Treatment Guidelines for Antimicrobial Management of Syphilis.*

For primary and secondary syphilis in nonpregnant adults, including HIV-infected adults:
Penicillin G benzathine, 2.4 million units in a single IM dose
Doxycycline, 100 mg orally twice a day for 14 days (first alternative)
Ceftriaxone, 1–2 g daily, IM or IV, for 10–14 days (second alternative)

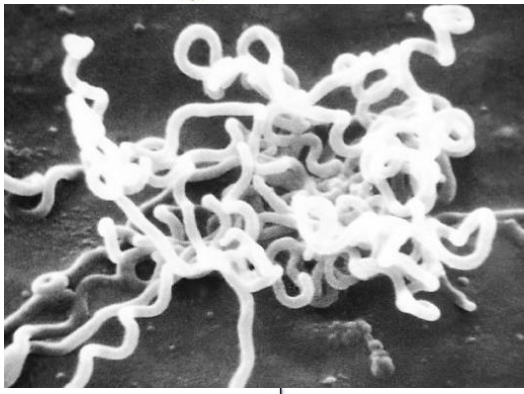
For latent syphilis in nonpregnant adults, including HIV-infected adults:
Early latent: penicillin G benzathine, 2.4 million units in a single IM dose
Late latent: penicillin G benzathine, 7.2 million units total, administered in 3 IM doses of 2.4 million units each at 1-week intervals
Doxycycline, 100 mg orally twice a day for 28 days (alternative)

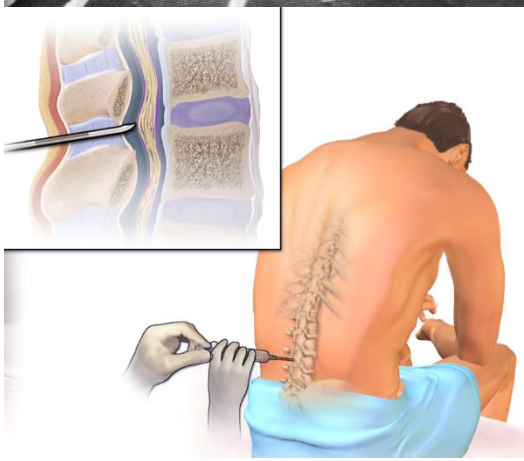
For late syphilis (gummas and cardiovascular manifestations) but not neurosyphilis:
Penicillin G benzathine, 7.2 million units total, administered in 3 IM doses of 2.4 million units each at 1-wk intervals

For neurosyphilis and ocular syphilis:
Aqueous crystalline penicillin G, 18–24 million units per day, administered in IV doses of 3–4 million units every 4 hr or as a continuous infusion, for 10–14 days
Penicillin G procaine, 2.4 million units in a single IM dose daily, plus probenecid, 500 mg administered orally four times a day, both for 10–14 days (alternative)

SUMMARY

- Syphilis IS still an active problem
- Highest risk demographic = MSM
- Neurosyphilis can occur an ANY STAGE of syphilis
- Neurosyphilis has a myriad of potential clinical presentations
- To diagnosis neurosyphilis start with serologies and if suspicious you need spinal fluid/lumbar puncture!





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QUESTIONS?

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