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Winter 2018-19

Disclosures

• In the past 12 months, Dr. Hsu has had the following 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:
  – None

• 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 STI epidemiology, management, and prevention
• Highlight areas of 2015 CDC STD Treatment Guidelines that should be read carefully for detailed recommendations
• Provide new clinical resources (smartphone applications, STD Clinical Consultation Network) to access expert guidance on STD management at the point of care

4. STIs have returned to 1990s levels
Syphilis and Gonorrhea Over Time

- Infectious Syphilis and Gonorrhea Cases
- Massachusetts 1990-2017

Decreases in syphilis cases were due to BOTH behavior change AND to deaths occurring in HIV-syphilis co-infected individuals

*Infectious syphilis is defined as primary, secondary and early latent stages of syphilis within one year of infection.


Interpret 2014 STI data with caution due to a mid-year conversion to a new surveillance system.
Gonorrhea by Gender Identity,*
Massachusetts, 2000-2017

N=56,312
Data are current as of 10/31/2018 and are subject to change.
Data Source: Massachusetts Department of Public Health/Bureau of Infectious Disease and Laboratory Sciences/ Division STD Prevention
*There were several cases reported as transgendered in 2014 through 2016. Transgender identity was not documented prior to the MA VEN transition in 2014 and transgendered individual are included in the specified gender categories.

Chlamydia Infection Incidence Rate by Gender Identity,*
Massachusetts, 2000-2017

2017 N = 29202
Data are current as of 10/31/2018 and are subject to change.
Data Source: Massachusetts Department of Public Health/Bureau of Infectious Disease and Laboratory Sciences/ Division STD Prevention
*There were several cases reported as transgendered in 2014 through 2016. Transgender identity was not documented prior to the MA VEN transition in 2014 and transgendered individual are included in the specified gender categories.
Chlamydia Incidence Rate per 100,000 Among Individuals 50 and Older, Massachusetts, 2000-2017

2017 N = 613
Data are current as of 10/31/2018 and are subject to change.
Data Source: Massachusetts Department of Public Health/Bureau of Infectious Disease and Laboratory Sciences/ Division STD Prevention
*There were several cases reported as transgendered in 2014 through 2016. Transgender identity was not documented prior to the MAVEN transition in 2014 and transgendered individual are included in the specified gender categories.

STI COMPLICATIONS ARE THEREFORE MORE COMMON
Epi Take Home Points

• STI rates are at record highs
  – Reflective of national and regional trends
  – Male signal dominating reporting trends for syphilis and gonorrhea
  – Increases not limited to those ≤25 years of age
  – We are seeing more STI complications

• Are these increases reflective of increased
  – Screening
  – Reporting
  – True increases in underlying incidence in specific sexual networks
  – All of the above?

3. FOCUS SCREENING ON HIGH-RISK POPULATIONS FOR HIGHEST YIELD
Population-level Control of STIs

Basic Reproductive Rate

\[ R_0 = T \cdot C \cdot D \]

Screening decreases D (duration) of carriage and therefore transmission

Anderson & May, 1980s

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3A. MSM STI SCREENING IS IMPORTANT FOR MAINTAINING MALE SEXUAL HEALTH
Proportion of CT and GC infections MISSED among 3398 asymptomatic MSM if screening only urine/urethral sites, San Francisco, 2008-2009

Marcus et al, STD Oct 2011; 38: 922-4

The q3mth “Triple Dip” for at-risk MSM

*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

Slide courtesy of Brad Stoner
Screen more or screen more often?

- Agent-based model of syphilis transmission representing 2,000 high-risk MSM from Toronto, Canada data

Figure 2. Model-projected annual rates of reported infectious syphilis. Results are based on 1000 realizations of each intervention scenario and are presented as mean values with corresponding 95% uncertainty bounds. Prior to 2011, all scenarios included annual screening only, with the specified interventions implemented at the start of 2011 (indicated by a dashed line).

Tuite et al. BMC Pub Health, 2013

Evolution of Syphilis Test

Traditional syphilis tests - Manual
- Nontreponemal
- Treponemal

Automated Test platforms
- Treponemal

Rapid syphilis test
- Nontreponemal
- Treponemal

... but concerns about sensitivity & specificity abound

Fakile Y, STD Prevention Conference, 2016
https://cdc.confex.com/cdc/std2016/webprogram/Paper38173.html
Self-collected STI Testing

- Acceptable to many patient populations
- FDA-approved for certain GC/CT/trich NAAT testing platforms and sample types
- Equivalent or greater sensitivity than clinician-collected samples
- Improved uptake of STI screening

Gaydos. Sex Trans Dis, 2018

Dean St Express Clinic, Soho, London

- Walk-ins
  - Treatment for positive gonorrhoea and chlamydia tests
  - If you’ve had sex with a person who tells you they had gonorrhoea or chlamydia
  - HIV PrEP three monthly monitoring
  - Follow up for people who started emergency HIV PEP at 56 Dean Street
  - Vaccines
- Appointments
  - Sexual health screening for people without symptoms (STI/STD and HIV tests) with results in 6 hours
3B. RE-SCREENING FOR STIs IN THOSE PREVIOUSLY INFECTED, REACHES THOSE AT HIGHEST STI RISK

Clinical Infectious Diseases 2018;67:99-104

Characteristics of Cases With Repeated Sexually Transmitted Infections, Massachusetts, 2014–2016

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Background. Persons with prior sexually transmitted infections (STIs) are at high risk for reinfection. No recent studies have examined frequency with which persons are diagnosed and reported with multiple bacterial STIs over time.

Methods. We conducted a retrospective, of confirmed syphilis, gonorrhea, and chlamydial infections reported to Massachusetts state surveillance system within a 2-year period, 28 July 2014–27 July 2016.

Results. Among Massachusetts population aged 13–65 years (4847510), 49,142 (1.0%) were reported with ≥1 STIs; 6999 (14.2%) of those with ≥1 STI had ≥2 STIs, accounting for 27.7% of STIs. Of cases with ≥5 or more STIs (high-volume repeaters), 118 (74%) were men and 42 (26%) were women. Men spanned the age spectrum and were predominantly non-Hispanic white; 87% reported same-sex contacts. Women were younger, predominantly nonwhite, and without known same-sex contacts. Women were reinfected with gonorrhea and chlamydia or chlamydia alone; none had syphilis or human immunodeficiency virus (HIV) infection. All men with syphilis also had gonorrhea and/or chlamydia; 35% were diagnosed with HIV before, during, or within 10 months after study period. The majority (56%) of high-volume repeaters were seen at more than 1 care site/system.

Conclusions. In Massachusetts, a large proportion of bacterial STIs are reported from a small subpopulation, many of whom have repeated infections and are likely to have higher impact on STI and HIV rates. Public health can play a crucial role in reaching high-volume repeaters whose STI histories may be hidden from clinicians due to fragmented care.

Keywords. repeated sexually transmitted infections; population-based surveillance.
Results: Cases of Confirmed Chlamydia, Gonorrhea, and Infectious Syphilis, Massachusetts 2014-2016

![Graph showing cases of Chlamydia, Gonorrhea, and Infectious Syphilis]

Of 13-65 year olds in Massachusetts (N = 4,847,510):
- 1% (49,142) were reported with bacterial STI
- 0.1% (6,999) accounted for 28% of all reported bacterial STIs
- 56% of high-volume repeaters sought care in >1 clinical system

Conclusions

- Repeaters are a small portion of the overall population, but contribute a large volume of STIs
  - Disproportionately high impact on circulation of STIs and HIV infection in the population
  - Representative of chronic poor sexual health?
- Infections in high volume repeaters may be hidden from clinicians and clinical systems due to fragmented care
- Public health can play a crucial role in identifying and reaching these individuals
  - State & local jurisdictions have sufficient identifying information to act
Next Steps

• New Model for Field Follow-up
  – Need a greater understanding of the underlying sexual network
    • In order to intervene in the spread of STIs and HIV
  – Provide Pre-Exposure Prophylaxis (PrEP) referrals and other services to repeatedly infected HIV-negative cases
  – Help reduce risk to reproductive-aged females
    • Infertility prevention
    • Contact tracing, treatment, and prevention during pregnancy results in double benefit (mother and infant)

Repeat Screening After STI

• 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.

2015 CDC STD Treatment Guidelines
One Massachusetts ACO:
Percent of *Chlamydia trachomatis* cases retested within recommended time period

“Among cases with repeat tests, 17.3% of pregnant females, 16.2% of non-pregnant females, and 18.1% of males had positive results.”

Dee et al., manuscript in progress.

We are underutilizing repeat testing as a tool for identifying higher risk patients

Many thanks to Laura Bachmann and IDWeek 2016!

2. **TREAT STI SYNDROMES QUICKLY**
Population-level Control of STIs

Basic Reproductive Rate

\[ R_0 = T \cdot C \cdot D \]

Screening and **RAPID APPROPRIATE** treatment decrease D (duration) of carriage and therefore transmission

Principles of STI Treatment

- Symptomatic
  - Test AND treat **immediately**, based on STI syndrome

- Reports contact
  - Test AND treat **immediately**, according to reported exposure

- Asymptomatic, no specific contact
  - Screen and treat according to results
Delays in Gonorrhea Treatment Massachusetts 2015-2017

• 599/2523 randomized cases agreed to interview
  – Symptomatic/contact cases
    • Median time to treatment = 0 days
    • BUT 42% not treated on day 0
  – Asymptomatic
    • Median time to treatment = 4 days
    • BUT 51% treated $\geq$ 5 days after sample collection
  – Delays more common in symptomatic women, asymptomatic MSM

Symptomatic/contact cases had shorter time to treatment compared to asymptomatic cases, who may contribute more to population transmission of gonorrhea.

BUT, in both groups, treatment delays are common.

MA unpublished data, 2018

2A. NEW CONSIDERATIONS FOR PERSISTENT URETHRITIS
Case

20yo M treated with doxycycline for NGU 2 weeks prior ...

• His initial chlamydia and GC tests were negative. His urethral symptoms never fully resolved and he now returns for evaluation. NGU is demonstrated again.
• He reports compliance with treatment and sexual abstinence.
• He reports only female partners.

What’s next on your differential for persistent urethritis?

1. *T. vaginalis*
2. *M. genitalium*
3. *U. urealyticum*
4. HSV
5. *N. meningitidis*
Recurrent and Persistent Urethritis

• Check first for objective signs of urethritis
  – Mucoid, mucopurulent, or purulent discharge on exam
  – Gram, methylene blue, or gentian violet stain of urethral secretions: ≥2 WBC per oil immersion field
  – Positive leukocyte esterase test on first void urine
  – Urine micro of first void urine sediment: ≥10 WBC per high-power field

• If urethritis confirmed, re-treat with initial regimen if initially non-compliant or if re-exposed to untreated partner
  – Not this patient’s case, but this is the usual next step

DDx for Recurrent or Persistent Urethritis

• Consider azithromycin or doxycycline-resistant *U. urealyticum* or *M. genitalium*
  – May benefit from treatment with moxifloxacin 400 mg orally once daily for 7 days

• Consider *T. vaginalis*
  – More common in heterosexual men
    • Test using first-void urine or urethral swab, send for culture (not always available) or NAAT (now commercially available)
    • May benefit from treatment with metronidazole or tinidazole
  – Low probability in MSM

• Consider HSV if recurrent
What is *Mycoplasma genitalium*?

- **Mollicute**
  - Lacks a cell wall
- **Smallest known genome**\(^1,2\)
  - 580 kb translating to <500 genes
- **First identified in 1981 from 2 of 13 men with NGU\(^3\)**
- **Extremely fastidious**
  - Culture only achieved by ~3-4 laboratories worldwide
  - Takes ~6 months\(^4\)

Slide courtesy of LE Manhart

\(^1\)Glass et al, PNAS 2006; \(^2\)Gibson et al. Science 2008; \(^3\)Tully et al, Lancet 1981; \(^4\)Jansen et al, J Clin Micro 1986

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**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 also less clear
**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)

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**Treatment of MG:**

**RCTs Comparing Doxycycline vs. Azithromycin**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Drugs &amp; Dosages</th>
<th>Micro Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mena</td>
<td>2009</td>
<td>36</td>
<td>DOXY 100mg PO bid X 7d AZM 1g PO X1</td>
<td>45%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>42</td>
<td></td>
<td>87%</td>
</tr>
<tr>
<td>Schwebke</td>
<td>2011</td>
<td>39</td>
<td>DOXY 100mg PO bid X 7d AZM 1g PO X 1 +/− Tinidazole</td>
<td>31%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45</td>
<td></td>
<td>67%</td>
</tr>
<tr>
<td>Manhart</td>
<td>2013</td>
<td>35</td>
<td>DOXY 100mg PO bid X 7d AZM 1g PO X 1</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35</td>
<td></td>
<td>40%</td>
</tr>
</tbody>
</table>

- Doxycycline largely ineffective against *M. genitalium*: median cure rate of ~31%
- Resistance to azithromycin appears to be emerging: median cure rate for men and women ~85%, but only 40% in most recent trial
- Longer courses of AZM (e.g. 500 mg PO X 1 followed by 250 mg QD X 4d) yield higher cure rates and may lead to decreased emergence of resistance

Take Home Points

- Use strict objective criteria to define recurrent or persistent urethritis
- Likely pathogens depend on sexual behaviors and risk history
- Management is difficult if neither gonorrhea nor chlamydia are diagnosed on subsequent testing
  - Rule out reinfection
  - Test for *T. vaginalis* using NAAT
  - Strongly consider *M. genitalium* in DDx (may be difficult to test for and treat)
  - Consider referral to urologist
2B. Recurrent bacterial vaginosis is common, can be treated with prolonged therapy, but optimal management is in evolution

Case

• JG is a 21 yo F who presents with 3d history of abnormal vaginal discharge and odor

• PMH – BV diagnosed 6 times in the last year (at least 3 of 4 Amsel Criteria fulfilled at each diagnosis)
**Recurrent BV**

- Recurrent disease remains common
  - Rates up to 70% within 3 months
- Reasons for recurrence unclear
  - Re-infection
  - Failure of lactobacilli to re-colonize
  - Inadequate length of therapy
  - Persistence of unidentified host factor
  - ?Resistance
- Despite comparable early cure rates, higher recurrence rates associated with shorter treatment
  - Single-dose 2 g metronidazole no longer recommended
  - 3-day clindamycin course no longer first-line

What strategy should this patient employ to prevent future BV recurrence?

1. Initiate suppression with twice weekly intravaginal metronidazole gel following treatment of current episode
2. Get a new partner
3. Use condoms 100% of time for vaginal sex
4. Pull out the boric acid!
5. All of the above
Present Day Recurrent BV Management

- Suppression with metronidazole gel twice weekly for 4-6 months
- Oral metronidazole, then intravaginal boric acid, then suppressive metronidazole gel twice weekly for 4-6 months
- Oral metronidazole administered monthly with fluconazole

Adherent Biofilms in Bacterial Vaginosis

G. vaginalis

Fig. 4. A continuous biofilm can be detected histologically on the vaginal epithelial surface in patients with bacterial vaginosis (Brown–Hopps modifications of the Cajal stain). Original magnifications: left panel, ×400×64; right panel, ×200×64. Note the disaggregation of surface epithelial cells containing the biofilm that can be detected as “clear cells” in the vaginal smear specimens.

Swidsinski, Obstet. Gynecol 2005

Slide courtesy of Marrazzo, IDSA 2011
What is new with BV?

- Biofilm disrupters – boric acid, octenidine, retrocyclin, quorum sensing inhibitors?
- New data presented in Durban, South Africa at the 21st International AIDS Conference
  - Follow-up studies of women in CAPRISA (PrEP study of vaginal gel)
  - Association of specific pathogens with increased inflammation/susceptibility
    - *P. bivia*
    - *G. vaginalis*
    - Lack of *Lactobacilli*

Partner Management

- Treatment of male sex partners has not been found to reduce BV recurrence
- ?Evaluate and treat female partners
- Patients should also be advised to refrain from douching and either abstain from sex or use a condom during and for a month after treatment
Take Home Points

• BV is a common clinical entity
• Understanding of BV continues to evolve
  – Biofilms may be important
• Use of appropriate diagnostic tests are critical for management
• Several strategies exist to treat recurrent BV, but more work is needed

4. STIs have returned to 1990s levels (complications are more common)

  Therefore, to reduce transmission ...

3. Focus screening on high-risk populations for highest yield
   3A. MSM STI screening is important for maintaining male sexual health
   3B. Re-screening for STIs in those previously infected, reaches those at highest STI risk

2. Treat STI syndromes quickly
   2A. New considerations for persistent urethritis
   2B. Recurrent BV is common, can be treated with prolonged therapy, but optimal management is in evolution

Drum roll please ...
1. CDC STD Treatment Guidelines:
A Rose by Any Other Name ...

- 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
**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

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**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
STD Clinical Consultation Network
STDCCN – 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 expert faculty
• Just a click away!
• www.STDCCN.org

National STD Curriculum
www.std.uw.edu

The National STD Curriculum integrates the most recent CDC STD Treatment Guidelines into a free, up-to-date, educational website. The site addresses the epidemiology, pathogenesis, clinical manifestations, diagnosis, management, and prevention of STDs.

• Seven Self-Study Modules
• Twelve Question Bank topics with 100+ interactive board-review style questions
• Modular learning in any order with progress tracker
• Group registration and tracking for staff, students, and health care organizations
• FREE CME and CNE credits

This curriculum was funded by a grant from the CDC and developed by the National Network of STD Clinical Prevention Training Centers