Sexually Transmitted Diseases: What’s New in the Guidelines and Beyond?

Susan S. Philip, MD, MPH
Director, Disease Prevention and Control Branch
Population Health Division
San Francisco Department of Public Health
Assistant Clinical Professor of Medicine
Division of Infectious Diseases
University of California, San Francisco

Disclosures
The views expressed herein do not necessarily reflect the official policies of the City and County of San Francisco; nor does mention of the San Francisco Department of Public Health imply its endorsement.

S. Philip has received research support from Roche Diagnostics, SeraCare Life Sciences, Melinta Therapeutics, GlaxoSmithKline and Cepheid Inc.

Overview

- (Very!) Brief US STD Epidemiology
- Sexual History
- Select STDs: Updates in screening, prevention or treatment

http://www.cdc.gov/std/tg2015/

CDC Treatment Guidelines App for iOS and Android
Available now, FREE! (accept no competitors)
Development of CDC STD Treatment Guidelines

- Recommended regimens (“in the box”) preferred over alternative regimens
- Treatments are typically alphabetized unless there is a preferred choice
- Language in yellow highlighted boxes reflects changes

Why Diagnose and Treat STDs?

- > 19 million STDs in US annually
- Cost: 16.4 billion (2009)
- Health consequences
  - Pelvic Inflammatory Disease
  - Ectopic pregnancy
  - Infertility
  - Neonatal HIV, herpes simplex virus (HSV) and congenital syphilis
  - Increase risk of HIV
- Screening as a quality indicator
  - HEDIS (CT screening in young women)
  - HIV Primary Care

Health Disparities

- Nationally there are populations who bear a disproportionate share of STDs
  - Men who have sex with men (MSM)
  - Adolescents
  - African Americans
  - Transgender persons
- Studies demonstrate that individual behaviors alone do not account for the increased rates\(^1\)\(^3\)

\(^1\) Ellen STD 1998 \(^2\)Laumann STD 1999 \(^3\)Oster AIDS 2011

High rates of syphilis and HIV in US MSM

<table>
<thead>
<tr>
<th></th>
<th>Rates per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syphilis</td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>91</td>
</tr>
<tr>
<td>MSW</td>
<td>2</td>
</tr>
<tr>
<td>Woman</td>
<td>1</td>
</tr>
<tr>
<td>HIV</td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>522</td>
</tr>
<tr>
<td>MSW</td>
<td>12</td>
</tr>
<tr>
<td>Woman</td>
<td>13</td>
</tr>
</tbody>
</table>

\[\text{CDC 2010} \]
As HIV Pre-Exposure Prophylaxis (PrEP) Expands, STD screening is important

| STI Incidence After 12 Months of PrEP Use in Kaiser SF PrEP Cohort |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Any STI          | Rectal STI      | Chlamydia       | Gonorrhea       | Syphilis        |
| 50%              | 33%             | 33%             | 28%             | 5.5%            |
| 0%               | 50%             | 33%             | 33%             | 28%             |

Sexual History in Primary Care?

<table>
<thead>
<tr>
<th>Felt Adequately Trained</th>
<th>Sexual History at routine visit</th>
<th>Full Components of Sexual History</th>
</tr>
</thead>
<tbody>
<tr>
<td>70%</td>
<td>60%</td>
<td>50%</td>
</tr>
<tr>
<td>50%</td>
<td>40%</td>
<td>30%</td>
</tr>
<tr>
<td>30%</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td>20%</td>
<td>10%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Keep it Simple

- Neutral language:
  - “Do you have sex with men, women, or both?”
  - “What are you doing to prevent unwanted pregnancies or STDs” rather than “You use condoms 100%, right?”
- Consider adding questions to self-registration materials
- Find referral resources for complex trauma or sexual dysfunction

Practical Provider Tools for Sexual History

- Fenway Institute and National Association of Community Health Centers
  - Scripts
  - Downloadable presentation
  - Coding Guides
  - EMR implementation

CDC STD Treatment Guidelines
**Case 1**
At a new patient’s initial visit, you learn he is a gay man who has had 3 sex partners in the last year. He feels fine and says all STD tests were negative a year ago. In addition to an HIV test, what else would you order?

1. No additional tests – he is asymptomatic
2. Urine gonorrhea and chlamydia
3. Syphilis serology
4. Pharyngeal GC, rectal GC and CT, syphilis serology
5. I need to know more before deciding

---

**STD Asymptomatic Screening for Women**

<table>
<thead>
<tr>
<th>Category</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexually Active women up to age 25</td>
<td>Routine annual chlamydia and gonorrhea screening</td>
</tr>
<tr>
<td></td>
<td>Other STDs and HIV based on risk</td>
</tr>
<tr>
<td>Women over 25 years of age</td>
<td>STD/HIV testing based on risk</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>Chlamydia</td>
</tr>
<tr>
<td></td>
<td>Gonorrhea (&lt;25 years of age or risk)</td>
</tr>
<tr>
<td></td>
<td>HIV</td>
</tr>
<tr>
<td></td>
<td>Syphilis serology</td>
</tr>
<tr>
<td></td>
<td>HepB sAg</td>
</tr>
<tr>
<td></td>
<td>Hep C (if high risk)</td>
</tr>
</tbody>
</table>

---

**STD Asymptomatic Screening for MSM**

- Screen at least annually, or every 3-6 mos if high risk*  
- HIV  
- Syphilis  
- Urethral GC and CT  
- Rectal GC and CT (if anal sex)  
- Pharyngeal GC (if oral sex)  

Also screen for:  
- Hepatitis B surface Ag (frequency not specified)  
- Hepatitis C if IDU, born 1945-65 or transfusion before 1992  

* High risk: multiple and/or anonymous partners, drug use, or these risks in patient’s partners

---

**STD Asymptomatic Screening for HIV+ MSM**

Same as HIV uninfected MSM plus:

- Anal Cancer in HIV+ MSM: Annual digital rectal exam may be useful, some centers perform anal Pap and HRA for ASC-US or worse.

- HCV: “HCV antibody tests should be serially monitored, at least yearly and more frequently depending on local circumstances (HCV prevalence, incidence, resources, and other factors), to detect conversion from HCV-antibody-negative to positive.”

---

[CDC 2015 STD Tx Guidelines](www.cdc.gov/std/treatment)
Proportion of asymptomatic rectal and urethral chlamydial and gonococcal infection among MSM– San Francisco City Clinic, 2011

Rectal Infections
- Chlamydia: 42%
- Gonorrhea: 9%

Urethral Infections
- Chlamydia: 91%
- Gonorrhea: 5%

Proportion of Chlamydia or Gonorrhea infections in asymptomatic MSM MISSED if only urine screened
- Chlamydia: 77% identified, 23% MISSED
- Gonorrhea: 95% identified, 5% MISSED

Case 1, continued
Patient reports receptive anal sex (intermittent condom use) and oral sex. The GC/CT NAAIs come back first – positive for rectal gonorrhea. All others neg. Treatment? Oh, and by the way, patient has documented anaphylaxis to cephalosporins

1. Azithromycin 2 g PO x 1
2. Levofloxacin 250 mg PO x 1
3. Cefixime 400 mg PO x 1 PLUS azithromycin 1 PO x 1
4. Gentamicin 240 mg IM + azithromycin 2 g PO
5. Gemifloxacin 320 mg PO + azithromycin 2 g PO
6. 1, 4 or 5
7. 4 or 5

Gonorrhea Treatment is one of CDC’s key strategies to reducing risk of resistant *Neisseria gonorrhoeae*
Current Recommended Gonorrhea Treatment – any anatomic site

<table>
<thead>
<tr>
<th>Ceftriaxone 250mg IM x 1</th>
<th>Azithromycin 1g PO x 1</th>
</tr>
</thead>
</table>

This is Dual treatment for GC – add the azithromycin or doxycycline regardless of CT result

Example: If patient is treated empirically with azithromycin for urethritis and the NAAT is GC+ 3 days later, must repeat azithro in combination with ceftriaxone to meet treatment recommendations

CDC 2015 STD Tx Guidelines www.cdc.gov/std/treatment

Gonorrhea changes: 2015 Treatment Guidelines

- Doxycycline no longer recommended (leave only Ceftriaxone + Azithromycin as recommended tx)
- Limit Test of cure only to pharyngeal GC treated with alternative regimen, may extend interval to 14 days
- For cephalosporin allergic, add 2 regimens
  - Gentamicin 240 mg IM (or 5mg/kg IM) with azithromycin 2g orally
  - Gemifloxacin 320 mg orally with azithromycin 2g orally

NIH-CDC GC Dual Treatment Study

- Two-arm RCT in five US sites from May 2010-Nov 2012 (San Francisco, Birmingham, Pittsburgh, Los Angeles, Baltimore)
  - Gentamicin 240mg IM x 1 + azithromycin 2g PO x 1
  - Gemifloxacin 320mg PO x 1 + azithromycin 2g PO x 1
- 401 men and women 15 – 60 years with uncomplicated urogenital gonorrhea (culture-positive)
- Followed at 10-17 days for microbiologic cure (culture)

Kirkcaldy CID 2014

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Gentamicin/Azithro</th>
<th>Gemifloxacin/Azithro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urethral/cervical</td>
<td>(n=202/202)</td>
<td>(n=199/199)</td>
</tr>
<tr>
<td>100% (95%CI 98.5% – 100%)</td>
<td>99.5% (95% CI 97.6% - 100%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Outcomes</th>
<th>Gentamicin/Azithro</th>
<th>Gemifloxacin/Azithro</th>
</tr>
</thead>
<tbody>
<tr>
<td>pharyngeal</td>
<td>n/N=10/10 (100%)</td>
<td>n/N=15/15 (100%)</td>
</tr>
<tr>
<td>rectal</td>
<td>N=1/1 (100%)</td>
<td>N=5/5 (100%)</td>
</tr>
</tbody>
</table>

Mild-mod GI side effects were common in both arms (47-55%)
Case 2
A 17 year old girl comes in for a sports physical. She has no complaints and is hoping to get in and out of the office quickly. You see she lists oral contraceptives on her med history and think about chlamydia screening.

Would you:
1. Ask her if she is willing to have a pelvic exam today, and collect an endocervical swab for CT NAAT
2. Make a note in her chart to do CT screening at her next visit
3. Ask her to give a urine sample for CT NAAT
4. Ask her to perform a self collected vaginal swab for CT NAAT

Chlamydia Treatment
Adolescents and Adults

**Recommended regimens (non-pregnant):**
- Azithromycin 1 g orally in a single dose
- Doxycycline 100 mg orally twice daily for 7 days

**Recommended regimens (pregnant):**
- Azithromycin 1 g orally in a single dose

CT Treatment – Changes to 2015 Guidelines

**Additional Alternative Regimen (non-pregnant):**
- Doxycycline (delayed release) 200 mg po QD x 7 d
  - Equally efficacious to BID dose, less GI side effects
  - More $$$

**Move to Alternative Regimen (PREGNANCY):**
- Amoxicillin 500 mg po TID x 7 days
  - CT persistence documented in vitro after treatment prompted removal from recommended to alternate
Expedited Partner Therapy (EPT)* is recommended to reduce repeat infection in the index patient

*EPT is providing GC/CT treatment to your patient to give to their sex partner(s) without a clinical visit

March 2015 legal status of EPT by jurisdiction:
http://www.cdc.gov/std/EPT
Updated March 2016

Practical Implementation for STD screening?

- Sexual history documented at least once for each patient
- Consider standing orders for screening at recommended intervals
- Use self-collected vaginal swabs (FDA-cleared) – can separate screening from pelvic exams and simpler than urine (no need to aliquot!)
- Consider self-collected rectal, pharyngeal swabs in consultation with lab
- Provide prescriptions for your patient to take to their partner, if allowable by law where you practice

Case 3

48 year old man, new to your practice, previously injected drugs but none in the past 10 years. HIV and HCV screen negative and he is asymptomatic. The lab calls to tell you they are using a new testing algorithm for syphilis and the patient’s results are:

EIA+, RPR negative, TPPA+  Best next step?

1. Treat with benzathine PCN 2.4 mu IM x 1
2. Treat with benzathine PCN 2.4 mu IM x 3
3. Need more information before proceeding
4. Do nothing as this is unlikely to be syphilis
5. Perform an LP to rule out neurosyphilis

Syphilis Screening Paradigm

**TRADITIONAL**

Non-treponemal tests (e.g., RPR, VDRL)
- NON-SPECIFIC ANTIBODY TO LIPOIDAL ANTIGENS
- QUANTITATIVE
- REACTIVITY DECLINES WITH TIME

Treponemal tests (e.g., TPPA, FTA-Abs)
- SPECIFIC TO TP
- QUALITATIVE
- REACTIVITY PERSISTS OVER LIFETIME

reflex to
Syphilis Screening Paradigm

Reverse Algorithm

- Treponemal tests (e.g., EIA, CIA, MBIA)
  - SPECIFIC TO TP
  - QUALITATIVE
  - REACTIVITY PERSISTS OVER LIFETIME

Second treponemal test (TPPA) is 'tie-breaker'

- Non-treponemal tests (e.g., RPR, VDRL)
  - NON-SPECIFIC ANTIBODY TO LIPOIDAL ANTIGENS
  - QUANTITATIVE
  - REACTIVITY DECLINES WITH TIME

EIA+ RPR- TPPA + cannot distinguish old vs. new infection so must review diagnosis and treatment history! Call public health!

Discordant Results Reverse Sequence Screening

- EIA
  - 3.4% n=4834
  - 96.6%

- RPR
  - 43% n=2091
  - 57% n=2743

- TPPA
  - 68% 32%

What are these?
1) Old, untreated syphilis
2) Old, treated syphilis
3) Early syphilis

**False Positive; Syphilis unlikely (0.6% of overall sample)**

CDC MMWR 2011;60:133-137

Syphilis Treatment – no change in 2015 Guidelines

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

*Should be used with caution and not in MSM or pregnant women

In pregnancy, benzathine penicillin is the only recommended therapy. No alternatives
Syphilis – When to LP?

- Clinical signs of neurosyphilis
  - Cranial nerve dysfunction, meningitis, stroke, acute or chronic altered mental status, auditory or ophthalmic abnormalities
- Serologic treatment failure
- Evidence of active tertiary syphilis (e.g. aortitis and gumma)
- HIV positive and late latent syphilis or syphilis of unknown duration

CDC 2015 STD Tx Guidelines [www.cdc.gov/std/treatment]

Case 3, continued

Patient does not recall ever being diagnosed or treated for syphilis, and this is confirmed by calling local public health in Miami, where he lived for 30 years before moving to your town. You proceed with treatment for late latent syphilis and he receives his first IM benzathine penicillin dose.

He’s not crazy about the idea of coming back in a week. “Can we make it 9 days from now instead of 7?”

Your answer:
1. No way, it has to be exactly a week
2. Sure, that should be fine as long as you do come in at 9 days
3. Good question, I’m not sure

In Late Latent Syphilis, What is the Maximum time Allowed Between Benzathine PCN Doses?

Clinical experience suggests 10-14 days ok for non-pregnant adults
- <9 days is best based on limited pharmacologic data

In pregnancy, must adhere to strict 7 days between doses
- 40% of pregnant women are below treponemical levels after 9 days
- If a dose is missed, the entire series must be restarted

Additional Screening after an STD infection

- Women with CT, GC or trich should be rescreened at 3 months after treatment.
- Men with CT or GC should be rescreened at 3 months after treatment.
- Patients diagnosed with syphilis should undergo follow up serologic serology per current recommendations as well as be screened for other STDs including HIV.
- HIV testing should also be considered in all patients with a prior STD history

Should also perform pregnancy testing in women diagnosed with an STD

Slide Courtesy I. Park MD, MS  CDC 2015 STD Tx Guidelines [www.cdc.gov/std/treatment]
Congenital Syphilis increased 38% in the US between 2012-14

![Graph showing the increase in congenital syphilis cases from 2006 to 2014.]

Screen all pregnant women at start of prenatal care, and if high risk at start of 3rd trimester and again at delivery (3 total screens)

Additional Points on Preventing Congenital Syphilis

- Congenital cases are sentinel events for clinical delivery systems AND public health
- Public health prioritizes female partners of male syphilis cases – please prepare patients and encourage them to work with us to ensure partners are treated
- Remember that penicillin is the only acceptable treatment for pregnant women with syphilis – must desensitize if serious true allergy
- Must adhere to strict 7-day interval for weekly benzathine penicillin in pregnant patients with late latent syphilis. If longer, must restart series. Reinforces importance of annual (at least) screening which narrows infection window and allows us to stage as early syphilis and rx with benzathine PCN 2.4mu IM x 1

---

Syphilis Rapid Test

Trinity Biotech Health Check™
Treponemal-Specific Test (Like TPPA, FTA-ABS)
FDA approved, CLIA-waived (2014)
Can be performed on fingerstick whole blood, serum, plasma
Results in 10 minutes
Not helpful in patients with prior syphilis because remains positive after treatment

Excellent summary and FAQ via CDPH and CA STD/HIV Prevention Training Center:

---

One last, Important Syphilis Item:
Clusters of Ocular Syphilis in Western States

Cluster of four cases Washington State Dec 2014 – Jan 2015
All MSM, 75% HIV-infected
Two patients with permanent visual loss
Subsequently eight cases identified in San Francisco Dec 2014-March 2015 (75% MSM, 88% HIV-infected)
Providers should have a high suspicion for syphilis in patients with visual complaints, especially HIV-infected MSM
Treatment for ocular syphilis is IV PCN as for neurosyphilis even if the CSF lab tests are negative

---

Notes from the Field


[Links to additional resources]
Case 4
A 22 year old woman presents requesting to start the HPV vaccine series. She has had a history of genital warts as well as ASCUS with HPV+ from her most recent pap. Would you:

1. Advise against HPV vaccine since she already has demonstrated HPV infection
2. Start Merck Gardasil™ quadrivalent vaccine (HPV4)
3. Start Merck Gardasil9™ nonavalent vaccine (HPV9)
4. Start GSK Cervarix™ bivalent vaccine (HPV2)

HPV Vaccines

Bivalent: GSK Cervarix®
- Types 16, 18
- Prevents cervical cancer
- FDA-approved for females and males 9-26
- 3-dose series; $365

Quadrivalent: Merck Gardasil®
- Types 6, 11, 16, 18
- Prevents warts, cervical cancer, anal cancer
- FDA-approved for females and males 9-26
- 3-dose series; $375

Nonavalent: Merck Gardasil9®
- Types 6, 11, 16, 18, 31, 33, 45, 52, 58
- FDA approved for females 9-26 yrs. and males 9-15 yrs.
- 3-dose series; $486

Reduction in pre-cancer endpoints
Nonavalent vs quadrivalent vaccine

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Nonavalent  n=7099</th>
<th>Quadrivalent n=7105</th>
<th>% reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN 2/3 or AIS, VIN2/3, VaIN 2/3</td>
<td>1</td>
<td>30</td>
<td>96.7% (80.9-99.8)</td>
</tr>
</tbody>
</table>

Non-inferior immunogenicity for types 6/11/16/18
99% seroconversion for all 4 types

ACIP HPV Vaccine Recommendations

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females 11-12</td>
<td>Routine vaccination with either HPV2, HPV4 or HPV9</td>
</tr>
<tr>
<td></td>
<td>(may start at 9)</td>
</tr>
<tr>
<td>13-26</td>
<td>Routine vaccination with either HPV2, HPV4 or HPV9</td>
</tr>
<tr>
<td>Males 11-12</td>
<td>Routine vaccination: HPV4 or HPV9</td>
</tr>
<tr>
<td></td>
<td>(may start at 9)</td>
</tr>
<tr>
<td>13-21</td>
<td>Routine vaccination: HPV4 or HPV9</td>
</tr>
<tr>
<td>22-26</td>
<td>Permissive rec: HPV 4 or HPV9</td>
</tr>
<tr>
<td>MSM &amp; HIV+ Males</td>
<td>Routine vaccination: HPV 4 or HPV9</td>
</tr>
</tbody>
</table>

MMWR, May 28 2010; 59(20):626-629, 630-632
MMWR, December 23 2011; 60(50);1705-1708

CIN = Cervical Intraepithelial Neoplasia
AIS = Adenocarcinoma in situ
VIN = Vulvar Intraepithelial Neoplasia
VaIN = Vaginal Intraepithelial Neoplasia

Joura et al. NEJM 2015
ACIP HPV Vaccine Recommendations for Common Clinical Scenarios

• HPV vaccination can provide protection against infection with HPV vaccine types not already acquired. Therefore, vaccination is recommended through the recommended age for females regardless of whether they have an abnormal Pap test result, and for females or males regardless of known HPV infection, HPV-associated precancer lesions, or anogenital warts.

• If vaccination providers do not know or do not have available the HPV vaccine product previously administered, or are in settings transitioning to 9vHPV... any HPV vaccine product may be used to continue and complete the series for females; 4vHPV or 9vHPV may be used to continue or complete the series for males

• No indication to restart series with 9vHPV if a patient has completed 4vHPV or 2vHPV previously


What’s Next?

• Sexual transmission of Ebola and Zika viruses documented
• Condoms recommended (CDC, WHO) for prevention

Thank You!

Ina Park
California STD/HIV Prevention Training Center
Stephanie Cohen

2015 CDC STD Treatment Guidelines:

Contact information:
Susan.Philip@sfdph.org
www.sfcityclinic.org