Sexually Transmitted Infections in HIV Care

Jeanne Marrazzo, MD, MPH
Division of Infectious Diseases
University of Alabama at Birmingham, U.S.

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Wrap It Up Alaska Condoms
Disclosures

▪ Funding from NIH, CDC for study of sexually transmitted infection, vaginitis management & diagnosis
▪ Board member: International Antiviral Society-USA (IAS-USA); ISSTDR; Anaerobe Society of the Americas; American Board of Internal Medicine Council & Infectious Disease Specialty Board
▪ Educational materials: IAS-USA; UpToDate; InPractice
▪ Industry: Gilead; BioFire
What’s New?

- Epidemiology in the era of PrEP/TasP
- Gonorrhea: continued antimicrobial resistance; hope for vaccine?
- Syphilis: the ongoing saga; OI guidelines
- Chlamydia: reappearance of LGV proctitis?
- STI immunizations in HIV care
National HIV Behavioral Surveillance, San Francisco

Reported behaviors among MSM

Chen YH
AIDS Behav 2016
Reported primary and secondary syphilis case rates (per 100,000), by sex, NYC, 2011-2016 (N=1,867)

Median age of women with P&S syphilis = 27 (2015) and 25.5 (2016)
Male anorectal chlamydia and gonorrhea cases reported to the DOHMH, NYC, 2011-2016*

*Preliminary

Year

2011 1245
2012 1878
2013 2332
2014 3498
2015 5051
2016 7555

No. anorectal infections

50% [Slide courtesy of Julia Schillinger, MD]
Key Points

- An estimated 31% of all gonorrhea cases in 2015 occurred in the 2% of the U.S. population who are MSM

- Most infections are asymptomatic and detected only by screening
  - Serve as a reservoir for ongoing transmission
  - Rectal infection increases HIV risk
  - Pharynx supplies genetic material that may contribute to resistance & presents challenge for eradication
Penicillin cures gonorrhea in 4 hours. See your doctor today.
Neisseria gonorrhoeae — Percentage of Urethral Isolates with Elevated Ceftriaxone Minimum Inhibitory Concentrations (MICs) (≥0.125 μg/ml) by Reported Sex of Sex Partner, Gonococcal Isolate Surveillance Project (GISP), 2006–2015

* MSM = Gay, bisexual, and other men who have sex with men (collectively referred to as MSM); MSW = Men who have sex with women only.
Neisseria gonorrhoeae — Distribution of Azithromycin Minimum Inhibitory Concentrations (MICs) by Year, Gonococcal Isolate Surveillance Project (GISP), 2012–2016
Fig 2. Percentage of isolates with resistance to azithromycin according to most recent WHO Gonococcal Antimicrobial Surveillance Programme (GASP) data (2014 for most countries)

http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002344
2015 CDC STD Treatment Guidelines: Uncomplicated Gonorrhea Infection

- Ceftriaxone 250 mg injection x 1

PLUS:

- Azithromycin 1 g orally x 1
  - For now!

Doxycycline removed as second agent
2015 Gonorrhea Treatment Guidelines: If Cephalosporin Allergy

Gentamicin
240 mg IM x 1

OR

Gemifloxacin
320 mg PO x 1

+ 

Azithromycin
2 g PO x 1

NOTES:
• Urogenital infections only
• Gemifloxacin remains in shortage
• Gentamicin can be challenging to administer
A Dangerous, ‘Silent Reservoir’ for Gonorrhea: The Throat

By ANERI PATTANI  JULY 31, 2017

Cases of gonorrhea in the throat are on the rise. BISP/UG, via Getty Images
Managing Treatment Failures

- Most treatment failure likely due to reinfection
  - Ensure partner treatment!
- If suspect treatment failure, obtain culture & susceptibility, ensure partner treatment
  - If reinfection likely (after ceftriaxone/azi): Rx ceftriaxone 250 mg + azithromycin 1 g
  - If treatment failure suspected, gemifloxacin 320 mg + azithromycin 2 g or gentamicin 240 IM + azithromycin 2g
- Report to local or state health department; call us!
- Test of cure 7-14 days after retreatment (culture/susceptibility test with NAAT)
Gonorrhea Treatment: Summary

- Dual therapy
  - Azithromycin monotherapy not recommended due to ease of & increasing rates if resistance
  - Ceftriaxone treatment failures rare, all outside U.S.

- Perform test of cure only in these scenarios:
  - Pharyngeal infection treated with anything other than CTX/azithro
  - Urogenital infection treated with anything other than CTZ/azithro or cefixime/azithro
  - Persistent signs or symptoms

- >95% of NAAT tests post-treatment clear within 7 days (RNA tests) or 14 days (DNA tests) (Wind Clin Infect Dis 2016)
- Many “new” clinical manifestations
  - Ocular disease
- Indications for lumbar puncture
- Serologic non-response
- Treatment
388 cases

Most among MSM with HIV
- A few among HIV-negative persons, including heterosexual men and women
- Several resulted in significant sequelae including blindness
- All should be reported within 24 h of diagnosis to Public Health

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>Suspected ocular syphilis 2014</th>
<th>Suspected ocular syphilis 2015</th>
<th>Total surveillance syphilis cases 2014</th>
<th>Total surveillance syphilis cases 2015</th>
<th>% surveillance syphilis cases with suspected ocular syphilis 2014</th>
<th>% surveillance syphilis cases with suspected ocular syphilis 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>California*</td>
<td>48</td>
<td>60</td>
<td>6,238</td>
<td>7,824</td>
<td>0.77</td>
<td>0.77</td>
</tr>
<tr>
<td>Florida</td>
<td>10</td>
<td>32</td>
<td>6,030</td>
<td>7,154</td>
<td>0.17</td>
<td>0.45</td>
</tr>
<tr>
<td>Indiana†</td>
<td>—</td>
<td>8</td>
<td>—</td>
<td>714</td>
<td>—</td>
<td>1.10</td>
</tr>
<tr>
<td>Maryland</td>
<td>10</td>
<td>17</td>
<td>1,524</td>
<td>1,779</td>
<td>0.66</td>
<td>0.96</td>
</tr>
<tr>
<td>New York City</td>
<td>14</td>
<td>12</td>
<td>5,798</td>
<td>6,116</td>
<td>0.24</td>
<td>0.20</td>
</tr>
<tr>
<td>North Carolina</td>
<td>21</td>
<td>42</td>
<td>1,799</td>
<td>2,435</td>
<td>1.20</td>
<td>1.70</td>
</tr>
<tr>
<td>Texas</td>
<td>27</td>
<td>46</td>
<td>7,337</td>
<td>8,400</td>
<td>0.37</td>
<td>0.19</td>
</tr>
<tr>
<td>Washington</td>
<td>27</td>
<td>44</td>
<td>857</td>
<td>1,125</td>
<td>3.20</td>
<td>3.90</td>
</tr>
<tr>
<td>Total</td>
<td>157</td>
<td>231</td>
<td>29,583</td>
<td>35,547</td>
<td>0.53</td>
<td>0.65</td>
</tr>
</tbody>
</table>

* California does not include syphilis reports from San Francisco or Los Angeles.
† Indiana reviewed data from 2015 only.
### TABLE 2. Demographic characteristics of patients with suspected ocular syphilis — eight jurisdictions, United States, 2014–2015

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

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>388</td>
<td>(100.0)</td>
</tr>
<tr>
<td>Stage of syphilis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>8</td>
<td>(2.1)</td>
</tr>
<tr>
<td>Secondary</td>
<td>101</td>
<td>(26.0)</td>
</tr>
<tr>
<td>Early latent</td>
<td>79</td>
<td>(20.4)</td>
</tr>
<tr>
<td>Late or latent of unknown duration</td>
<td>193</td>
<td>(49.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>7</td>
<td>(1.8)</td>
</tr>
<tr>
<td>Additional symptoms of neurosyphilis</td>
<td>87</td>
<td>(22.4)</td>
</tr>
<tr>
<td>Reported ocular symptoms (among 326 with symptoms)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blurry vision</td>
<td>210</td>
<td>(64.4)</td>
</tr>
<tr>
<td>Vision loss</td>
<td>107</td>
<td>(32.8)</td>
</tr>
<tr>
<td>Eye pain or red eye</td>
<td>46</td>
<td>(14.1)</td>
</tr>
<tr>
<td>Eye exam</td>
<td>158</td>
<td>(40.7)</td>
</tr>
<tr>
<td>Diagnosis (among 158 with documented eye exam)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uveitis</td>
<td>72</td>
<td>(45.6)</td>
</tr>
<tr>
<td>Retinitis</td>
<td>20</td>
<td>(12.7)</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>18</td>
<td>(11.4)</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>6</td>
<td>(3.8)</td>
</tr>
<tr>
<td>CSF analysis performed</td>
<td>188</td>
<td>(48.5)</td>
</tr>
<tr>
<td>CSF VDRL (among 174 with a documented result)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reactive</td>
<td>122</td>
<td>(70.1)</td>
</tr>
<tr>
<td>Nonreactive</td>
<td>52</td>
<td>(29.9)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aqueous penicillin G IV</td>
<td>230</td>
<td>(59.3)</td>
</tr>
<tr>
<td>Other treatment</td>
<td>146</td>
<td>(37.6)</td>
</tr>
<tr>
<td>No/Unknown treatment</td>
<td>12</td>
<td>(3.1)</td>
</tr>
</tbody>
</table>

Abbreviations: CSF = cerebrospinal fluid; IV = intravenous; VDRL = Venereal Disease Research Laboratory test.
* Can be included in multiple categories.
### LP in Syphilis / HIV

#### In Favor
- CNS involvement in early syphilis is common (40%) & predicted clinical neurosyphilis in the pre-antibiotic era
- BZN PCN does not penetrate CNS
- Syphilis contained by cell-mediated immunity, and may be more severe in HIV
  - NS associated with CD4 <350, serum RPR >1:32 (Marra 2004; Libois 2007)

#### Against
- Frequency of serious neurosyphilis low in both untreated syphilis & early syphilis treated with BZN PCN
- PCN in CNS may not be needed to suppress early CNS invasion
- Cost & inconvenience of LP

**Recommendation:** careful evaluation for signs & symptoms, treatment failure
Single Dose Versus 3 Doses of Intramuscular Benzathine Penicillin for Early Syphilis in HIV: A Randomized Clinical Trial

Roberto Andrade,1 Maria C. Rodriguez-Barradas,2,3 Kosuke Yasukawa,4 Erick Villarreal,1 Michael Ross,4 and Jose A. Serpa1

1Section of Infectious Diseases, Department of Medicine, Baylor College of Medicine, and 2Section of Infectious Diseases, Department of Medicine, Michael E. Debakey Veterans Affairs Medical Center, Houston, Texas; 3Department of Medicine, Albert Einstein College of Medicine, Bronx, New York; and 4Department of Family Medicine and Community Health, University of Minnesota Medical School, Minneapolis

- Open-label randomized trial enrolling 64 participants; mean CD4 388
- Serologic treatment success 12 mos.
  - 28 of 35 (80%) in single-dose regimen
  - 27 of 29 (93%) in 3-dose regimen
  - Per-protocol analysis: 93% vs. 100%; absolute difference 7% (95% C.I. -7%, 22%); P=0.49
  - Not modified by CD4 count, RPR titer, syphilis stage
- Not powered to demonstrate non-inferiority

Figure 2. Intention-to-treat and per-protocol analyses of the comparison between a single dose vs 3 doses of 2.4 million units of intramuscular benzathine penicillin G (BPG) for early syphilis in human immunodeficiency virus-infected individuals. Abbreviation: BPG, benzathine penicillin G.
Identified 1693 reports in the literature, reviewed 20

Median proportion of patients with serological non-response was 12.1% overall (interquartile range, 4.9–25.6)

Serofast proportion estimated from 2 studies, which ranged from 35.2–44.4 %. Serological cure primarily associated with younger age, higher baseline nontreponemal titers, and earlier syphilis stage

Relationship between serological cure and HIV status inconsistent; among HIV-infected patients, CD4 count and HIV viral load not associated with serologic cure
Summary

- Impressive resurgent epidemic of syphilis, especially in MSM
  - Includes neurologic syndromes, including auditory, facial nerve palsy, visual abnormalities
- Among infected MSM, at least half are co-infected with HIV
- Infection is occurring nationwide, across race / ethnicities
- Congenital syphilis events are still occurring
- Early syphilis PREDICTS HIV acquisition in those not already infected with HIV
- Serologic non-response state is probably common; careful follow-up and consideration of neurosyphilis are key
So what do we do while we wait for a vaccine?
On-Demand Post-Exposure Prophylaxis With Doxycycline for MSM: Follow on to IPERGAY

Open-Label Study (n=232)
HIV-negative high-risk MSM enrolled in the open-label Ipergay extension study
No contraindication to doxycycline

On Demand PEP Doxycycline 200 mg (~24 hours after sex, up to 72 hours)
No PEP

Visits: baseline and every 2 months
Serologic assays for HIV and syphilis
PCR assays for chlamydia and gonorrhea
Urine, anal, and throat samples collected

Baseline characteristics:
Median age: 38-39 years
White: 95%
History of PEP use in Ipergay: 19%.
Use of psychoactive drugs (ecstasy, crack, cocaine, crystal, speed, GHB/GBL): 42%
Circumcised: 21%
Prior gonorrhea, chlamydia, syphilis infection: 16%
Number of sexual acts in prior 4 weeks: 10

Time to First STI With On-Demand PEP With Doxycycline for MSM


Incidence of STIs (n=73 with STI):
No PEP (n=45): 70/100 person-years.
PEP (n=28): 38/100 person-years.

Median follow-up: 8.7 months

HR: 0.53 (P=0.008)
Time to First Chlamydia and Syphilis With On-Demand PEP With Doxycycline for MSM


Incidence of chlamydia (n=28):
No PEP (n=21): 29/100 person-years.
PEP (n=7): 9/100 person-years.

HR: 0.30 (P=0.003)

Incidence of syphilis (n=13):
No PEP (n=10): 13/100 person-years.
PEP (n=3): 4/100 person-years.

HR: 0.27 (P=0.04)
Time to First Gonorrhea With On-Demand PEP With Doxycycline for MSM

- No effect on gonorrhea incidence
- Number sites of gonorrhea infection (PEP versus no PEP)
  - Anus: 11 versus 19
  - Throat: 15 versus 12
  - Urine: 1 versus 7

Conclusions

- PEP reduced overall incidence of bacterial STI by 47% in MSM on PrEP (8.7 months of follow-up)
- No effect on gonorrhea, but strong reduction in chlamydia and syphilis
- Analysis of antibiotic resistance is pending
- Long-term benefit of PEP is not yet known
- Antibiotic prophylaxis for STIs still not recommended
- More research is needed

Cluster of Lymphogranuloma Venereum Cases Among Men Who Have Sex with Men — Michigan, August 2015–April 2016

Alex de Voux, PhD1, 2; James B. Kent, MS3; Kathryn Macomber, MPH3; Karen Krzanowski, MA, MPH4; Dawn Jackson5; Tayneta Starr4; Sandra Johnson4; Deborah Richmond, MSN3; Lawrence R. Crane, MD5; Jonathan Cohn, MD5; Christopher Finch5; Jevon McFadden, MD6; Allan Pillay, PhD2; Cheng Chen, PhD2; Laurie Anderson2; Ellen N. Kersh, PhD2

BOX. Case definition of lymphogranuloma venereum (LGV) included in Michigan Health Alert Network sent out on October 22, 2015

<table>
<thead>
<tr>
<th>Suspected case</th>
</tr>
</thead>
<tbody>
<tr>
<td>• A clinically compatible illness in a person with one or more signs or symptoms compatible with LGV (proctocolitis, inguinal/femoral lymphadenopathy, or genital or rectal ulcers), and</td>
</tr>
<tr>
<td>• A sexual partner of a person meeting the probable or confirmed case definition.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Probable case, either or both of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• A patient meeting the suspected case definition, in whom other causes of LGV-like symptoms (e.g., syphilis, gonorrhea, and herpes simplex virus) have been ruled out, and a positive <em>Chlamydia trachomatis</em> from culture or nucleic acid amplification test (NAAT) from a body site associated with symptoms.</td>
</tr>
<tr>
<td>• Sexual partner of a person meeting the probable or confirmed case definition and a positive <em>C. trachomatis</em> from culture or NAAT.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Confirmed case</th>
</tr>
</thead>
<tbody>
<tr>
<td>• A probable case with laboratory confirmation for <em>C. trachomatis</em> genotypes L1, L2, or L3 by genetic analysis (LGV-specific polymerase chain reaction or sequencing).</td>
</tr>
</tbody>
</table>

- 38 cases reported to CDC
- All HIV+ MSM
- Median CD4 483
- Suspect in severe or persistent proctitis, especially with lymphadenopathy Treat with doxycyline 100 mg bid x 3 weeks
- Report to local health department
“STI” Immunizations in HIV

- Hepatitis A/B
- Either 9vHPV or 4vHPV vaccination through age 26 years if not vaccinated previously
- Meningococcal vaccine
  - MenACWY-D (Menactra) or MenACWY-CRM (Menveo)
From: Population-Based Incidence Rates of Cervical Intraepithelial Neoplasia in the Human Papillomavirus Vaccine Era

JAMA Oncol. Published online September 29, 2016. doi:10.1001/jamaoncol.2016.3609

A Incidence of CIN1 per 100,000 tested women

Age range
- 15-19 (P < .001)
- 20-24 (P = .07)
- 25-29 (P = .05)

B Incidence of CIN2 per 100,000 tested women

Age range
- 15-19 (P = .03)
- 20-24 (P = .02)
- 25-29 (P = .23)

C Incidence of CIN3 per 100,000 tested women

Age range
- 15-19 (P = .05)
- 20-24 (P = .47)
- 25-29 (P = .002)

D Cervical cytology screening rates per 100,000 women

Age range
- 15-19 (P < .001)
- 20-24 (P < .001)
- 25-29 (P < .001)
Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study

Helen Petousis-Harris, Janine Paynter, Jane Morgan, Peter Saxton, Barbara Mc"
STD Screening for MSM

- HIV
- Syphilis
- Urethral GC and CT
- Rectal GC and CT (if RAI)
- Pharyngeal GC (if oral sex)

- Hepatitis C (HIV+MSM, at least annually)

Anal Cancer in HIV+ MSM: Data insufficient to recommend routine screening, some centers perform anal Pap and HRA
UW PTC STI Self-Testing Program
Serologic Screening for Genital Herpes Infection
US Preventive Services Task Force
Recommendation Statement

US Preventive Services Task Force

**IMPORTANCE** Genital herpes is a prevalent sexually transmitted infection in the United States, occurring in almost 1 in 6 persons aged 14 to 49 years. Infection is caused by 2 subtypes of the herpes simplex virus (HSV), HSV-1 and HSV-2. Antiviral medications may provide symptomatic relief from outbreaks but do not cure HSV infection. Neonatal herpes infection, while uncommon, can result in substantial morbidity and mortality.

**OBJECTIVE** To update the 2005 US Preventive Services Task Force (USPSTF) recommendation on screening for genital herpes.

**EVIDENCE REVIEW** The USPSTF reviewed the evidence on the accuracy, benefits, and harms of serologic screening for HSV-2 infection in asymptomatic persons, including those who are pregnant, as well as the effectiveness and harms of preventive medications and behavioral counseling interventions to reduce future symptomatic episodes and transmission to others.

**FINDINGS** Based on the natural history of HSV infection, its epidemiology, and the available evidence on the accuracy of serologic screening tests, the USPSTF concluded that the harms outweigh the benefits of serologic screening for genital HSV infection in asymptomatic adolescents and adults, including those who are pregnant.

**CONCLUSIONS AND RECOMMENDATION** The USPSTF recommends against routine serologic screening for genital HSV infection in asymptomatic adolescents and adults, including those who are pregnant. (D recommendation)

Take-Home Messages

- Screen, appropriately!
- Be aware of antibiotic-resistant GC
- Syphilis: it’s not going away. Recognize neuroinvasive disease
- Hepatitis C
- Sexual health
  - Vaccinate for HPV, meningococcus, hepatitis A/B
    - Continue Pap screening
  - Prevention messages
Thank you!

KEEP CALM
ITS NOT AS BAD AS GONORRHEA
Emerging Issues: 
*Mycoplasma genitalium*

- Recognized cause of urethritis
- Role in cervicitis and PID emerging
- No diagnostic test FDA cleared for use
  - NAAT available in some large medical centers and commercial laboratories
- Suspect in persistent or recurrent urethritis and consider in persistent cervicitis and PID
- Treatment implications
  - Azithromycin better than doxycycline, but…
    - Emerging resistance to azithromycin
  - Moxifloxacin for recurrence
Non-Gonococcal Urethritis (NGU) Treatment

- Azithromycin or doxycycline
- Limited data on the public health impact of *M. genitalium* to demote doxycycline
- Persistent or recurrent urethritis
  - *M. genitalium* most common cause
    - Higher azithromycin doses not effective
  - *Trichomonas vaginalis*
    - Metronidazole or tinidazole for men who have sex with women in areas of high prevalence
- Urology referral with persistence after treatment
Persistent / Recurrent NGU Treatment

- If initially tx’d with doxy → Azithromycin
- If failed azithro → moxifloxacin 400mg qday x 7 days
- If sexually active with women & high trich prevalence add → Metronidazole or tinidazole