2020 Ryan White HIV/AIDS Program
CLINICAL CONFERENCE

Syphilis: Reemergence of the Great Pretender? (It never really left!)

Michael H. Augenbraun, MD
Professor of Medicine
SUNY Downstate at Brooklyn
Brooklyn, New York

Financial Relationships With Commercial Entities

Dr Augenbraun has no relevant financial affiliations to disclose. (Updated 08/05/20)

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Learning Objectives

After attending this presentation, learners will be able to:

- Describe the natural history of syphilis
- Initiate diagnostic work up for syphilis
- Manage syphilis

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- spirochete *Treponema pallidum spp. pallidum*

- Other treponemal pathogens:

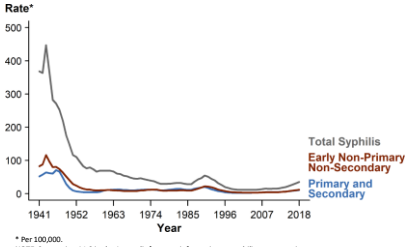
T. pallidum spp. pertenue (yaws)
T. pallidum spp. endemicum (bejel)
T. carateum (pinta)
Cannot be cultivated in vitro



Darkfield Microscopy

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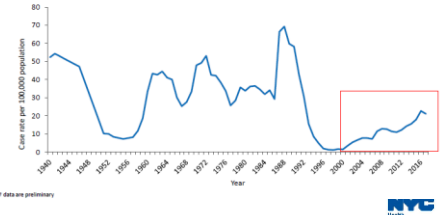
Syphilis — Rates of Reported Cases by Stage of Infection, United States, 1941–2018



* Per 100,000.
NOTE: See section A1.3 in the Appendix for more information on syphilis case reporting.

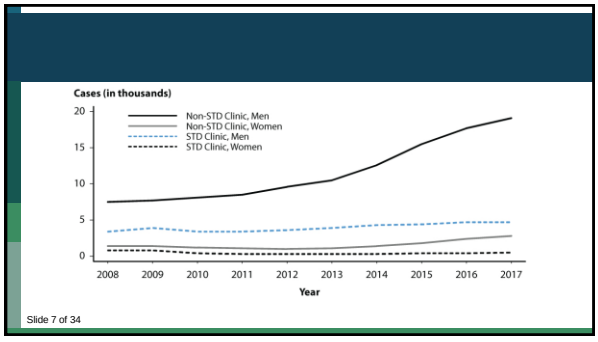
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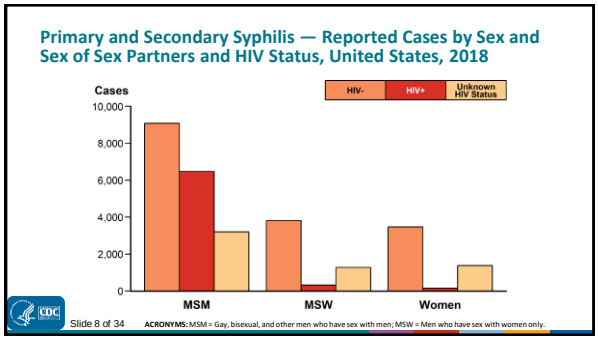
Primary and secondary syphilis case rates (per 100,000), New York City, 1940-2017*

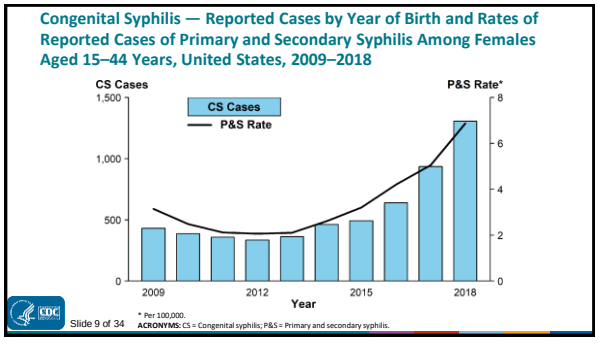


* 2017 data are preliminary

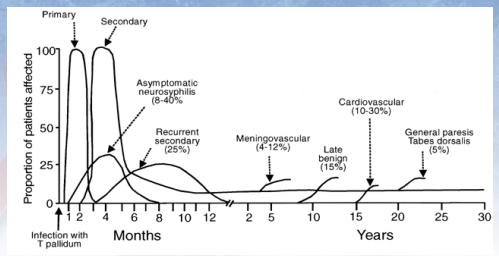
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Cases (in thousands)
20
15
10
5
0
Non-STD Clinic, Men
Non-STD Clinic, Women
STD Clinic, Men
STD Clinic, Women
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
Year
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Primary and Secondary Syphilis — Reported Cases by Sex and Sex of Sex Partners and HIV Status, United States, 2018
Cases
HIV-
HIV+
Unknown HIV Status
10,000
8,000
6,000
4,000
2,000
0
MSM
MSW
Women
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ACRONYMS: MSM = Gay, bisexual, and other men who have sex with men; MSW = Men who have sex with women only.


Congenital Syphilis — Reported Cases by Year of Birth and Rates of Reported Cases of Primary and Secondary Syphilis Among Females Aged 15–44 Years, United States, 2009–2018
CS Cases
P&S Rate*
1,500
1,000
500
0
CS Cases
P&S Rate
8
6
4
2
0
2009
2012
2015
2018
Year
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* Per 100,000.
ACRONYMS: CS = Congenital syphilis; P&S = Primary and secondary syphilis.

Natural History of Syphilis



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Neurosyphilis

- Early CNS invasion-clinical implications?
- Acute Symptomatic Meningitis
- Asymptomatic Meningitis
- Meningovascular events
- General Paresis
- Tabes dorsalis
- Gumma
- Ocular and otic

- Neurosyphilis should be considered for anyone with serologic evidence of syphilis and neuropsychiatric and/or ocular or otic disease.

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Chancre of Primary Syphilis



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Secondary Syphilis



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Kingston, A. A. et al. Arch Dermatol 2005;141:431-433.

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Condylomata lata/Condyloma latum



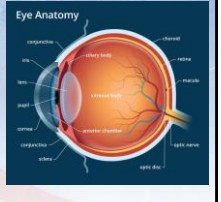
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Ocular Syphilis

- **Eye involvement occurs most frequently in secondary syphilis and late syphilis**
- **Almost every part of the eye can be involved.**
- **The vast majority of eye problems associated with syphilis are also associated with many other infectious and non-infectious diseases.**
- **Therefore- there are almost no eye findings that are absolutely specific for syphilis.**



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CDC, MMWR November 4, 2016
Ocular Syphilis – Eight Jurisdictions, U.S., 2014-2015

- Following April 2015 report, eight jurisdictions (CA, FL, IN, MD, NYC, NC, TX, WA) reviewed syphilis surveillance and case data
- 388 suspected ocular syphilis were identified: 157 in 2014 and 231 in 2015 (0.53% and 0.65%)
- 93% men (high proportion MSM), 51% HIV co-infected
- 84% had symptoms: 54% blurry vision; 28% vision loss
- 158 (41%) had a specific dx: Uveitis (n=72); retinitis (N=20), optic neuritis (N=18) and retinal detachment (N=6)
- Of 136 patients with available data, 64 (47%) had one eye involved and 72 (53%) had both eyes involved
- 174 had CSF results, 122 (70%) had +CSF VDRL

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Diagnostics: Traditional Serologic Testing

Two-step testing:

NTST: Non-Treponemal Serologic Test (e.g RPR, VDRL)
- can be quantified
- rises with active disease or failed therapy
- declines with successful therapy or latency

If reactive then followed by

TST: Treponemal Serologic Test (e.g. FTA, TPPA, Treponemal IgG)
- not quantifiable
- life long reactivity

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Screening for Syphilis: Updated Evidence Report and Systemic Review for the US Preventive Service Task Force
JAMA 2016(315): 2328

Table 1. Sensitivity and Specificity of Commonly Used Syphilis Tests[a,10a]

Syphilis Screening Test	Sensitivity by Stage of Untreated Syphilis, % (Range)[b]					Specificity, % (Range)[b]
	Mixed	Primary	Secondary	Latent	Tertiary	
Nontreponemal						
VDRL[c]		78 (74-87)	100	96 (88-100)	71 (37-94)	98 (96-99)
RPR[c]		86 (77-99)	100	98 (95-100)	73	98 (93-99)
TRUST[c]		85 (77-86)	100	98 (95-100)		99 (98-99)
USR[c]		80 (72-88)	100	95 (88-100)		99
Treponemal						
FTA-ABS[d]		84 (70-100)	100	100	96	97 (84-100)
TPPA[e]		88 (86-100)	100	97 (97-100)	94	96 (95-100)
Enzyme immunoassay		(77-100)	(85-100)	(64-100)	NA	(99-100)
Trep-Check	95.9[e]					98.5[e]
Trep-Sure	96.9[e]					95.4[e]
Chemiluminescence immunoassay		98	100	100	100	99
LIAISON®	99.2					99.9
Multiplex flow immunoassay						
BioPlex 2200, Syphilis IgG	96.9[e]					98.0[e]
Syphilis Health Check	95.6,[e] 98.5[d]					90.5,[e] 97.4[d]

Abbreviations: FTA-ABS, fluorescent treponemal antibody absorption; NA, not applicable; RPR, rapid plasma reagin; TPPA, *Treponema pallidum* particle agglutination; TRUST, toluidine red unheated serum test; USR, unheated serum reagin; VDRL, Venereal Disease Research Laboratory.

[a] This is not a comprehensive list of tests available in the United States.

[b] Sensitivity and specificity of tests are also dependent on the disease prevalence in the population tested and may vary considerably by manufacturer or the standard used as a comparison.

[c] Unknown reference standard.

[d] When compared with FTA-ABS test results.

[e] When compared with results from Western blotting.

[f] When compared with nontreponemal test results.

[g] When compared with treponemal test results.

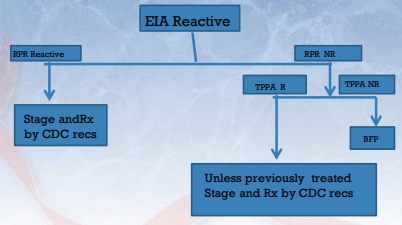
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Treponemal Serologic Tests (TSTs) as Screening Tests- 'Reverse Algorithm'

- **EIA (*T.pallidum* sonicate or recombinant antigen)**
- **Low cost, automation, standardization etc.**
- **More sensitive and more specific than traditional NTSTs**
- **Doesn't distinguish new, old, treated or untreated**
- **Recent CAP survey- 63% used traditional algorithm (Rhoads et al Arch Pathol Lab Med 2017)**

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Testing and Treatment Approach

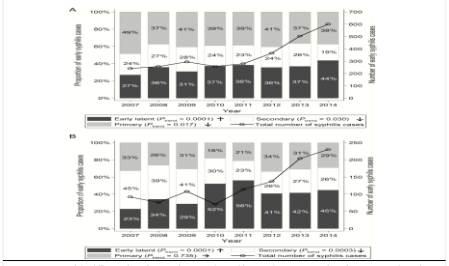


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CDC Syphilis Screening Recommendations

- **All pregnant women at 1st prenatal (early)**
- **Retest at 28 weeks and at delivery if high risk**
- **MSM at least annually**
- **MSM every 3-6 months if high risk**
- **HIV if sexually active at first visit and annually**
- **HIV more frequently if high risk**

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From: Increased Syphilis Testing of Men Who Have Sex With Men: Greater Detection of Asymptomatic Early Syphilis and Relative Reduction in Secondary Syphilis
Clin Infect Dis. 2017;65(3):389-395. doi:10.1093/cid/cix326
Clin Infect Dis | © The Author 2017. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com.

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To Treat is First to Stage

- **Primary, Secondary and Early Latent**
  - **Benzathine penicillin 2.4million units IM once (Jarisch-Herxheimer Rxn)**
- **Late Latent and Latent of Unknown Duration***
  - **Benzathine penicillin 2.4million units IM once weekly for three weeks**
- **Late Tertiary Syphilis Except Neurosyphilis - R/O Neurosyphilis then same as latent syphilis**

***Intervals between weekly doses optimally no more than 7-9 days.**
In pregnancy definitely no missed doses!

***Pregnant women and HIV+ pts get standard therapies.**

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Alternatives to Penicillin

- **Tetracyclines (Doxycycline)**
  - **Two weeks for early or four weeks for latent**
- **Ceftriaxone**
  - **-Dose and duration unclear**

- **There are no alternatives to penicillin in pregnancy**

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Who needs an LP to Rule Out Neurosyphilis?

- 'If you think about doing an LP then do an LP'
- Diagnosis requires CSF evaluation
- CDC STD Rx Guideline:
  - neurologic or ophthalmic signs or symptoms,
  - evidence of active tertiary syphilis (e.g., aortitis and gumma),
  - treatment failure-definition?
  - HIV: RPR>1:32 and/or CD4 <350???

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CSF Abnormalities

- CSF VDRL-highly specific, variably sensitive
- CSF WBC-lymphocytic pleocytosis/ not specific in HIV+
- CSF protein elevations
- CSF FTA-ABS-sensitive, not approved for this use
- PCR?
- Cytokines?

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Neurosyphilis Treatment

Aqueous PCN G 18-24mu qd in divided doses for 10-14 days (follow with Rx for latent)

Alternative: Procaine PCN G 2.4mu IM daily + probenecid 500mg po qid 10-14days

Ceftriaxone- dose? Duration?

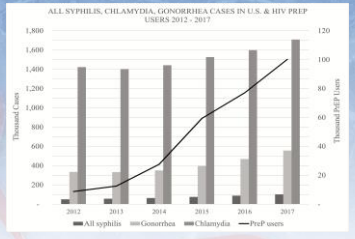
- Doxycycline?
- Ocular Syphilis- treat as NS with or without +CSF findings but LP should be done to follow if abnormal

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Syphilis Post Rx follow-up for all stages

- **Partner notification**
- **HIV testing**
- **Two fold declines in non treponemal serologic test like the RPR over 3-6m early and 12-24m in latent**
- **Some titers never go away**
- **Some titers don't decline properly**
- **CSF WBC should resolve 3-6 months, VDRL over a much longer period**
- **CSF usually normal if the RPR becomes non reactive.**

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OXFORD

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Question-and-Answer Session