Update on Sexually Transmitted Diseases

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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.

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Overview

- (Very!) Brief US STD Epidemiology
- Sexual History
- Select STDs: Preview of possible new directions in screening, prevention or treatment*

*caveat: subject to change until new guidelines published

CDC STD Treatment Guidelines

December 17, 2010

2015 Update coming soon!
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 proposed draft changes, final language may differ

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
• Quality Indicator (HEDIS, HIV 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 do not account for all the increase\(^1\)-\(^3\)

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

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High rates of syphilis and HIV in US MSM

![Graph showing rates per 100,000 for syphilis and HIV among MSM, MSW, and Women.]

- CDC 2010
Poll

What is your usual approach to taking a sexual history (no wrong answers!)

1. Don’t Ask, Don’t Tell
2. Do this at least once for all patients
3. Expect that a patient will initiate if needed
4. Do this if the chief complaint is related to sexual health

Sexual History in Primary Care?

- Felt Adequately Trained
- Sexual History at routine visit
- Full Components of Sexual History

Wimberly J Nat Med Assoc 2006
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
- 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

http://www.lgbthealtheducation.org/publications/top/briefs/sexual-history-toolkit/
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. The whole enchilada: pharyngeal GC, rectal GC and CT, syphilis serology
5. I need to know more before deciding

STD Asymptomatic Screening for Women

Sexually Active women up to age 25
- Routine annual chlamydia and gonorrhea screening
- Other STDs and HIV based on risk

Women over 25 years of age
- STD/HIV testing based on risk

Pregnant women
- Chlamydia
- Gonorrhea (<25 years of age or risk)
- HIV
- Syphilis serology
- HepB sAg
- Hep C (if high risk)

CDC 2010 STD Tx Guidelines www.cdc.gov/std/treatment
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

CDC 2010 STD Tx Guidelines  www.cdc.gov/std/treatment

STD Asymptomatic Screening for HIV+ MSM

Same as HIV uninfected MSM plus:

Proposed: 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 draft STD Tx Guidelines  www.cdc.gov/std/treatment
Proportion of asymptomatic rectal and urethral chlamydial and gonococcal infection among MSM– San Francisco, 2003

Rectal Infections

<table>
<thead>
<tr>
<th></th>
<th>Chlamydia</th>
<th>Gonorrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>14%</td>
<td>16%</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>86%</td>
<td>84%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Chlamydia</th>
<th>Gonorrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>58%</td>
<td>10%</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>42%</td>
<td>90%</td>
</tr>
</tbody>
</table>

Chlamydia n=316
Gonorrhea n=264

Rectal Infections

Proportion of CT/GC MISSED if screening only performed at urethral site (urine), San Francisco, 2008-2009

n=3398

Chlamydia

MISSED 77%
Identified 23%

Gonorrhea

MISSED 95%
Identified 5%

Marcus et al. STD Oct 2011; 38: 922-4
Summary:
• Use Nucleic Acid Amplification Tests (NAATs) for symptomatic AND asymptomatic patients
• Optimal Specimens:
  • Women – vaginal swabs (may be self collected)
  • Men – first catch urine
• Extragenital (oropharyngeal, rectal) NAAT not FDA-cleared, but recommended – need lab validation

Practical Implementation?
- Sexual history documented at least once for each patient
- Consider standing orders for screening at recommended intervals
- Use self-collected vaginal swabs (FDA-cleared)
- Consider self-collected rectal, pharyngeal swabs in consultation with lab

Freeman STD 2011, Soni STD 2011, Moncada J Clin Microbiol 2009
Case 1, continued

Patient reports receptive anal sex (intermittent condom use) and oral sex. The GC/CT NAATs 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) Levofoxacin 250 mg PO x 1
3) Cefixime 400 mg PO x1 PLUS azithromycin 1 PO x1
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
Current Recommended Gonorrhea Treatment – any site

Ceftriaxone 250mg IM x 1 + Azithromycin 1g PO x 1
OR
Doxycycline 100mg PO bid x 7 days

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

CDC 2010 STD Treatment Guidelines.
Current Recommended Gonorrhea Treatment – any site

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 2010 STD Treatment Guidelines.

Alternative Gonorrhea Treatment for Uncomplicated Urogenital GC (not pharyngeal)

Cefixime
400mg PO x 1

Azithromycin 1g PO x 1
OR
Doxycycline 100mg PO bid x 7 days

OR

Azithromycin 2g PO x 1
Use with caution as high level resistance demonstrated!

Test of Cure with NAAT now recommended (7 days) if using an alternative regimen

CDC 2010 STD Treatment Guidelines.
Gonorrhea proposed changes

- Move Doxycycline out of box (leave only Ceftriaxone + Azithromycin as recommended tx)
- Limit TOC only to pharyngeal GC treated with alternative regimen, may extend interval to 14 days
- For cephalosporin allergic, add 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 non-comparison RCT of 401 men and women 15 – 60 years with uncomplicated urogenital gonorrhea (culture-positive)
  - Gentamicin 240mg IM x 1 + azithromycin 2g PO x 1
  - Gemifloxacin 320mg PO x 1 + azithromycin 2g PO x 1
- Followed at 10-17 days for microbiologic cure (culture)

*or 5mg/kg if weight <45kg
NIH-CDC Dual Treatment Study

Primary Outcome

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Urethral/cervical</th>
<th>Pharyngeal</th>
<th>Rectal</th>
</tr>
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<tbody>
<tr>
<td>Gentamicin/Azithro</td>
<td>(n/N=202/202)</td>
<td>n/N=10/10 (100%)</td>
<td>N=1/1 (100%)</td>
</tr>
<tr>
<td>Gemifloxacin/Azithro</td>
<td>(n/N=198/199)</td>
<td>n/N=15/15 (100%)</td>
<td>N=5/5 (100%)</td>
</tr>
</tbody>
</table>

- 100% (95% CI 98.5% – 100%)
- 99.5% (95% CI 97.6% - 100%)

Secondary Outcomes

<table>
<thead>
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</table>

Mild-mod GI side effects were common in both arms (47-55%)

Will be added as alternative treatment in 2014 Guidelines

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
- Amoxicillin 500mg PO TID x 7 days

* Test of cure at 3-4 weeks only in pregnancy
CT Treatment
2015 Guidelines proposed changes

Additional Alternative Regimen (non-pregnant):
- Doxycycline (delayed release) 200 mg QD x 7 d
  - Equally efficacious to BID doxy, 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 is recommended to reduce repeat infection in the index patient

March 2015 legal status of EPT by jurisdiction:

http://www.cdc.gov/std/EPT
Case 3

48 year old HIV+ man, new to your practice, previously injected drugs but none in the past 10 years. 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

reflex to

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

Reverse Algorithm

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

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

Second treponemal test (TPPA) is ‘tie-breaker’

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

Syphilis Proposed Changes 2015 STD Treatment Guidelines

- Incidence estimates: 55,000 new cases per year
- Diagnostic issues:
  - More labs using treponemal EIA (reverse sequence screening)
  - If a treponemal EIA is used and results are: EIA+, RPR-, TPPA-, repeat in 2 weeks
- Treatment: No changes
- LP for neurosyphilis: No changes
- Follow-up: 21% of patients w/ early syphilis do not have 2-dilution decline in titer in 6-12 mos., optimal mgmt. unclear
Rapid Treponemal Syphilis Test

Syphilis Health Check™
(Diagnostics Direct/Trinity Biotech)

FDA CLIA-waived (2014)
point of care

Treponemal test, so persistent reactive - must follow with non-treponemal test

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

No enhanced efficacy of additional doses of BPG, amoxicillin or other antibiotics even if HIV infected
### Syphilis Treatment
**Primary, Secondary & Early Latent**

<table>
<thead>
<tr>
<th>Alternatives (non-pregnant penicillin-allergic adults):</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Doxycycline 100 mg po bid x 2 weeks</td>
</tr>
<tr>
<td>- Tetracycline 500 mg po qid x 2 weeks</td>
</tr>
<tr>
<td>- Ceftriaxone 1 g IV (or IM) qd x 10-14 d</td>
</tr>
<tr>
<td>- Azithromycin 2 g po in a single dose*</td>
</tr>
</tbody>
</table>

*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
Case 3, variation
Same 48 year old HIV+ man, viral load undetectable on ART, now with new lab finding: EIA+, RPR 1:16
During history and exam which would you assess for:

1. Skin rash on trunk
2. Perianal lesions
3. Genital ulcer
4. Vision changes
5. All of the above

Clusters of Ocular Syphilis in Western States

- Cluster of six cases Washington State Dec 2014
- Mix of heterosexual and gay men, HIV infected and uninfected
- Two patients with permanent visual loss
- Subsequently seven cases reported in San Francisco
- Two under investigation in Los Angeles

- Providers in affected jurisdictions should have a high suspicion for syphilis in patients with visual complaints
- Treatment for ocular syphilis is IV PCN as for neurosyphilis even if the CSF lab tests are negative
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 treponemicidal levels after 9 days
  - If a dose is missed, the entire series must be restarted

Collart 1980, Fretz 1984, Hagrup 1986

Syphilis: Areas of Uncertainty, Proposed changes

- If a treponemal EIA is used in pregnancy and results are: EIA+, RPR-, TPPA-, repeat in 2 weeks if high risk for syphilis

- 21% of patients w/ early syphilis do not have 2-dilution decline in titer in 6-12 mos, optimal management of these patients is unclear
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 Gardasil 9™ 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 10-25
- 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.
**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

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**

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td><strong>Age</strong></td>
</tr>
<tr>
<td>Females</td>
<td>11-12 (may start at 9)</td>
</tr>
<tr>
<td></td>
<td>Routine vaccination with either HPV2, HPV4 or HPV9</td>
</tr>
<tr>
<td></td>
<td>13-26</td>
</tr>
<tr>
<td></td>
<td>Routine vaccination with either HPV2, HPV4 or HPV9</td>
</tr>
<tr>
<td>Males</td>
<td>11-12 (may start at 9)</td>
</tr>
<tr>
<td></td>
<td>Routine vaccination : HPV4 or HPV9</td>
</tr>
<tr>
<td></td>
<td>13-21</td>
</tr>
<tr>
<td></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>22-26</td>
</tr>
<tr>
<td></td>
<td>Routine vaccination: HPV 4 or HPV9</td>
</tr>
</tbody>
</table>

* Irrespective of history of abnormal Pap, HPV, genital warts

MMWR. May 28 2010; 59(20):626-629 ; 630-632  
MMWR. December 23 2011; 60(50):1705-1708
ACIP Draft Language: Interchangeability

- 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

ACIP Meeting February 2015

Want to know more about STDs? There’s an app for that.

CDC Treatment Guidelines App for Apple and Android

Available now, FREE! (accept no competitors)
Thank You!

Ina Park
California STD/HIV Prevention Training Center
Stephanie Cohen

2010 CDC STD Treatment Guidelines:

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