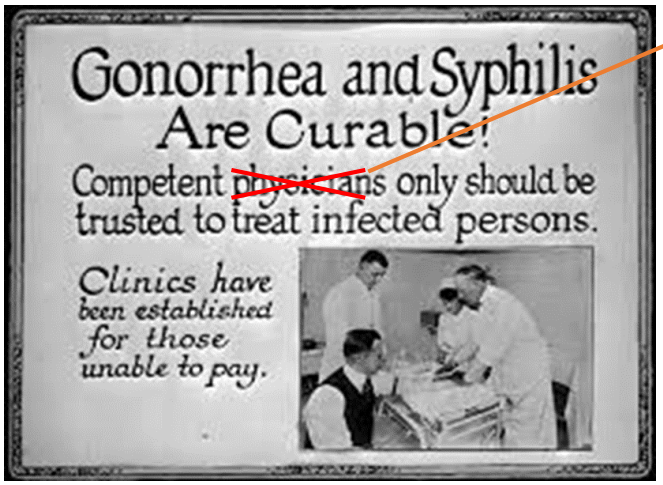

AND Nurse Practitioners!!!
AND Physician Assistants!!!

Syphilis Update

Oliver Bacon, MD, MPH
Physician, SF City Clinic
Disease Prevention and Control Branch
Population Health Division

City Clinic
A landmark in prevention

roadmap

1. Syphilis: diagnosis and treatment of 1ary, 2ary, Latent
2. Infectivity and partner services
3. Diagnostic challenges: window periods, titers, new algorithms
4. Approach to possible Neurosyphilis, including eyes and ears
5. Preventing congenital syphilis

2

Some Syphilis Basics

- Treponema Pallidum: motile (bendy) coiled spirochete with 6-14 spirals
- 6-15 uM long, 0.24uM wide, non-Gram staining: invisible on light microscopy
- Humans only host
- Cannot be cultured; no commercially available antigen/PCR testing
- Diagnosis: clinical, direct visualization by darkfield microscopy or immune fluorescence, plus serology
- Primary pathologic lesion: obliterative endarteritis with inflammatory infiltrate (plasma cells, macrophages, lymphocytes, +/- granulomas
- Systemic dissemination within 24 hours of inoculation
- Rapidly killed by penicillin, doxycycline

3

https://youtu.be/KIsfl50IrMU

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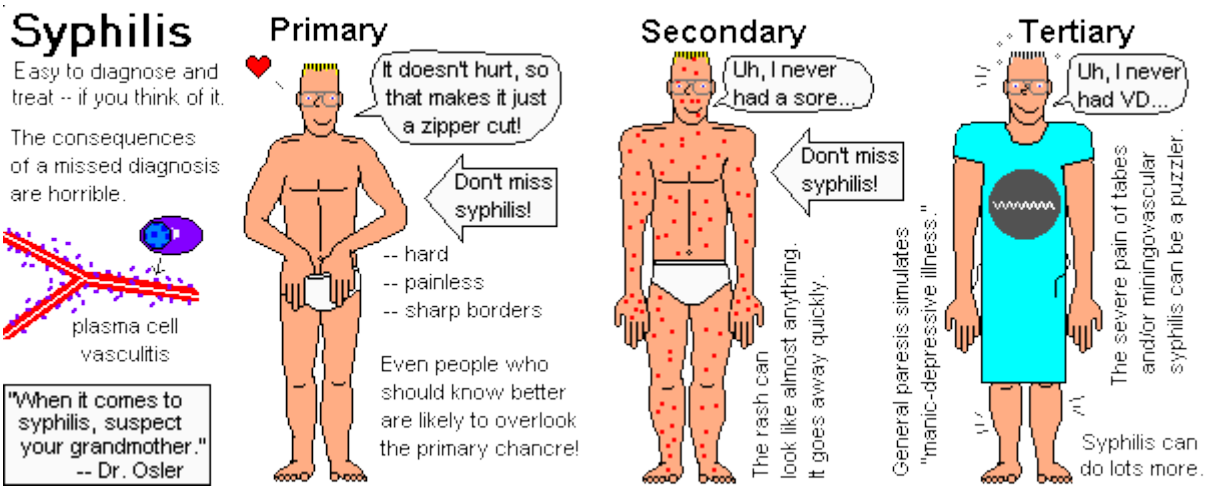

Primary, secondary syphilis: how it's *supposed* to happen:

1. See a typical lesion of primary or secondary syphilis
2. Confirm diagnosis with positive nontreponemal, treponemal serology, and direct visualization (darkfield or fluorescent microscopy—rarely available) or tissue staining (impractical)
3. Treat (penicillin or doxycycline)

But……it's often not so straightforward……..

6

Case 1: 35, MSM, HIV(-), PrEP

- 11/1/17: PrEP quarterly follow-up at Magnet: RPR non-reactive
- 1/10/18: 2 small, dry "sores" on penis
- 1/17/18: Comes to City Clinic. STAT RPR, automated RPR, TPPA all negative
- 1/22/18: dermatologist. "this is syphilis," and gives doxycycline 100mg BID x 14d
- 1/22/18: returns to City Clinic: STAT RPR nonreactive; automated RPR 1:2, TP-PA reactive: given benzathine Penicillin 2.4MU IM

7

Audience Response Question:

What's going on here?

1. Secondary syphilis with a low titer RPR
2. Early latent syphilis: the penile lesions are something else
3. Primary syphilis in the serologic window period
4. Yaws

8

Serologic Syphilis Screening/Testing Paradigm

TRADITIONAL

Non-treponemal (NTT) tests (i.e., RPR, VDRL)

- **Non-specific to TP**
- **Quantitative: reported as titer**
- **(1:1, 1:2, 1:4, 1:8, 1:16, 1:32……1:2048 and higher)**
- **Reactivity increases, then declines with time (usually highest in secondary)**
- **Susceptible to prozone phenomenon (usually in secondary)**
- **With treatment, some revert to nonreactive, others to low-reactive (serofast)**

If NTT (+), reflex to:

Treponemal tests (i.e., TPPA, FTA-Abs)

- **Specific to *TP***
- **Qualitative**
- **Reactivity persists over time**

Timeline and infectivity: early through late disease

STAGE	STARTS	LASTS (untreated)	Other sxs	Infectivity
Primary	10d-12 weeks after inoculation (median time 21 d)	1-6 weeks	• Papule->Chancre • Nontender regional adenopathy	• Infectious by direct contact or blood
Secondary	• 2-8 weeks after chancre heals *or* • 4-8 weeks after onset of chancre • can overlap with 1ary	"Several weeks"	• symmetric, bilateral rash • mucous patches/condyloma lata • fever, headache, pharyngitis • hepatitis, osteitis, glomerulonephritis • meningitis/ocular/oto-	• Infectious by direct contact (when mucosal lesions present) or blood
Early Latent	After resolution of 2ary symptoms	• Until 1 year after inoculation • can alternate with 2ary	• Neurologic: meningitis, ocular, oto-, meningovascular (strokes)	• Infectious by direct contact (when mucosal lesions present) or blood
Late Latent	1 year after inoculation	Until treatment or development of late symptomatic disease		• Infectious by blood
Late Symptomatic	15-25 years after inoculation	Until treatment	• General paresis (CNS parenchyma) • Tabes dorsalis (posterior columns: sensory/proprio) • Cardiac (aortitis, infarction) • Late benign (gummatous)	

10

Partner Services by SFDPH

- Offered to all patients with a new P&S syphilis diagnosis
- Offered to patients with new HIV infection
- Voluntary, culturally appropriate services

For patients with HIV or syphilis… When you partner with us, you help your partners	
Who are we?	• We're highly trained specialists who work at San Francisco City Clinic, with the Department of Public Health.
What do we do?	• We help improve the health of people in San Francisco by partnering with Magnet.
Why do we do it?	• HIV and Syphilis rates are high, especially among gay men. • People who may have been exposed to HIV should get tested. Anyone exposed to syphilis should get both testing and treatment. • Syphilis can be cured, but without treatment it can spread and cause serious health consequences. • HIV can be managed, but unless people are tested and know their status, they may not get the care important to keeping them healthy.
How do we do it?	• In a CONFIDENTIAL, RESPECTFUL, and NONJUDGMENTAL conversation, we'll… • Make sure you receive the best care and treatment. • Answer your questions. • Help you figure out which of your sex partners may have been exposed and discuss the best ways to get them tested and/or treated. • Help you contact your partners or, if you'd like, contact them anonymously for you. • Ask you some questions to help us better understand patterns of syphilis and HIV infection in San Francisco.
When and where do we do it?	• We'll call you within a few days. • We'd like to meet in person or talk on the phone at a time that works for you.
So that's us. What about you?	• Talking with us is your choice. We hope you'll partner with us to stop the spread of syphilis and HIV in .
Got questions about what we do?	• Call us at (415)-487-5506
www.SFCityClinic.org	

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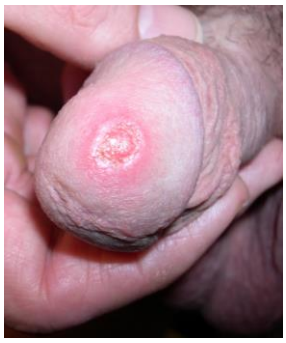
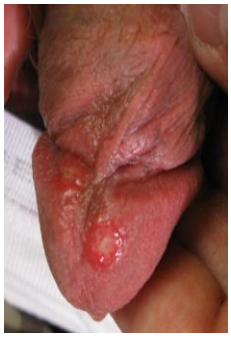
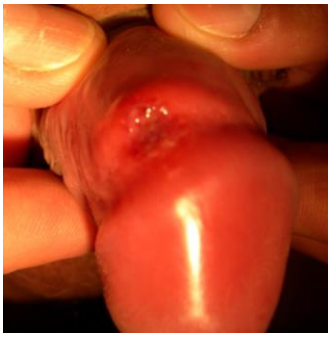
Primary Syphilis

Textbook cases

- Painless ulcer at site of inoculation (unless superinfected)
- Usually indurated edges
- Darkfield positive (if darkfield microscopy available)
- Serology often, but not always, reactive

Photos courtesy of Joe Engelman, MD, SF City Clinic

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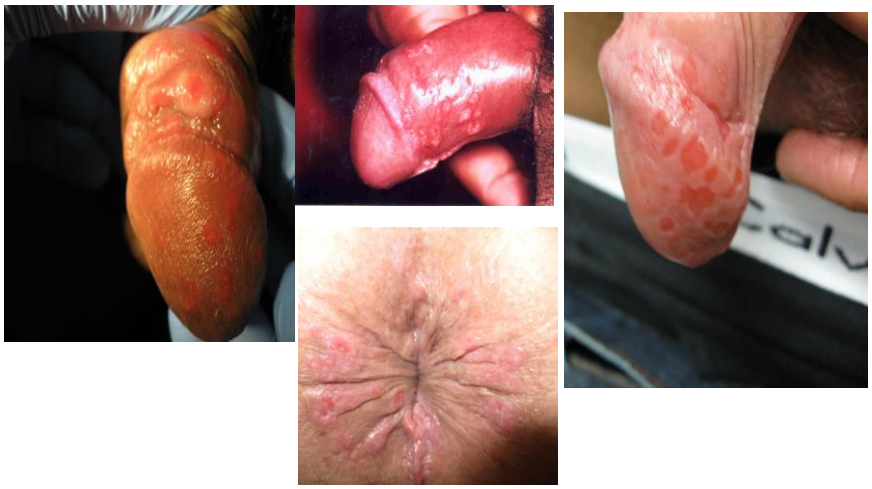
Primary Syphilis and HIV+

Multiple Ulcers, Atypical presentation



Photos courtesy of Joe Engelman, MD, SF City Clinic

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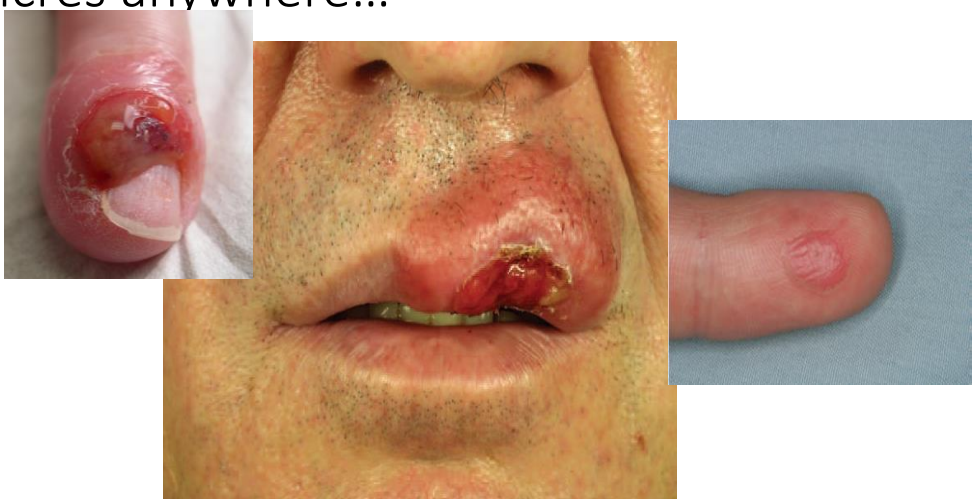
Primary syphilis- Chancres anywhere…



Raguse et al. Ann Int Med March 2012.

How often is the RPR negative in primary syphilis?

1) 5% of the time
2) 10% of the time
3) 20% of the time
4) 30% of the time

Audience Response Question:

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Performance of syphilis serologic tests

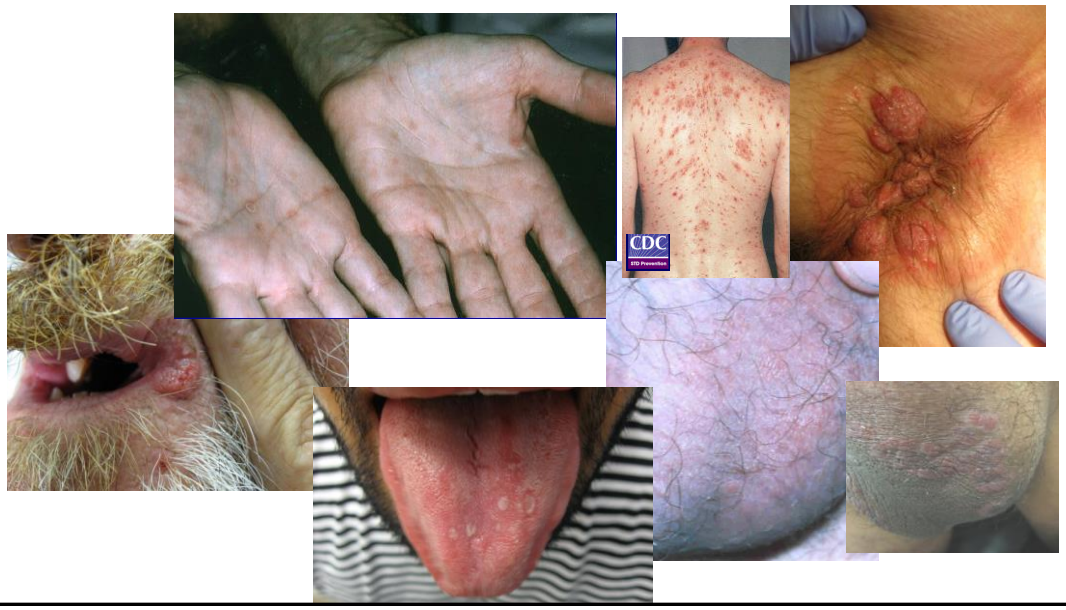
Test	Sensitivity during stage of infection, % (range)				Specificity, % (range)
	Primary	Secondary	Latent	Late	
Nontreponemal tests					
VDRL [14]	78 (74–87)	100	96 (88–100)	71 (37–94)	98 (96–99)
TRUST [14]	85 (77–86)	100	98 (95–100)	NA	99 (98–99)
RPR [14]	86 (77–99)	100	98 (95–100)	73	98 (93–99)
Early treponemal tests					
MHA-TP [15]	76 (69–90)	100	97 (97–100)	94	99 (98–100)
TPPA [16]	88 (86–100)	100	100	NA	96 (95–100)
TPHA [17]	86	100	100	99	96
FTA-ABS [14]	84 (70–100)	100	100	96	97 (94–100)
Enzyme immunoassays					
IgG-ELISA [18]	100	100	100	NA	100
IgM-EIA [19]	93	85	64	NA	NA
ICE [20]	77	100	100	100	99
Immunochemiluminescence assays					
CLIA [21]	98	100	100	100	99

NOTE. CLIA, chemiluminescence assay; ELISA, enzyme-linked immunosorbent assay; EIA, enzyme immunoassay; FTA-ABS, fluorescent treponemal antibody absorption assay; ICE, immune-capture EIA; MHA-TP, microhemagglutination assay for *Treponema pallidum;* NA, not available; TPHA, *T. pallidum* hemagglutination assay; TPPA, *T. pallidum* particle agglutination; TRUST, toluidine red unheated serum test.

Sena, CID 2010

17

Secondary Syphilis



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Early latent syphilis

1. Positive, confirmed serology (NTT *and* Treponemal) *AND*
2. No signs of 1ary, 2ary disease *AND*
3. Evidence of infection with syphilis within the last year (any of the following):
   - 4-fold or greater rise in nontreponemal titer
   - History indicative of infection/exposure in the last year:
     - Unequivocal symptoms of 1ary or 2ary syphilis in the prior year
     - A sex partner within the prior year documented to have 1ary, 2ary, or early latent syphilis

Late Latent or Latent of Unknown Duration:

1. Positive, confirmed serology (NTT *and* Treponemal) *AND*
2. No signs of 1ary, 2ary disease *AND*
3. No evidence of infection with syphilis within the last year
   - If negative titer>1 year ago: late latent
   - If no prior titer: Latent of unknown duration

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Early Syphilis Treatment

Primary, Secondary & Early Latent:

❖Benzathine penicillin G 2.4 million units IM in a single dose

Only one dose of PCN is recommended for early syphilis in HIV-infected persons, extra doses not needed

20

Staging determines Treatment

If you cannot ascertain that infection was acquired in the prior year, then must treat for late disease

What can help pinpoint timing of infection?

- Signs or symptoms of primary or secondary
- Can recall those symptoms in past year
- Contact to a known case in past year
- Negative syphilis test in the past year

–In HIV-infected patients, consider getting syphilis test with every CD4 or VL , approx every 3-6 months

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Syphilis Treatment

Primary, Secondary & Early Latent:

❖Benzathine penicillin G 2.4 million units IM in a single dose

Late Latent and Unknown Duration:

❖Benzathine Penicillin G 7.2 million units total, given as 3 doses of 2.4 million units each at 1 week intervals

Neurosyphilis:

❖Aqueous Crystalline Penicillin G 18-24 million units IV daily administered as 3-4 million IV q 4 hr for 10 -14 d

Only one dose of PCN is recommended for early syphilis in HIV-infected persons, extra doses not needed

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Follow-up/determining response to treatment:

- Repeat nontreponemal titer at (3), 6, (9), 12, (24) months
- (#)= HIV+, or patient at high risk of reinfection
- Serologic Rx failure: confirmed failure to achieve 4-fold decline in titer at 12 mo.; sustained 4-fold rise in titer in absence of repeat infection
- The NON-treponemal titer of many, but not all, patients treated for early syphilis will revert to zero.
- Some patients will achieve a 4-fold drop in titer, but remain NTT-reactive (serofast).
- It has been observed that serofast titers *can* be higher in some HIV(+) vs. HIV(-) patients.
- *Please draw day-of-treatment titer (to establish a baseline) as they can fluctuate widely and quickly early in disease!!*

Slow response or non-response:

- 15-27% of patients with early syphilis fail to achieve a fourfold decline in titer after 12 months, irrespective of HIV-infection status
- Declines are slower for late vs. early syphilis; and in patients with a prior history of syphilis
- *May be* slower in HIV-infected patients, esp. if NOT on ART or low CD4
- *If inadequate response is confirmed: CSF to look for neurosyphilis*
  - *If(+): treat*
  - *If (-): 3 weekly doses of 2.4MU benzathine PCN, and stop*

Sena CID 2011; Sena CID 2013; Ghanem K. CID 2008; Horberg M. *STD* 2010; Knaute DF CID 2012; CDC STD Treatment Guidelines MMWR 2015.

A Single Dose of Benzathine Penicillin G Is as Effective as Multiple Doses of Benzathine Penicillin G for the Treatment of HIV-Infected Persons With Early Syphilis

- Participants in US HIV Natural History Study (NHS) from Jan 1986- August 2013
- Retrospective cohort study
- 478 syphilis cases
- 141 (29%) received 1 dose
- 253 (53%) received ≥ 2 doses
- 85 (18%) received “other”

Ganesan CID 2015

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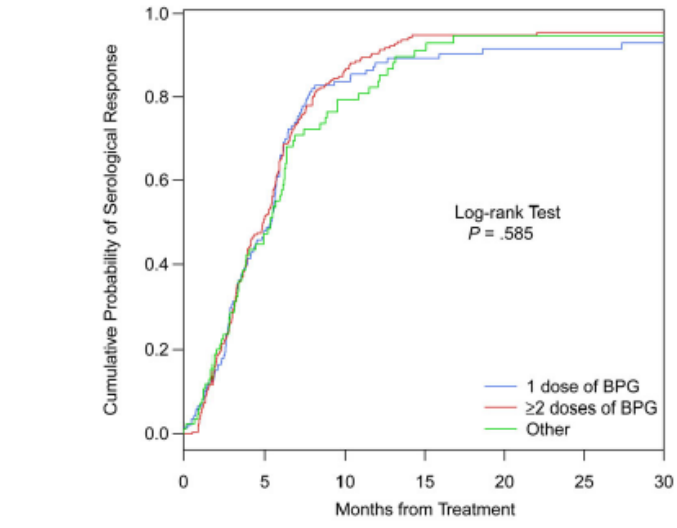


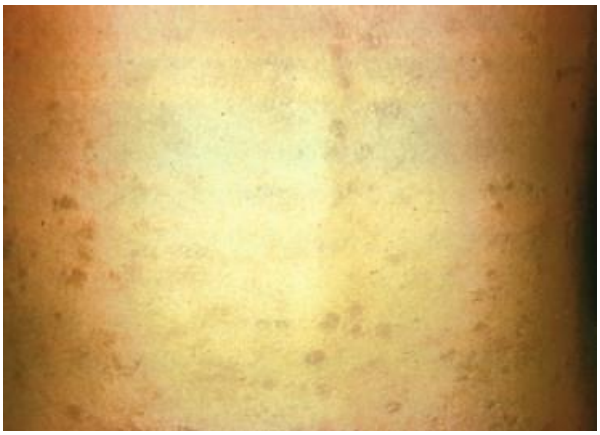
1 dose of BPG	141	70	18	10	7	6	4
≥2 doses of BPG	252	119	30	9	9	7	7
Other	85	42	14	5	3	3	3

Ganesan CID 2015

26

Case No. 2

- **27 yo male, HIV+**
  - **Well-controlled on ART**
    - **CD4 451 cells/µL**
    - **VL undetectable**
- **Presents to clinic with 1 week history of rash on chest, back**
  - **Papular, nonpruritic, hyperpigmented**
  - **Spares the palms & soles**
- ***AND (when you ask about it)…….***
  - **Intermittent headache**
  - **Blurry vision, especially at night**
  - **Occasional "flashing lights"**



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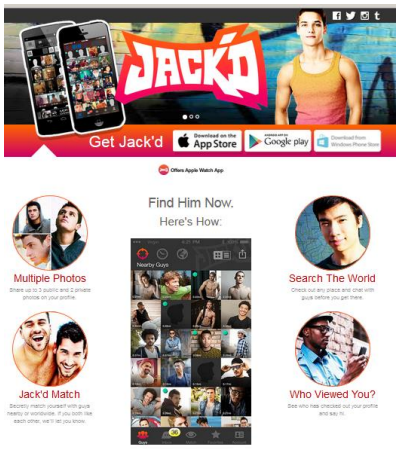
- **Sexual history**
  - **MSM, insertive/receptive oral & anal exposure**
  - **Reports ≈ 10 partners in past year**
    - **Location-based dating app with seroadaptive search strategy**



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Case 2, cont'd:

- **Additional history**
  - **3 weeks of**
    - **intermittent headache**
    - **blurry vision, esp. at night**
    - **occasional flashing lights**
- **RPR 1:128**
  - **TP-PA reactive**

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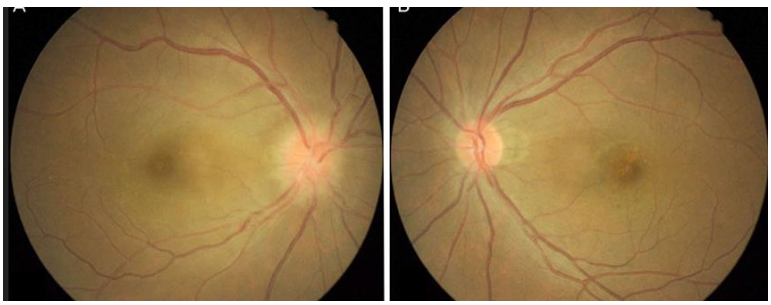
Audience Response Question:

What would you like to do?

1. Benzathine penicillin 2.4 MU
2. Obtain CSF
3. Refer urgently to ophthalmology
4. Notify partner services
5. All of the above
6. (1), (3), and (4)

30

- **CSF: WBC 4, Protein 41, glucose 65, CSF-VDRL nonreactive**
- **Referred to ophthalmologist for funduscopic examination**
- **Ophthalmologic exam reveals**
  - **anterior uveitis both eyes**
  - **left fundus: hyperemia, retinal inflammation, vasculitis**



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Syphilis – When to LP?

- Clinical signs of neurosyphilis
  - Cranial nerve dysfunction, meningitis, stroke, acute or chronic altered mental status, **auditory** or **ophthalmic** abnormalities (Ocular and Oto-syphilis ***ARE*** neurosyphilis)
- Confirmed serologic treatment failure
- Evidence of active tertiary syphilis (e.g. aortitis and gumma)
- ~~HIV positive and late latent syphilis or syphilis of unknown duration~~: CSF does not seem to change outcome [REF: Marra]

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Ocular Syphilis: occurs at any stage of syphilis

- Clinicians should be on the alert for ocular syphilis => delays in diagnosis have been associated with visual loss*
  - Order syphilis serology test in patients with:
    - visual complaints who have risk factors for syphilis or
    - ophthalmologic findings compatible with syphilis
    - order both treponemal and nontreponemal tests as prozone effect has been noted in patients with ocular syphilis
- Ask patients with syphilis about changes in their vision
- Patients with positive syphilis serology and visual complaints should receive immediate ophthalmologic evaluation

*Moradi Am J Ophthal 2015

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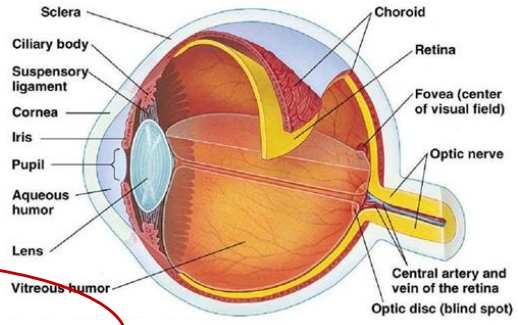
Ocular Syphilis

Manifestations:
- Conjunctivitis, scleritis, and episcleritis
- **Uveitis**: anterior and/or posterior
- Elevated intraocular pressure
- **Chorioretinitis**, retinitis
- Vasculitis

Symptoms:
- Redness
- Eye pain
- Floaters
- Flashing lights
- Visual acuity loss
- Blindness

Diagnosis:
- Ophthalmologic exam
- Serologies: RPR, VDRL, treponemal tests
- Lumbar puncture



Slide courtesy of Sarah Lewis, MD

Wender, JD et al. How to Recognize Ocular Syphilis. Review of Ophthalmology. 2008.

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Morbidity and Mortality Weekly Report

Ocular Syphilis — Eight Jurisdictions, United States, 2014–2015

MMWR / November 4, 2016 / Vol. 65 / No. 43

TABLE 2. Demographic characteristics of patients with suspected ocular syphilis — eight jurisdictions, United States, 2014–2015

Characteristic	No.	(%)
Total	**388**	**(100.0)**
Male	362	(93.3)
Known MSM (among 362 males)	249	(68.8)
Race		
White	217	(55.9)
Black	81	(20.9)
Hispanic	48	(12.4)
Asian	13	(3.4)
Native Hawaiian/Pacific Islander	1	(0.3)
Other/Unknown	28	(7.2)
HIV-positive	198	(51.0)

Abbreviations: HIV = human immunodeficiency virus; MSM = men who have sex with men.

TABLE 3. Clinical characteristics, laboratory results and diagnoses for syphilis and suspected ocular syphilis — eight jurisdictions, United States, 2014–2015

Characteristic	No.	(%)
Total	**388**	**(100.0)**
Stage of syphilis		
Primary	8	(2.1)
Secondary	101	(26.0)
Early latent	79	(20.4)
Late or latent of unknown duration	193	(49.7)
Unknown	7	(1.8)
Additional symptoms of neurosyphilis	87	(22.4)
Reported ocular symptoms (among 326 with symptoms)		
Blurry vision	210	(64.4)
Vision loss	107	(32.8)
Eye pain or red eye	46	(14.1)
Eye exam	158	(40.7)
Diagnosis (among 158 with documented eye exam)*		
Uveitis	72	(45.6)
Retinitis	20	(12.7)
Optic neuritis	18	(11.4)
Retinal detachment	6	(3.8)

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Ocular Syphilis Management

- Patients with suspected ocular syphilis should receive a lumbar puncture and be treated for neurosyphilis
  - CSF may be normal, but obtain to help guide follow-up
  - Note: a negative LP does not rule out ocular syphilis
  - Treatment for ocular syphilis is IV PCN (neurosyphilis regimen) *even if the CSF lab tests are negative*
- **HIV test** if not already known to be HIV-infected
- **Report** cases of ocular syphilis to the local health department within 1 business day.
- TREAT IN COLLABORATION WITH OPHTHALMOLOGIST!

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Otosyphilis: occurs at any stage of syphilis

- Diagnosis: (+) serology with clinical evidence of infection of the cochleovestibular system with *T. pallidum* including:
  - Sensorineural hearing loss (sudden or fluctuating)
  - Tinnitus (often precedes hearing loss)
  - Vertigo (sudden or fluctuating)
  - May include osteitis of temporal bone—role for imaging?

2017 Workowski, Sosa, Kidd. National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Yimtae et al. Otolaryngology–Head and Neck Surgery (2007) 136, 67-71

- No other source of symptoms
- Consult with ENT for audiometry, co-management
- CSF may be normal, but obtain to help guide follow-up

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Case 3

One of your new primary care patients is a 35 year old HIV positive woman who says she is taking antiretroviral therapy (Genvoya) and has an undetectable HIV RNA. She just moved here from out of state

At her initial visit, you obtain baseline labs. Her pregnancy test is positive, and she wants to keep her pregnancy.

The lab tells you that they have a new protocol for syphilis screening – they are using "treponemal EIA" as the screening test

Your patient's results:

EIA positive, RPR negative. Now what?

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Case 3: What to do next?

Audience Response Question:

1) Treat with one dose of 2.4 MU of Benzathine Penicillin IM

2) Treat with three weekly doses of 2.4 MU of Benzathine Penicillin IM

3) Tell her you would like to schedule an LP to rule out neurosyphilis, prior to deciding about treatment course

4) Obtain another syphilis test

5) Do nothing further as this is unlikely active syphilis

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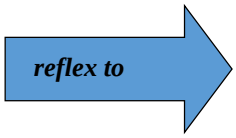
Syphilis Screening Paradigm

TRADITIONAL

Non-treponemal tests (i.e., RPR, VDRL)

- **Non-specific to TP**
- **Quantitative**
- **Reactivity declines with time**



Treponemal tests (i.e., TPPA, FTA-Abs)

- **Specific to *TP***
- **Qualitative**
- **Reactivity persists over time**

Treponemal EIA/CIA Tests

- Reduce time and labor required for screening
- If positive, need quantitative RPR/VDRL for confirmation and to guide clinical management
- Remain detectable for life, even after successful treatment
- Limited utility as a screening test in previously treated patients

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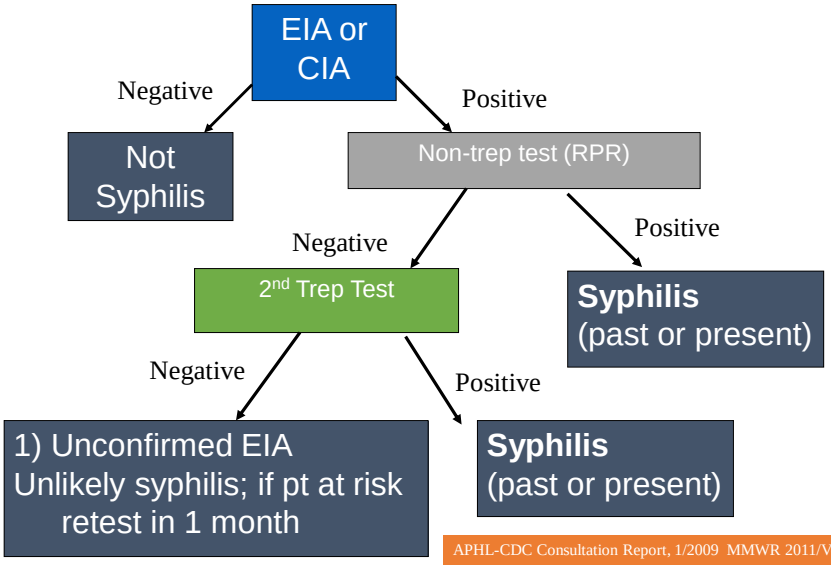
"Reverse Sequence" Syphilis Screening: Screening with Treponemal Immunoassay



APHL-CDC Consultation Report, 1/2009 MMWR 2011/Vol 60 (5)

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Back to the patient

- You order a TPPA which comes back positive

(EIA +, RPR-, TPPA+)

- You perform a thorough physical exam and do not detect any signs of syphilis
- The patient reports no prior history of syphilis and no known syphilis contacts in last year
- CD4 456, VL <40

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Case 3 – What now?

Audience Response Question:

1. Treat with one dose of 2.4 MU benzathine penicillin
2. Treat with three weekly doses of 2.4 MU benzathine penicillin
3. Repeat syphilis testing in the 3rd trimester, using the traditional testing algorithm, and again at delivery
4. call partner services to help identify and test her partners
5. perform NON-treponemal test (RPR or VDRL, whichever was used to test the mother on neonatal blood (NOT cord blood) at delivery.
6. (2), (3), (4) and (5)

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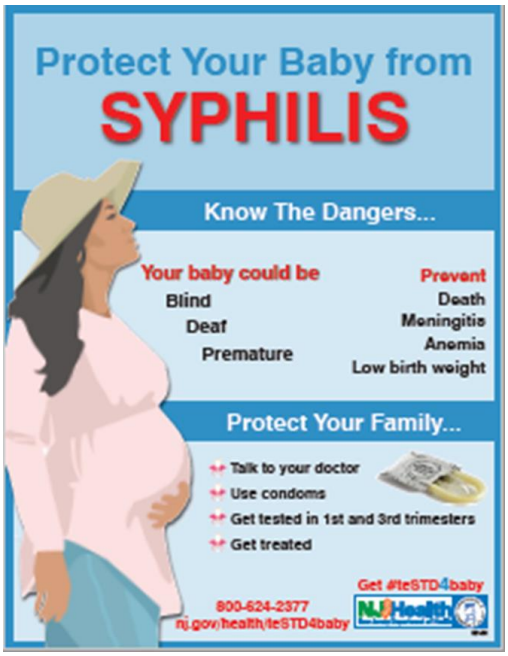

https://www.cdc.gov/std/tg2015/congenital.htm
https://www.cdc.gov/std/tg2015/pen-allergy.htm

- Test in 1st trimester
- Repeat test in 3rd trimester if increased risk of infection*
- If (+), staging determines treatment
- If late latent or unknown duration: no missed doses of benzathine PCN are acceptable. Restart 3-dose series.
- Benzathine PCN the ONLY treatment.
- If early syphilis, consider 2nd dose of benzathine PCN 1 week after initial dose
- If PCN-allergy, desensitize and give benzathine PCN
- See CDC STD Guidelines for very detailed recommendations for allergy testing and desensitization (links below)
- For women diagnosed during pregnancy, in addition to treatment:
  - Jarisch-Herxheimer reaction may cause premature labor, fetal distress, but not a reason to withhold treatment
  - Any woman who delivers a stillborn infant should be tested

***SF Screening criteria for syphilis:**
- MSM; pregnancy; Transwomen; Trans-MSM
- Pregnancy
- Substance use; hx of syphilis; hx of incarceration; partner who is MSM; sex work; intimate partner violence

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Thanks!!

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Extra slides

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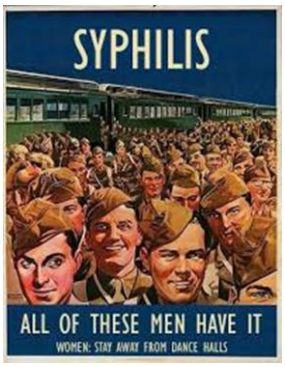

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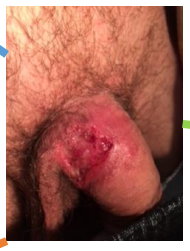
Differential diagnosis of a genital ulcer

Infection
Syphilis
HSV-2 or HSV-1
Pyogenic
Chancroid
LGV
Donvanosis



Allergic & Autoimmune
Fixed drug eruption
Behcets Disease
Stevens-Johnson
Reactive Arthritis
Aphthous ulcers

Traumatic
Mechanical
Chemical

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