Syphilis Update:
Defense Against a Resurgent Foe

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Disclosures

• None

• Non FDA labeled uses:
  – Exragenital NAATs
Objectives

• State at which stage(s) of syphilis neurologic involvement may be found

• State CDC’s recommended therapy for primary, secondary, and late stages of syphilis

• State the criteria for a presumptive diagnosis of ocular syphilis

• Describe U.S. trends in syphilis incidence in the past decade among men and women

• State the baseline incidence of bacterial STI’s among HIV PrEP users

• Describe the syphilis screening recommendations for persons taking HIV PrEP
Syphilis

https://www.cdc.gov/std/sam/2017syphilis.htm
Case A: 48 y.o. male with rash and LFT abnormalities

- Presents to office
  - Rash for 5 days
  - Nausea and poor appetite
  - History of chronic HCV and alcohol abuse
- Exam
  - Pustular rash on trunk & arms, sparing palms & soles
  - Normal mini-mental, no asterixis
- AST 52 U/L; ALT 58 U/L (baseline)
- AP 1260 U/L; T-bili 1.2 mg/dl (baseline 0.5)
- A test was performed...
Case A: 48 y.o. male with rash and LFT abnormalities

- Presents to office
  - Rash for 5 days
  - Nausea and poor appetite
  - History of chronic HCV and alcohol abuse
- Exam
  - Pustular rash on trunk & arms, sparing palms & soles
  - Normal mini-mental, no asterixis
- AST 52 U/L; ALT 58 U/L (baseline)
- AP 1260 U/L; T-bili 1.2 mg/dl (baseline 0.5)
- **Serum Treponemal Ab reactive, RPR 1:128**
- Sexual HX: “Maybe a dozen” men & women / year
Case B: 43 male with vision loss

- Progressive vision loss beginning 6 weeks ago
  - First-week R-sided only (blurriness, dark shapes), then left
  - Pain bilaterally, dry eye sensation, mild light sensitivity
  - No longer distinguishing faces – ophthalmologist (2 wk ago)
    - “Uveitis and possible infection”
    - Antibiotic eye drops and prednisone
  - Initial improvement, but now presents with worsening again
  - NO: h/a, neck stiffness, fevers, focal neuro, cognitive probs

- Other history
  - Immigrant from Central America, landscaper
  - Male and female partners, no further disclosure

- Office Exam: barely counting fingers
Case B: 43 male with vision loss

- Serum Treponemal Ab reactive, RPR 1:256

- Ophthalmal Exam
  - Bilateral anterior & intermediate uveitis, vitritis
  - No retinal whitening

- LP
  - WBC 1 / 0; RBC 0 / 0
  - Pro 24, Glucose 63
  - VDRL (resulted 9 days later): Neg

- HIV pos; CD4 85, HIV RNA 731,000
Stages of Syphilis

Golden M et al. JAMA 2003;290(11):1510-4
Serologic Tests for Syphilis

Non-treponemal Tests

- Flocculation tests (RPR, VDRL), complement fixation
- Detect antibodies to biomarkers released by cellular damage
- Quantitative titers

Treponemal Tests

- Fluorescent treponemal antibody absorption (FTA-ABS), Treponema pallidum hemaglutination assay (TPHA), Enzyme immunoassays (EIA), etc...
- Detect antibodies to *T. pallidum*
- Qualitative, easier to run
- Increased sens/spec
Syphilis Serology Algorithms

Traditional algorithm

- RPR/VDRL
  - No further testing
  - Treponemal Test
    - Syphilis unlikely
    - Syphilis (past or present)

Reverse algorithm

- Treponemal Immunoassay
  - No further testing
  - RPR/VDRL
    - Confirmatory Treponemal Test
    - No further testing
Poll Question #1

Case A: 48 y.o. male with rash and LFT abnormalities
Serum Treponemal Ab reactive, RPR 1:128

What is the recommended therapy?

A. Benzathine PCN-G 2.4 MU IM x 1
B. Azithromycin 2000mg PO x 1
C. Benzathine PCN-G 2.4 MU IM qweek x 3
D. Aqueous PCN-G 3MU IV q4hr x 10-14 days
Syphilis Therapy: 1°, 2°, Early latent (<1 yr)

• Benzathine PCN 2.4 million units IM x1
  – No documented resistance
  – Other PCN forms NOT substitutable

• Penicillin allergies / reactions
  – Doxycycline 100mg PO BID x 14 days
  – Ceftriaxone 1-2000mg qday IM or IV x 14 days
  – Azithromycin 2000mg PO x 1
    • NOT in MSM or pregnancy
    • Reports of treatment failures (23s rRNA mutations)

• Pregnancy: only use PCN! Desensitize if necessary
Late (>1 yr) latent or latent with unknown duration

- Benzathine PCN G 2.4 MU x3 doses (1 week intervals)
  - Careful exam for lesions c/w prim, sec, or tertiary
  - Careful history and exam for neurologic findings
  - PCN-allergy: doxy (or tetra) for 28 days

- What if they miss a week?
  - One 10-14 day interval may be acceptable
  - Based on clinical experience, not pharmacology

- Pregnancy: only use PCN!
  - Desensitize if necessary
  - Repeat whole course if miss a 7-9 day interval
Follow-up Testing

- Follow-up of quantitative non-treponemal titers
  - At least 6, 12, 24 months
  - Failure to decline 4-fold
    - CSF exam (for all?) but at least if starting ≥ 1:32
    - Repeat treatment (at least x 1)
- HIV-testing after any syphilis diagnosis
- NG/CT screening
Tertiary

• Tertiary (cardiovascular or gummatous lesions)
  – CSF exam before treatment in all cases
  – If CSF negative, then treat as late latent
  – Some treat cardiovascular disease with CNS regimen
Syphilitic Hepatitis

• **Early (primary and secondary) stage**
  – LFT abnormalities **10-20%** (HIV neg and HIV pos)
  – Mostly asymptomatic
  – Hepatomagaly common
  – Disproportionately elevated AP typical, but not 100%
  – Treponemes identifiable in necrotic liver material
  – Resolution with treatment (**1-4 months**)

• **Late stage:** fibrosis, gummas, and hepar lobatum (pre-antibiotic era)

*Int J STD AIDS*. 2012;23(8):e4-6
Poll Question # 2

Case B: 43 male with vision loss
• Serum Treponemal Ab reactive, RPR 1:256

What is the recommended therapy?

A. Azithromycin 2000mg PO x 1
B. Benzathine PCN-G 2.4 MU IM qweek x 3
C. Aqueous PCN-G 3-4 MU IV q4hr x 10-14 days
D. Ceftriaxone 2000mg IV qday x 10-14 days
Ocular Syphilis

- **Every** part of the eye can be involved / **any** stage of the infection
- No eye findings are specific for syphilis
- **Presumptive diagnosis**
  - Objective (otherwise unexplained) eye findings
  - Active syphilis
- **Definitive diagnosis**
  - Treponemes in vitreal sample
  - CSF VDRL reactive

*Semin Ophthalmol 2005; 20:161–167*

Review all TP cases*
• 388 / 65,130 (0.6%)
• Range 0.17 – 3.9%
• Male 93%
• Known MSM 69%
• HIV-infected 51%

(Chart review, data not prospectively collected. CA (partial), FL, IN, MD, NYC, NC, TX, WA)

MMWR Nov 4, 2016; 65(43): 1185-88
Ocular Findings

Are ocular syphilis and neurosyphilis the same entity?
No, but a lot of co-occurrence (~70% have neurosyphilis)
Embyrologically, neuroectoderm forms
posterior layers of iris, retina, optic nerve

Ophthalmal findings
(8 district review)
• Uveitis 46%
• Retinitis 13%
• Optic neuritis 11%
• Ret. detach. 4%

MMWR Nov 4, 2016; 65(43): 1185-88
Diagnosis of Ocular Syphilis

• Presumptive diagnosis
  – (Ocular signs in a person with syphilis)
  – Most diagnoses are presumptive
  – Indicates a full treatment course!

• Most patients will have positive serological tests
  • In late ocular syphilis, ~30% have a NEGATIVE serum RPR but all will have a positive serum treponemal test
  • VERY rarely, primary stage will have negative serologies (both treponemal and RPR) that will later turn positive
Do you need to do an LP in someone who only has eye symptoms and no neurological symptoms?

• **YES**, and here’s why:
  – CSF VDRL = DEFINITIVE diagnosis of ocular syphilis
    • Helpful in excluding other causes
    • Abnormal CSF profile with negative VDRL: still consistent with syphilis (but not definitive)
  – Practical
    • While the antibiotic regimen is the same for ocular and neurosyphilis, patients with neurosyphilis (about 70%) need follow-up LP(s)
    • Normalization of the CSF parameters is an objective way to track cure if visual symptoms fail to improve

• **Do not delay antibiotics waiting for the LP!**
Ophthalmology involvement and steroids

- **Ophthalmologist:** recommended in all cases
  - In questionable cases, can help determine if objective eye signs
  - Help manage complications
  - Exam should be right away (24 hours?); in some cases ocular syphilis progresses rapidly to blindness (refer to ED if no urgent ophthalmologist available)

- **Do not delay antibiotics waiting for the ophthalmologist!**

- **Steroids**
  - No clear benefit or harm
  - Topical: adjunct for interstitial keratitis, anterior uveitis
  - Systemic: adjunct for posterior uveitis, scleritis, optic neuritis

Retina 2012; 32:1915–1941
Complications

- Incidence of visual impairment
  - 0.29/eye year for HIV uninfected
  - 0.21/eye year for HIV infected
- Incidence of permanent blindness
  - 0.07/eye year for HIV uninfected
  - 0.06/eye year for HIV infected

- Risk factors for poor visual outcomes: longer duration of untreated infection; macular chorioretinitis
- Long-term complications: glaucoma, cataract, epiretinal membrane and macular edema, choroidal neovascularization, widespread chorioretinal scarring

Am J Ophthalmol 2015; 159:334-43
Diagnosis of Neurosyphilis

• CSF exam if
  – Neurologic signs/symptoms
  – Ocular / otologic signs/symptoms
  – (During any stage of syphilis)

• Dx by any combination of
  – abnormal CSF cell count (> 5 WBC)
  – abnormal CSF protein
  – Reactive CSF-VDRL with or without symptoms
  – CSF-FTA reactive (More sensitive than CSF-VDRL, but less sensitive)
Neurosyphilis therapy

- **Recommended**: Aqueous crystalline PCN G 18-24 MU per day, divided 3-4 MU IV q4hr or continuous infusion for 10-14 days.

- **Alternative**: Procaine PCN G 2.4 MU IM qday **PLUS** probenecid 500mg PO 4 times daily for 10-14 days.

- **Penicillin allergy**
  - Consider ceftriaxone 2000mg qday IM or IV x 10 - 14 days, **OR**
  - Skin test and desensitize.

- **Pregnancy**: only use PCN! Desensitize if necessary.

- **Practical**: B PCN G in clinic while arranging for LP and IV therapy (if any chance LTFU after leaving clinic).

- **Late stage**: consider B PCN G 2.4 MU IM qweek x3 after finishing IV.
Follow-up of neurosyphilis

• **Serial CSF exam q6 months**
  - Until cell count normal
  - Also follow protein +/- VDRL
    • Slower to normalize than WBC
    • Significance less clear

• **Consider retreatment**
  - WBC not decreased by 6 months
  - WBC or protein not normal after 2 years
“Total combined cases of chlamydia, gonorrhea, and syphilis reported in 2015 reached the highest number ever...”

_CDC 2015 STD Surveillance Report_

<table>
<thead>
<tr>
<th></th>
<th>Cases, 2015</th>
<th>Increase vs. 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydia*</td>
<td>1,526,658</td>
<td>6%</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>395,216</td>
<td>13%</td>
</tr>
<tr>
<td>Syphilis (P&amp;S)</td>
<td>23,872</td>
<td>19%</td>
</tr>
</tbody>
</table>

* Most frequently reported infectious disease in U.S.

P&S Syphilis per 100,000, U.S.

CDC STD Surveillance reports 1996-2015

Women  Men

CDC STD Surveillance reports 1996-2015

Johns Hopkins School of Medicine

* 37 states were able to classify ≥70% of reported cases of primary and secondary syphilis as either MSM†, MSW†, or women for each year during 2011–2015.

† MSM = Gay, bisexual, and other men who have sex with men (collectively referred to as MSM); MSW = Men who have sex with women only.
Estimated Annual Rate of P&S Syphilis

Syphilis trends in HIV-uninfected MSM

P&S Syphilis by HIV status and risk*, King County, WA

<table>
<thead>
<tr>
<th></th>
<th>2010</th>
<th>2016</th>
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</thead>
<tbody>
<tr>
<td>HIV +, high risk</td>
<td>43%</td>
<td>26%</td>
</tr>
<tr>
<td>HIV +, low risk</td>
<td>17%</td>
<td>9%</td>
</tr>
<tr>
<td>HIV -, high risk</td>
<td>6%</td>
<td>10%</td>
</tr>
<tr>
<td>HIV -, low risk</td>
<td>21%</td>
<td>38%</td>
</tr>
</tbody>
</table>

*High risk: prior syphilis +/- meth use

Matthew Golden, Syphilis in the Era of Treatment as Prevention & PrEP, CROI 2017
Addressing the Ugly Trends

PROTECT OUR YOUTH
JOIN THE CRUSADE TO
STAMP OUT SYPHILIS
Be Examined NOW by your Doctor
or at a Department of Health Clinic

ST. GEORGE
RICHMOND -- 302 CENTER ST, old Court House
TOTTENVILLE -- 7389 AMBOY ROAD
STATEN ISLAND CASE FINDING PROJECT

http://www.loc.gov/pictures/collection/wpapos/item/98514735/
Risk compensation: anonymous partners via the internet

MSM who used the internet had ~2-fold higher odds of engaging in unprotected anal intercourse, a 3.4 higher odds of having anonymous sex, and a higher average number of partners in the past 6 months (10 vs 5)

Liau. Sex Transm Dis 2006;33:576–84
Taylor. Sex Transm Dis 2004;31:552–6
Ng. m J Public Health 2013; 103:1450–6

Sex on demand: geosocial networking phone apps and risk of sexually transmitted infections among a cross-sectional sample of men who have sex with men in Los Angeles county

Beymer. Sex Transm Infect 2014;90:567–572

Recent outbreaks of infectious syphilis, United Kingdom, January 2012 to April 2014

“Targeting at-risk populations was complicated as many sexual encounters involved anonymous partners. Outbreaks among MSM were influenced by the use of geospatial real-time networking applications that allow users to locate other MSM within close proximity.”

HIV PrEP and STI risk - 1

- Baseline incidence for one or more NG, CT, or TP is 50-90/100PY (high!) among MSM initiating PrEP in real world settings
- How much does risk compensation due to PrEP contribute?

**Meta-Analysis* STI’s among MSM**

<table>
<thead>
<tr>
<th></th>
<th>PrEP</th>
<th>No PrEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>NG</td>
<td>38%</td>
<td>4%</td>
</tr>
<tr>
<td>CT</td>
<td>38%</td>
<td>7%</td>
</tr>
<tr>
<td>TP</td>
<td>15%</td>
<td>1%</td>
</tr>
</tbody>
</table>

* PrEP studies recruit high risk, have more frequent monitoring

**Incidence of STI’s in PROUD**

<table>
<thead>
<tr>
<th></th>
<th>Immediate</th>
<th>Deferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>NG</td>
<td>39%</td>
<td>37%</td>
</tr>
<tr>
<td>CT</td>
<td>30%</td>
<td>22%</td>
</tr>
<tr>
<td>TP</td>
<td>11%</td>
<td>9%</td>
</tr>
</tbody>
</table>

* RCT randomizing to immediate vs. 1-year deferral, stopped early b/c 86% effective

PrEP and STI risk - 2


- Median annual: urine NG/CT 4.5, rectal NG/CT 3.6, oral NG/CT 3.8, syphilis 4.9
- 342/972 with ≥ 1 STI during follow-up, total 771 STI’s (90.7 per 100PY)

* p<0.05 for increasing trend

JAIDS 2016:540
What to do about bacterial STI’s among MSM?

1. Do nothing about asymptomatic STI’s among MSM?

2. Screen **broadly, at every relevant body site, and frequently** as per guidelines?

3. Antibiotic prophylaxis for STI’s?
Do nothing about asymptomatic STI’s among MSM?

1. Cannot conceive of leaving syphilis untreated, and we know our MSM patients are getting it!

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Early (489)</th>
<th>Unknown/Late (84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed Neuro Disease 2012-13</td>
<td>489</td>
<td>84</td>
</tr>
<tr>
<td>Early (489)</td>
<td>489</td>
<td>2.9%</td>
</tr>
<tr>
<td>Unknown/Late (84)</td>
<td>84</td>
<td>7.1%</td>
</tr>
</tbody>
</table>

2. Some asymptomatic NG/CT will progress

Sex Trans Dis 2015:702
Women (and babies) will get these STIs

5-14% of MSM with syphilis report recent female partners*

*Golden, CROI 2017; CDC STD Surveillance
Screening to Fight the Syphilis Trend

BMC Public Health 2013, 13:606
Frequent Syphilis Screening

- Simulation models of MSM populations
  - Syphilis elimination possible by q12 month screening of 62% or Q3 month screening of 23%
  - Q3 month screening of high-risk individuals much more effective and cost-efficient than contact tracing or condom promotion


  - 54% received an HIV test in previous 12 months
  - 31% had received a syphilis test
  - 72% of unscreened had seen a healthcare provider

  *AIDS Behav 2015, 19:2036*
# CDC Screening Guidelines for Sexually Active Persons

<table>
<thead>
<tr>
<th></th>
<th>Syphilis</th>
<th>NG/CT</th>
<th>HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td>Pregnancy</td>
<td>&lt;25: annual ≥25: consider*</td>
<td>13-64 (opt-out) If other STI</td>
</tr>
<tr>
<td><strong>MSW</strong></td>
<td></td>
<td>Consider CT*</td>
<td>13-64 (opt-out) If other STI</td>
</tr>
<tr>
<td><strong>MSM</strong></td>
<td>≥ annual**</td>
<td>≥ annual** at sites of contact (urethra, rectum, pharynx) regardless of condoms</td>
<td>≥ annual if new partner(s) since last test</td>
</tr>
<tr>
<td><strong>PLW HIV</strong></td>
<td>≥ annual**</td>
<td>≥ annual**</td>
<td></td>
</tr>
</tbody>
</table>

* New or multiple partners, transactional sex, partners with STI’s

** q3-6 months based on risk factors above

Frequent screening produces results

18 mon before/after **opt-out syphilis** screening for all bloods among 500 MSM, Melbourne HIV Clinic

**US Guidelines**
**NG/CT and syphilis:**
- “Q3-6 months if high risk”
- PrEP clinics “at least q6 months”

**For me q3 months:**
- Any prior bacterial STI and age <45
- Patients expect and request screening

*JAIDS 2010:211*
Doxycyline prophylaxis for high-risk MSM

- CT and syphilis resistance non-existent
- NG resistance already widespread
- Randomized, controlled, open-label pilot
  - Quarterly payments ($25-$100) for remaining syphilis-free vs. doxycycline 100mg daily
  - 30 HIV+ MSM with multiple prior syphilis infections

<table>
<thead>
<tr>
<th></th>
<th>$ incentives</th>
<th>Doxy prophylaxis</th>
<th>P-value</th>
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<tbody>
<tr>
<td>NG/CT</td>
<td>8</td>
<td>4</td>
<td>0.36</td>
</tr>
<tr>
<td>Syphilis</td>
<td>7</td>
<td>2</td>
<td>0.10</td>
</tr>
<tr>
<td>Any STI</td>
<td>15</td>
<td>6</td>
<td>0.02</td>
</tr>
</tbody>
</table>

- Two ongoing RCT’s of daily doxy (NCT02864550, NCT02844634)
On-Demand Doxy PEP, IPERGAY extension

- IPERGAY trial: on-demand TDF/FTC PrEP/PEP for HIV
- Randomized 232 participants in extension phase
  - No Doxy PEP, or
  - Doxy 200mg x1 at 24-72 hours after sex

<table>
<thead>
<tr>
<th></th>
<th>No PEP</th>
<th>Doxy PEP</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>NG</td>
<td>25</td>
<td>22</td>
<td>0.83 (0.47, 1.47)</td>
</tr>
<tr>
<td>CT</td>
<td>21</td>
<td>7</td>
<td>0.30 (0.13, 0.70)</td>
</tr>
<tr>
<td>Syphilis</td>
<td>10</td>
<td>3</td>
<td>0.27 (0.07, 0.98)</td>
</tr>
<tr>
<td>Any STI</td>
<td>45</td>
<td>28</td>
<td>0.53 (0.33, 0.85)</td>
</tr>
</tbody>
</table>

- 83% of PEP arm used PEP, median 7 (3-15) pills/month
- No evidence of risk compensation
- Higher incidence of GI adverse events

*Molina 91LB, CROI 2017*
Summary

• Hepatic syphilis case
• Syphilis stages, serologic tests, and treatment regimens
• Ocular syphilis and overlap with neurosyphilis
• Syphilis, NG, CT at highest levels
• MSM with steepest increases in syphilis incidence
• **Broad, frequent screening** key to reversing current STD trends
• PrEP users (among others) should be screened q3-6 months
We have reached a decisive moment for the nation. STD rates are rising, and many of the country’s systems for preventing STDs have eroded. We must mobilize, rebuild, and expand services – or the human and economic burden will continue to grow.

– Dr. Jonathan Mermin, Director

Centers for Disease Control and Prevention
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
STD Treatment Guidelines wall charts, pocket guides, and the full MMWR article at: www.cdc.gov/std/tg2015
The NNPTC provides:

- Clinical training
- STD clinical consultations
- Resources and tools for STD treatment

Visit: www.nnptc.org
Questions?

THANK YOU!