An Update for Generalists: The 2015 CDC STD Treatment Guidelines

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Off-Label Disclosure

This presentation will include discussion of the following non-FDA-approved or investigational uses of products/devices:

- Oral and rectal testing for *N. gonorrhoeae* and *C. trachomatis* with NAAT
- Testing for *T. vaginalis* by NAAT (in men)
- Testing for *M. genitalium* utilizing NAAT
Sexually Transmitted Diseases 
Treatment Guidelines, 2015

2015 CDC STD Treatment 
Guidelines

“Typical” Guidelines Subjects NOT 
Covered in This Talk

Adolescents

HPV

Tests You Do Not Do
Darkfield Microscopy
Gram Stain

2015 CDC STD Treatment 
Guidelines

Emerging Topics

STI Assessment and Management for the 
Generalist

Sex Partner Status – GLBTQ Awareness

Mycoplasma genitium

Hepatitis C as an STI
Lecture Overview

I. Sexual Health - A subtle but high impact paradigm shift

II. Changes to the CDC Treatment Guidelines/Hot Topics
   A. Gonococcal Antimicrobial Resistance
   B. Extragenital Testing
   C. Urethritis Diagnosis
   D. Trichomoniasis – NAATs/ Males
   E. Mycoplasma genitalium - an emerging pathogen

Sexual Health
Changing the Paradigm

Why are rates of curable STIs (Gonorrhea, Chlamydia, Syphilis) Higher in the U.S Than in Any Other Developed nation on Earth??

Stigma Intolerance
Evolving Foci for STI Management Efforts

<table>
<thead>
<tr>
<th>Major Focus</th>
<th>Pre-1960s</th>
<th>1960s &amp; 70s</th>
<th>1970s &amp; 80s</th>
<th>1990s</th>
<th>21st Century</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Syphilis</td>
<td>Gonorrhea, Syphilis</td>
<td>Chlamydia, Gonorrhea, Syphilis (Herpes)</td>
<td>Chlamydia, Gonorrhea, Syphilis, HPV (Herpes)</td>
<td>&gt;25 STIs including Chlamydia, Gonorrhea, Syphilis, HPV, Herpes, Trichomonas and Dysbiotic STI Syndromes</td>
</tr>
</tbody>
</table>

Widely Held Beliefs About STDs

“Nice” (normal?) people do not get STDs

If you are not “promiscuous” you will not get STDs, unless your partner betrays you

Testing for STDs is warranted primarily for persons with risks for STD

When STDs are present, its obvious

Discussion of the need for STD testing is offensive to patients

Sexual Health
Changing the Paradigm

Sexually Transmitted Infections, Not Diseases

STD STI
Consequences of STI-Related Stigma

Personal (Individual)
- Delays in using or seeking preventative health care
  - Condoms
  - Vaccines
  - Screening
- Delays in seeking care for perceived problems
- Ineffective partner notification

Provider
- Hesitancy in seeking relevant information
- Differential testing
- Changes to provider-client interactions

Population
- Guilt by association
- Differential Care
- Profiling

Sexual Health

Sexual health is a broad perspective that spans the entire lifespan encompassing topics which include:

<table>
<thead>
<tr>
<th>Sex Education</th>
<th>Family Planning</th>
</tr>
</thead>
<tbody>
<tr>
<td>STD/HIV Management</td>
<td>Reproductive Tract Care</td>
</tr>
<tr>
<td>Interpersonal Relationships</td>
<td>Erectile Dysfunction/ Diminished Desire</td>
</tr>
</tbody>
</table>

A sexual health framework shifts the approach from a more traditional loss frame approach to a gain frame

Framing – influenced by context; anticipated to have selective influence on perception, encouraging certain interpretation, discouragement, others (Wikipedia)

Gain frame – Emphasizes positives, benefits

Loss frame – Emphasizes risks, potential harm, potentially fueling shame and stigma
“If I ask you something, will you promise not to get mad?”

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**Loss Frame/Gain Frame Examples**

**Sexual History**

<table>
<thead>
<tr>
<th>Loss Frame</th>
<th>Gain Frame</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Partner Type</strong></td>
<td><strong>Partner Type</strong></td>
</tr>
<tr>
<td>Have you ever had homosexual</td>
<td>Are your partners men, women</td>
</tr>
<tr>
<td>sex?</td>
<td>or both?</td>
</tr>
<tr>
<td><strong>Sites of exposure</strong></td>
<td><strong>Sites of exposure</strong></td>
</tr>
<tr>
<td>Have you had oral or rectal</td>
<td>When you have sex, what sites</td>
</tr>
<tr>
<td>sex, or just regular sex?</td>
<td>are exposed—oral, rectal or</td>
</tr>
<tr>
<td></td>
<td>genital?</td>
</tr>
</tbody>
</table>

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**A Sexual Health “Litmus Test” for Clinicians**

Have you ever apologized to a patient for making a diagnosis of chlamydia, trichomoniasis or HIV?
Three Question Sexual History for Adults

Take the history, assess risks
- When was the last time you had sex?
- How many partners have you had in the past year?
- Were they men, women or both?

Don’t hesitate to screen. STI screening is not judgemental it is health promoting

Routinely provide STI prevention messages as part of continuing care
Emerging Gonococcal Antimicrobial Resistance – Deja Vu

<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-1937</td>
<td>Antiseptic Irrigation With Potassium Permanganate, Silver Salts, Mercurochrome</td>
</tr>
<tr>
<td>1937</td>
<td>Sulfonamide Therapy</td>
</tr>
<tr>
<td>1943</td>
<td>Penicillin Therapy (Mahoney et al)</td>
</tr>
<tr>
<td>1944</td>
<td>35% Treatment Failure With Sulfonamides</td>
</tr>
<tr>
<td>1972</td>
<td>Penicillin Regimen Increased to 4.8 Million Units Plus Probenecid</td>
</tr>
</tbody>
</table>
GONORRHEA THERAPY – HISTORICAL PERSPECTIVE

- Previously Recommended Medications For Gonorrhea Therapy
  
  - Sulfonamides
  - Penicillins
  - Macrolides
  - Tetracyclines
  - Aminoglycosides
  - Spectinomycin
  - Fluoroquinolones

Penicillin, Tetracycline, and Ciprofloxacin Resistance, 2013

JAMA 2013;309(2);163-170

Neisseria gonorrhoeae Treatment Failure and Susceptibility to Cefixime in Toronto, Canada

Cephalosporin-Resistant Gonorrhea in North America
Proportion of Isolates with MICs to Cefixime ≥ 0.25 µg/ml

- Percentage of isolates: 1.4% (n=77)
- * p trend < 0.05

Gonococcal Isolate Surveillance Project (GISP)

Percentage of Isolates with Elevated Ceftriaxone MICs (≥ 0.125 µg/ml) by Gender of Sex Partner, 2008–2013

N. Gonorrhoeae Treatment Failures to Cefixime, Toronto, Canada

Rx failure overall – 6.8% (95% CI – 3.1-12.5%)
If cefixime MIC ≥ 0.12 – 25% (95% CI 10.7-44.9%)
If cefixime MIC <0.12 – 1.9% (95% CI 0.23-6.7%)
RR 13.13 (95% CI 2.9-59.72)

Treatment failures:
- 4 of 76 urethral (5.3%)
- 2 of 7 pharyngeal (28.6%)
- 3 of 39 rectal (7.7%)

2015 CDC STD TREATMENT GUIDELINES
Uncomplicated Gonorrhea

Ceftriaxone 250 mg IM
PLUS
Azithromycin 1.0 g Single Dose or
Doxycycline 100 BID x 7d
Even if chlamydia negative

Alternative GC Treatment
2015 CDC STD Treatment Guidelines

Cefixime 400mg po x 1
Plus
Azithromycin 1gm po x 1
+ TOC in 1 week 14d

If cephalosporin allergy:
Azithromycin 2gm po x 1
+ TOC in 1 week 14d

Gonorrhea Treatment - What’s Next
Salvage Therapy:
Gentamicin 240 IM/ Azithromycin 2.0g PO
(IM Administration/Toxicity)
Gemifloxacin 340 mg/Azithromycin 2.0g PO
(GI Toxicity)

On The Horizon:
Solithromycin
Delafloxacin
AZ D0914
Others
Reasons for STD Treatment Failure

- Reinfection
- Wrong Therapy
  - Wrong diagnosis
  - Wrong dosage/duration
  - Self medication
- Resistant Organisms
- Other

Changing Paradigms For Urogenital Specimen Collection

Pre-NAAT’s:
- Specimen Quality Critical
  - Endocervical Or Urethral Swabs
  - Swab Order Impacts Test Results
- Culture > Non-Amplified Nucleic Acid Detection > Antigen Detection

NAAT’s:
- More Forgiving Specimen Collection
  - Vaginal Swab > Endocervical Swab > initial Void Urine
How common are extra-genital sexual behaviors?

**Males:**
- Active oral
  - Lifetime 77%
  - Last sex 27%
- Passive oral
  - Lifetime 79%
  - Last sex 26%

**Females:**
- Active oral
  - Lifetime 68%
  - Last sex 19%
- Passive oral
  - Lifetime 73%
  - Last sex 28%


Performance of NAATs for Diagnosis of Pharyngeal *N. Gonorrhoeae* and Infections

<table>
<thead>
<tr>
<th>Pharyngeal Gonococcal Infections (N=961)</th>
<th>% Sensitivity (95%)</th>
<th>% Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ProbeTec (SDA)</td>
<td>97.1 (85.1-99.9%)</td>
<td>94.2 (92.5-95.6%)</td>
</tr>
<tr>
<td>Amplicor (PCR)</td>
<td>91 (78.1-96.3%)</td>
<td>71.8 (68.7-74.6%)</td>
</tr>
<tr>
<td>Aptima Combo2 (TMA)</td>
<td>100 (89.7-100%)</td>
<td>96.2 (98.1-99.6%)</td>
</tr>
<tr>
<td>Culture</td>
<td>65.4 (50-78%)</td>
<td>99.0 (98.1-99.6%)</td>
</tr>
</tbody>
</table>


Performance of NAATs for Diagnosis of Pharyngeal *N. Gonorrhoeae* and Infections

<table>
<thead>
<tr>
<th>Pharyngeal Gonococcal Infection By Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>Genital and Oral</td>
</tr>
<tr>
<td>Genital Only</td>
</tr>
<tr>
<td>Oral Only</td>
</tr>
<tr>
<td>Total Genital or Oral</td>
</tr>
</tbody>
</table>

### Performance of NAATs for Diagnosis of Rectal N. Gonorrhoeae Infections

<table>
<thead>
<tr>
<th>Site</th>
<th>No (%) Individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital and Rectal</td>
<td>12 (31.6%)</td>
</tr>
<tr>
<td>Genital Only</td>
<td>11 (28.9%)</td>
</tr>
<tr>
<td>Rectal Only</td>
<td>15 (39.5%)</td>
</tr>
<tr>
<td>Genital or Rectal</td>
<td>28 (100%)</td>
</tr>
</tbody>
</table>


### Performance of NAATs for Diagnosis of Rectal C. trachomatis Infection

<table>
<thead>
<tr>
<th>Site</th>
<th>No (%) Individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital and Rectal</td>
<td>20 (40.8%)</td>
</tr>
<tr>
<td>Genital Only</td>
<td>6 (12.2%)</td>
</tr>
<tr>
<td>Rectal Only</td>
<td>23 (46.9%)</td>
</tr>
<tr>
<td>Genital or Rectal</td>
<td>49 (100%)</td>
</tr>
</tbody>
</table>

Case 1

History: 29yo male presents to your office with urethral “itching” 7 days. Two weeks ago while at a business convention he had unprotected sex with a colleague.

Case 1 (Cont.)

The most likely cause of his symptoms is:
1. Gonorrhea
2. Non gonococcal Urethritis (NGU)
3. Human Papillomavirus Infection
4. Post Coital Remorse

Case 1 (Cont.)

History: 29yo male presents to your office with urethral “itching” 7 days. Two weeks ago while at a business convention he had unprotected sex with a colleague.

Diagnosis: NGU
Urethritis Diagnosis Updates
2015 CDC STD Treatment Guidelines

- NGU cutoff will be lowered to ≥2 WBC/hpf
- *T. vaginalis* testing could also be considered in areas or populations of high prevalence
  - No FDA-cleared NAAT for *T. vaginalis* detection in men in the U.S.
  - Several large reference labs have performed the necessary CLIA validation of a urine-based *T. vaginalis* NAAT for men
- Currently no commercially available diagnostic test for *M. genitalium* cleared by the FDA for use in the U.S.
  - Some medical centers and commercial labs have developed a *M. genitalium* NAAT
- Methylene Blue/Gentian Violet (MB/GV) smear should be considered as an alternative to Gram stain for clinical diagnosis of urethritis

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Gram stain PMN Cutoff for Clinical Diagnosis of Urethritis
in Men with Urethral Signs and/or Symptoms

<table>
<thead>
<tr>
<th>Gram stain stratum</th>
<th>Number</th>
<th>CT+</th>
<th>%</th>
<th>95% CI</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>2612</td>
<td>126</td>
<td>4.8</td>
<td>4.0-5.7</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1083</td>
<td>71</td>
<td>6.6</td>
<td>5.2-8.1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>264</td>
<td>46</td>
<td>16.2</td>
<td>12.2-20.8</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>627</td>
<td>93</td>
<td>14.8</td>
<td>12.2-20.8</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>753</td>
<td>136</td>
<td>18.0</td>
<td>15.4-20.9</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>609</td>
<td>156</td>
<td>25.6</td>
<td>22.2-29.2</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>297</td>
<td>103</td>
<td>34.7</td>
<td>29.4-40.2</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>249</td>
<td>61</td>
<td>24.4</td>
<td>19.4-30.0</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>388</td>
<td>122</td>
<td>34.0</td>
<td>29.3-39.0</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>139</td>
<td>54</td>
<td>38.8</td>
<td>31.0-47.1</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>533</td>
<td>220</td>
<td>41.2</td>
<td>37.1-45.4</td>
<td></td>
</tr>
<tr>
<td>≥10</td>
<td>3878</td>
<td>1699</td>
<td>43.8</td>
<td>42.3-45.5</td>
<td></td>
</tr>
</tbody>
</table>

Reitmeijer Sex Trans Dis 2012;39(1):18-20

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Urethritis: Etiologies

+ Infectious
  - *N. gonorrhoeae*
  - NGU
    - *C. trachomatis*
    - *U. urealyticum*
    - *M. genitalium*
    - *T. vaginalis*
    - HSV
    - Other bacteria (i.e. GNR, <5%)
    - UNKNOWN! (20-30%)
    - Dysbiotic Origin?

+ Non-infectious
  - Chemical
  - Allergic
  - Autoimmune
  + ? Frequency
Does MG cause Male Urethritis?

- Acute urethritis – 38 studies
  - 15% MG+ (median) in urethritis cases
  - 22% MG+ (median) in NCNGU cases

- Persistent urethritis
  - 6 studies
  - 12-14% MG+ men with persistent/recurrent urethritis

NGU Treatment Updates
2015 CDC STD Treatment Guidelines

- Azithromycin and doxycycline regimens remain recommended for initial NGU treatment
- In areas with high T. vaginalis prevalence, heterosexual men with persistent/recurrent urethritis should be presumptively treated
- M. genitalium should be suspected in persistent/recurrent urethritis
  - Moxifloxacin 400mg daily x ≥7 days should be considered for subjects failing azithromycin treatment
- Persistent or recurrent NGU after presumptive treatment for M. genitalium or T. vaginalis should be referred to a urologist

Persistent/Recurrent Urethritis Treatment
2015 CDC STD Treatment Guidelines

If azithromycin NOT given for 1st episode:
- Azithromycin 1 g orally in a single dose
- Metronidazole 2 g orally in a single dose OR
- Tinidazole 2 g orally in a single dose

If azithromycin given for 1st episode:
- Moxifloxacin 400 mg orally qd x 7d
- Metronidazole 2 g orally in a single dose OR
- Tinidazole 2 g orally in a single dose

Compliments: Lisa Manhart
TRICHOMONAS WET PREP

Added Benefit of Nucleic Acid Amplification Testing for the Diagnosis of *Trichomonas vaginalis* Among Men and Women Attending a Sexually Transmitted Diseases Clinic


Background: *Trichomonas vaginalis* (TV) is the most common sexually transmitted infection (STI) in the world. However, TV is not a reportable STI and, with the exception of HIV, public health surveillance guidelines for reporting to clinicians are lacking. The objective of the study was to determine the added value of nucleic acid amplification tests (NAATs) for detection of TV in men and women at high risk for infection in addition to standard culture.

Methods: We performed a cohort study at 27 clinical sites in the United States from November 2009 to October 2010. NAATs and cultures were performed for male and female patients at each visit.

Results: Among 1,135,463 patients, 854 (0.08%) were positive for TV DNA/NA by NAAT. TV NAAT-positive women were older and more likely to have a younger partner, whereas men were more likely to have a greater number of recent sexual partners. TV NAAT positivity was associated with a prior infection in women but not men.

Conclusions: TV NAATs provide increased sensitivity and specificity compared with standard culture. These findings suggest that both groups should be routinely screened, including those aged 18 and older, impaired detection of TV by current implementation of NAATs.
STI Prevalence in Women by Pathogen and Age


Trichomoniasis Treatment
2015 CDC STD Treatment Guidelines

**New Episode**
- Tinidazole 2 g PO single dose OR
- Metronidazole 2 g PO single dose
- Metronidazole 500 mg po BID for 7d (alternative, rec if HIV+)

**Treatment Failure of 2 g metronidazole single dose**
- Metronidazole 500 mg BID x 7d

**Treatment Failure – Additional Options**
- Tinidazole or Metronidazole 2 g PO daily x 5d 7d
- Tinidazole 2-3g PO daily x 14d plus intravaginal tinidazole

**Treatment Failure – Alternative Additional Options**
- High-dose tinidazole + intravaginal paromomycin
- Nitazoxanide PO
- Intravaginal boric acid

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- Testing for *T. vaginalis* by NAAT (in men)
- Testing for *M. genitalium* utilizing NAAT
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Resources

www.stdptc.org  www.nnptc.org