STD Update for Clinicians 2019

Alison O. Marshall, RN, MSN, FNP-C
Boston College Connell School of Nursing
Chestnut Hill, MA

Sylvie Ratelle STD/HIV Prevention Center of New England
Disclosures

• In the past 12 months, Ms. Marshall has **NOT** had significant financial interests or other relationships with manufacturer(s) of product(s) or provider(s) of service(s) that will be discussed in this presentation.

• This presentation will include discussion of pharmaceuticals or devices that have not been approved by the FDA.
  • “Off-label” use of extra-genital (rectal and pharyngeal) nucleic acid amplification tests (NAATs) for gonorrhea and chlamydia
Goals

• Distinguish relevant updates to epidemiology, diagnosis, and treatment for bacterial, viral, and other STDs

• Highlight areas where changing STD epidemiology should effect clinical decision making and treatment choices.
CDC STD Treatment Guidelines Development

- Evidence-based on principal outcomes of STD therapy
  1. Microbiologic eradication
  2. Alleviation of signs & sx
  3. Prevention of sequelae
  4. Prevention of transmission
- Recommended regimens preferred over alternative regimens
- Alphabetized unless there is a priority of choice
- Reviewed April 2013; published 2015
- [www.cdc.gov/std/treatment](http://www.cdc.gov/std/treatment)
  - Pocket guides, teaching slides, charts, app

Language in yellow highlighted boxes reflects changes between 2010 and 2015 guidelines, and/or changes made since 2015.
MULTI-DRUG RESISTANT GONORRHEA
Microorganisms with the threat level of URGENT:

1. **C. difficile**
2. Carbapenem-resistant Enterobacteriaceae
3. Drug-resistant *N. gonorrhoeae*

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**Neisseria gonorrhoeae** — the drug-resistant form of this bacteria causes gonorrhea, the second most commonly reported infection in the United States. Gonorrhea can cause a variety of illnesses in men and women, including infertility. The CDC estimates there are 820,000 infections each year. In nearly a third of the cases, treatment of the sexually transmitted disease, is hampered by growing antibiotic resistance.

Sexually transmitted superbug could be major crisis

Frieden said if the current trends continue, "the medicine cabinet may be empty for patients who need them in the coming months and years."

To avoid what Frieden calls a "post-antibiotic" era, where none of the available antibiotics will be effective, the CDC hopes to slow the tide of drug-resistant infections by increasing the number of antibiotics available to patients. By developing and testing new antibiotics, the CDC hopes to empower patients when they need antibiotics, and keep them in their medicine cabinets.
Historical Perspective, Gonococcal Antimicrobial Resistance in United States

- 1936: Sulfanilamides introduced
- 1945: Penicillin therapy of choice
- 1976: Penicillinase producing Neisseria gonorrhoeae identified in U.S.
- 1985: Tetracycline resistance widespread; ceftriaxone one of several recommended regimens
- 1989: Penicillin no longer recommended; ceftriaxone primary regimen
- 1993: Ciprofloxacin or ceftriaxone recommended as a primary regimen
- 1998: Marked increase in QRNG in Hawaii
- 2002: Fluoroquinolones not recommended in California
- 2007: Fluoroquinolones not recommended

(till the 1970s...)


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### Table 13. Gonorrhea — Reported Cases and Rates of Reported Cases by State, Ranked by Rates, United States, 2016

<table>
<thead>
<tr>
<th>Rank*</th>
<th>State</th>
<th>Cases</th>
<th>Rate per 100,000 Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mississippi</td>
<td>7,157</td>
<td>239.2</td>
</tr>
<tr>
<td>2</td>
<td>Louisiana</td>
<td>10,782</td>
<td>230.8</td>
</tr>
<tr>
<td>3</td>
<td>Georgia</td>
<td>20,553</td>
<td>201.2</td>
</tr>
<tr>
<td>4</td>
<td>Alaska</td>
<td>1,454</td>
<td>196.9</td>
</tr>
<tr>
<td>5</td>
<td>North Carolina</td>
<td>19,687</td>
<td>196.0</td>
</tr>
<tr>
<td>6</td>
<td>Oklahoma</td>
<td>7,574</td>
<td>193.6</td>
</tr>
<tr>
<td>7</td>
<td>Arkansas</td>
<td>5,732</td>
<td>192.5</td>
</tr>
<tr>
<td>8</td>
<td>Missouri</td>
<td>11,479</td>
<td>188.7</td>
</tr>
</tbody>
</table>
Gonorrhea Treatment
Uncomplicated Genital, Rectal, or Pharyngeal Infections

Ceftriaxone 250 mg IM in a single dose

PLUS*

Azithromycin 1 g orally

* Regardless of CT test result

2015- Doxycycline demoted from recommended to alternative, because of tetracycline resistance in U.S. GISP isolates

2017- Doxycycline removed from regimen all together

CDC 2015 STD Treatment Guidelines
www.cdc.gov/std/treatment
Gonorrhea – Treatment Issues

• Dual therapy may hinder development of antimicrobial resistance

• Limited options in cephalosporin-allergic patients:
  • Spectinomycin is no longer manufactured
  • Consider azithromycin monotherapy, but
    • Requires 2 grams -- GI tolerance issues
    • Resistance likely increasing and treatment failures have been seen
Gonorrhea Treatment Alternatives Just for Anogenital Infections

**IF CEFTRIAXONE UNAVAILABLE**
- Cefixime 400 mg orally once
- **PLUS**
- Dual treatment with azithromycin 1 g

**IN CASE OF ALLERGY TO AZITHROMYCIN:**
- Cefixime 400 mg orally once
- **PLUS**
- Dual treatment with doxycycline 100 mg BID x 7 days

**Azithromycin 2 g orally removed as an alternative regimen**

Prior TOC recommendation: Test of cure in 1 week for anyone treated w/ alternative regimens

**New TOC recommendations:** Limit TOC only to pharyngeal GC not treated with recommended regimen, perform TOC at 14 days with either NAAT* or culture

*Not FDA-approved for extragenital testing, but has been validated.*
THE EPIDEMIC OF SYPHILIS (& HIV CO-INFECTION) IN MSM CONTINUES, EMERGING ISSUES WITH CONGENITAL SYPHILIS
HIV and Syphilis Diagnoses Have Increased in Young MSM

- Primary and secondary syphilis rates increased in 70% of areas
- Average increases in young black men
  - HIV: 68%
  - Syphilis: 203%

Torrone et al, JAIDS, 2011.
2017 Statistics

The STATE of STDs in the United States

1.59 million
CASES OF CHLAMYDIA
4.7% increase since 2015

468,514
CASES OF GONORRHEA
5% increase since 2015

27,814
CASES OF SYPHILIS
8% increase since 2015

STDS TIGHTEN THEIR GRIP ON THE NATION'S HEALTH AS RATES INCREASE FOR A THIRD YEAR

Anyone who has sex is at risk, but some groups are more affected

- YOUNG PEOPLE AGED 15-24
- GAY & BISEXUAL MEN
- PREGNANT WOMEN

LEFT UNTREATED, STDs CAN CAUSE:

- INCREASED RISK OF GIVING OR GETTING HIV
- LONG-TERM PELVIC/ABDOMINAL PAIN
- INABILITY TO GET PREGNANT OR PREGNANCY COMPLICATIONS

HELP INTERRUPT THE STEADY CLIMB IN STDs WITH THESE THREE STEPS:

TALK
Talk openly about STDs with your partners & healthcare providers.

TEST
Get tested. It's the only way to know if you have an STD.

TREAT
If you have an STD, work with your provider to get the right medicine.
Syphilis/HIV Co-infection Common

Proportion of MSM Attending STD Clinics with Primary and Secondary Syphilis Co-infected with HIV, STD Surveillance Network (SSuN), 2013

CDC, Sexually Transmitted Diseases Surveillance, 2013
Figure 40. Primary and Secondary Syphilis — Rates of Reported Cases by Sex and Male-to-Female Rate Ratios, United States, 1990–2017
Figure 42. Primary and Secondary Syphilis — Rates of Reported Cases by Age Group and Sex, United States, 2017

[Bar chart showing rates per 100,000 population for men and women across different age groups.]
Gay and bisexual men face the highest burden of syphilis in the United States. Learn how syphilis is affecting other communities.
Figure 47. Primary and Secondary Syphilis — Reported Cases by Reporting Source and Sex, United States, 2008–2017
Troubling rise in syphilis among newborns

- 2013: 362
- 2014: 462
- 2015: 492
- 2016: 639
- 2017: 918
Figure 1

Congenital Syphilis Cases by Year of Diagnosis

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>National Cases</td>
</tr>
<tr>
<td>2008</td>
<td>446</td>
</tr>
<tr>
<td>2009</td>
<td>431</td>
</tr>
<tr>
<td>2010</td>
<td>387</td>
</tr>
<tr>
<td>2011</td>
<td>358</td>
</tr>
<tr>
<td>2012</td>
<td>334</td>
</tr>
<tr>
<td>2013</td>
<td>361</td>
</tr>
<tr>
<td>2014</td>
<td>461</td>
</tr>
<tr>
<td>2015</td>
<td>492</td>
</tr>
<tr>
<td>2016</td>
<td>628</td>
</tr>
<tr>
<td>2017</td>
<td>918</td>
</tr>
</tbody>
</table>
Congenital Syphilis

• **Manifestations:**
  – Directly related to gestational age, stage of maternal syphilis, time until diagnosis and treatment.
  – Liver damage, hematologic abnormalities, hydrops, hepatomegaly, placentomegaly, polyhydramnios, preterm birth, miscarriage, stillbirth, neonatal/infant death, jaundice, skeletal abnormalities, deafness, meningitis, developmental delays, seizures, and many more...

• 1 million pregnant women worldwide infected annually (WHO; Porter et al., 2018).

• Penicillin treatment is 98% effective in preventing transmission from mother to fetus, and can treat both maternal and fetal disease

• Recent studies have shown that up to 50% of pregnant women with syphilis do not have any common risk factors ➔ Therefore... **UNIVERSAL SCREENING** is necessary
  – **ACOG guidelines:** Screen everyone at their first prenatal visit, and again between 28-32 weeks and at delivery if the individual is at risk
Syphilis Testing

Serologic testing:

- **Non-treponemal tests** - VRDL (Venereal Disease Research Laboratory) and RPR (Rapid Plasma Reagin)
  - Read as ratios, i.e. 1:4 or 1:32 which decrease with treatment
  - Non-treponemal tests will eventually become non-reactive in most treated patients

- **Treponemal tests** - FTA-ABS (fluorescent treponemal antibody absorbed) and TP-PA (T. pallidum particle agglutination)
  - Treponemal tests are more accurate, but more expensive.
  - These tests stay reactive for life, even after treatment

- **2010 Change** - treponemal with reflex to non-treponemal is now recommended standard of care. Use of just 1 serologic test is insufficient evidence for diagnosis.
Don’t forget the q3mth “triple dip” for at-risk MSM

- HIV/Syphilis/
  HepC* Serologies
- Pharyngeal GC NAAT**
- Urine GC/CT NAAT
- Rectal GC/CT NAAT**

*In HIV-coinfected individuals, screen Hep C at least annually

**Off-label use - not FDA-approved for testing at extragenital sites, but many reference labs have validated the assay for use
Syphilis Treatment

• Penicillin, penicillin, penicillin
  – Allergic patients: tetracycline, doxycycline used for years, no good evidence to support
  • Recommendation for non-adherent patients or those thought at risk for loss to follow-up be admitted and desensitized to PCN
MYCOPLASMA GENITALIUM HAS EMERGED
Mycoplasma genitalium: Epidemiology

• First identified in the early 1980’s
• Cause of male urethritis
  – 15-20% of non-gonococcal urethritis (NGU) cases
  – 20-25% of non-chlamydial NGU
  – 30% of persistent or recurrent urethritis
  – More common than *N. gonorrhoeae* but less common than *C. trachomatis*
  – Co-infection with *C. trachomatis* is not uncommon
• Unknown whether it can cause male infertility or other male anogenital tract disease syndromes
• Pathogenic role in women less clear
  – Found more commonly in those with cervicitis or PID than those without cervicitis or PID
Mycoplasma genitalium: Diagnostics

• Very slow-growing organism
  – Culture can take up to 6 months
  – Only a few laboratories in the world are able to recover clinical isolates

• Nucleic acid amplification testing (NAAT) is the preferred method to detect *M. genitalium*
  – Research settings
  – In-house PCR assays (?)
  – None commercially available (YET)
Mycoplasma genitalium: Treatment

• Organism has no cell walls, so ‘cillins are not effective

• Some support to try
  – Doxycycline (30% clearance rate)
  – Azithromycin (emerging resistance)
  – Moxifloxacin- (100% clearance rate in US studies, however treatment failures internationally)
Mycoplasma

• Bottom line -
  – No clear diagnostic or treatment algorithms at this time
  – Difficulty getting samples tested properly, must work with insurance companies
  – Consult with STD/HIV Prevention Center, CDC or other qualified clinician if you are presented with a clinical case.
Newer Testing Options for Trich

• Microscopy is inferior to new options, including
  – Rapid antigen testing (OSOM)
  – Nucleic acid amplification testing
    • APTIMA TMA *Trichomonas vaginalis* assay
    • BD ProbeTec TV Q Amplified DNA assay
    • May use same specimen types as used with gc/chl NAATs (i.e. vaginal swab, endocervical swab, urine)

Huppert CID 2007

<table>
<thead>
<tr>
<th>Test</th>
<th>Sens</th>
<th>Spec</th>
</tr>
</thead>
<tbody>
<tr>
<td>APTIMA TMA</td>
<td>98%</td>
<td>98%</td>
</tr>
<tr>
<td>OSOM</td>
<td>90%</td>
<td>100%</td>
</tr>
<tr>
<td>Culture</td>
<td>83%</td>
<td>100%</td>
</tr>
<tr>
<td>Wet prep</td>
<td>56%</td>
<td>100%</td>
</tr>
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</table>

Table 3. Differences in test sensitivity stratified by the presence or absence of vaginal symptoms.

<table>
<thead>
<tr>
<th>Test method</th>
<th>Sensitivity, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients (n = 330)</td>
</tr>
<tr>
<td>Wet mount</td>
<td>50.8 (37.7–63.9)</td>
</tr>
<tr>
<td>Culture</td>
<td>75.4 (62.7–85.5)</td>
</tr>
<tr>
<td>Rapid test</td>
<td>82.0 (70.0–90.6)</td>
</tr>
<tr>
<td>TMA</td>
<td>98.4 (91.2–99.9)</td>
</tr>
</tbody>
</table>

NOTE. The comparator was any test result positive for *Trichomonas vaginalis* infection. TMA, transcription-mediated amplification.
Trich Testing in Men

- No approved point of care tests
  - Wet prep not sensitive

- Culture available: urethral swab, semen or urine sediment
  - No conclusive studies on sensitivity/specificity

- Urine and urethral swab NAAT offered through certain labs using analyte-specific reagents (check before sending)

**MSM - T. vaginalis does not infect oral sites, and rectal prevalence is low. Do not test these sites.**
GENITAL HSV EPIDEMIOLOGY IS CHANGING
NHANES HSV2 Seroprevalence

Johnson et al. *NEJM* 321:7-12, 321, 1989
Schillinger et al. *STD* 31:753-60, 2004
Xu et al. *JAMA* 296:964-73, 2006
Xu et al. *MMWR* 59:456-9, 2010
Bradley et al. *JID* 209:325-33, 2014
Almost 1 in 10 adolescents who 10 years ago already would have acquired HSV1 earlier in life now are vulnerable to getting a primary infection as they enter their sexually active years.”
Kimberlin, JID 2013
What About Genital HSV-1?

**HSV1 now causes MOST of first genital HSV episodes in young adults**

Among >3400 HSV double-seronegative women 18-30 yrs from control arm of herpes vaccine trial who acquired disease during a 20 month period:

5.3% became infected

HSV1 2.3x *more common* than HSV2 infection

Genital HSV1 2.5x *more common* than oral HSV1

Increasing proportion of anogenital herpetic infections have been attributed to HSV-1 infection in women and MSM

Primary genital HSV1 and HSV2 remain *indistinguishable* clinically, and are treated with the same antiviral regimens

Genital HSV1 does not recur as often as genital HSV2

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 Bernstein DI et al., *CID* 2013
 Whitley RJ, *CID* 2013
 Ryder N et al., *STI* 2009
 Roberts CM et al., *STD* 2003
They are in the majority, *not* the minority ...
TREATING SEX PARTNERS SIGHT UNSEEN (EPT) IS LEGAL (MOSTLY)
PDPT can prevent reinfection of index case and has been associated with a higher likelihood of partner notification...

CDC EPT guidelines

“PDPT can prevent reinfection of index case and has been associated with a higher likelihood of partner notification...”

[www.cdc.gov/STD/EPT](http://www.cdc.gov/STD/EPT)
Infection During Follow-up Among Patients Completing The EPT Trial

- **Gonorrhea**: Standard care = 10.6%, Expedited care = 3.4%, P=.02
- **Chlamydia**: Standard care = 13.2%, Expedited care = 10.8%, P=.17
- **Gonorrhea or Chlamydia**: Standard care = 13%, Expedited care = 9.9%, P=.04

N=358, N=1595, N=1860

Golden MR, *NEJM 2005*
Chlamydia, Gonorrhea, and EPT

• EPT is supported by the CDC and permissible in at least 35 states

• Standard partner treatment for chlamydia infection is one oral dose of 1g of the antibiotic azithromycin

• Standard partner treatment for gonorrhea is one oral dose of 1g of the antibiotic azithromycin PLUS one oral dose of 400 mg of cefixime

• EPT has been shown to be safe and effective in the treatment of sex partners

• Most states with long-standing EPT programs also have had no reports of adverse events
S.T.D. Care for Two

By JAN HOFFMAN  FEBRUARY 2, 2015 4:52 PM  18 Comments

A “partner pack” is a method of delivering medication for STDs to partners of diagnosed patients. David Ryder for The New York Times

Recently, while William, 21, was manning the chicken-wing fryer at a fast-food restaurant in suburban Seattle, he pulled aside his sort-of girlfriend, 18, a pizza deliverer there. He had bad news.

He had tested positive for gonorrhea and chlamydia. That meant she was very likely infected.

Loud, insult-fueled cross-accusations ensued. But the conversation did not disintegrate, as might otherwise be expected.

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Harmony with USPSTF screening guidelines on gonorrhea/chlamydia in adolescents
New hepatitis C screening recommendations for HIV+ MSM
New information on clinical management of transgender men and women
Want to know more about STDs?

There’s an app for that.

CDC STD Treatment Guidelines App for Apple and Android

Available now, **FREE!**
(accept no competitors)

Search “STD Treatment” in App store
NEW!!!!

- Provides STD clinical consultation services within 1-5 business days, depending on urgency, to healthcare providers nationally
- Your consultation request is linked to your regional PTC’s STD faculty
- Just a click away!

www.STDCCCN.org