ACTHIV 2018: A State-of-the-Science Conference for Frontline Health Professionals
STIs: Evaluation and Treatment

Laura Hinkle Bachmann, MD, MPH
Professor
Wake Forest University Health Sciences
Winston-Salem, NC
Co-Director
AL/NC STD Prevention Training Center
Learning Objectives

Upon completion of this presentation, learners should be better able to:

• Implement currently recommended strategies for the evaluation and management of STI's in HIV-infected individuals.
Faculty and Planning Committee Disclosures
Please consult your program book.

Grant Recipient/Research Support
• Becton-Dickinson, Atlas Genetics, Inc, NIH, CDC

Off-Label Disclosure
The following off-label/investigational uses will be discussed in this presentation:
• Extra-genital testing for *N. gonorrhoeae* and *C. trachomotis* with nucleic acid amplification-based tests
Case

• 36yo male presents with urethral burning/tingling, discharge x 3 days
• 1 female partner/12mo who was treated for an infection 2 days ago
• Last contact 1 week ago
• Oral and penile exposure (oral, vaginal and penetrative anal sex)
• H/O chlamydia age 16

• PE – mucoid discharge
• Urethral Gram Stain - >/=2 PMN/oif
  • No GNID
What is the recommended treatment for NGU?

1. Doxycycline 100mg po BID x 7 days
2. Azithromycin 1gm po x 1
3. Ceftriaxone 250mg IM x 1 plus Azithromycin 1gm po x 1
4. Cefixime 400mg po x 1 plus Azithromycin 1gm po x 1
Insert Web Page

This app allows you to insert secure web pages starting with https:// into the slide deck. Non-secure web pages are not supported for security reasons.

Please enter the URL below.

https://api.cvent.com/polling/v1/api/polls/sp5dlumj

Note: Many popular websites allow secure access. Please click on the preview button to ensure the web page is accessible.
Continued...

- The patient is treated with azithromycin 1gm PO x 1 DOT
- GC/CT urethral NAAT negative
- Oral GC NAAT negative
- RPR negative

- The patient returns 2 weeks later with continued symptoms...
What is the next step?

1. Take a sexual history and repeat the evaluation
2. Give him doxycycline 100mg po BID x 7 days plus metronidazole 2gm PO x 1
3. Treat with moxifloxacin 400mg po qd x 7 days
4. 1 and 3
Insert Web Page

This app allows you to insert secure web pages starting with https:// into the slide deck. Non-secure web pages are not supported for security reasons.

Please enter the URL below.

https://api.cvent.com/polling/v1/api/polls/sp-uwqtcoq

Note: Many popular websites allow secure access. Please click on the preview button to ensure the web page is accessible.
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
M. *gent* Prevalence – U.S.  
Getman et al, JCM 2016  

- Specimens from clinical isolates, 7 sites in the U.S. (N=946)  
- M. *gent* prevalence  
  - Females – 16.1% *(50.8% macrolide resistance mutation)*  
  - Males – 17.2% *(42% macrolide resistance mutation)*  
- Resistance is not a regional phenomena but likely endemic in the U.S.  

- No FDA Approved Test in U.S.  
  - Several commercial labs have tests (?performance)
Treatment Algorithm for Non-gonococcal Urethritis

Treatment for initial episode of non-gonococcal urethritis (NGU):
- Preferred: Azithromycin 1 gram PO x 1 dose, OR Doxycycline 100 mg PO BID x 7 days
- Alternative: Erythromycin base 500mg PO QID x 7 days, OR Erythromycin ethylsuccinate 800 mg PO QID x 7 days, OR Levofloxacin 500 mg QD x 7 days, OR Ofloxacin 300mg PO BID x 7 days

Resolution of symptoms: No further treatment

Recurrent or persistent symptoms, AND objective evidence of urethritis

History of non-adherence to therapy or re-exposure to an untreated sexual partner

Repeat treatment regimen above for initial episode of NGU

History of completion of therapy and no re-exposure to an untreated sexual partner

Treatment for persistent or recurrent NGU:
- If Azithromycin is used for initial episode: Moxifloxacin 400 mg PO QD x 7 days
- If Doxycycline is used for initial episode: Azithromycin 1 gm PO x 1 dose
- PLUS
  - For men who have sex with women who live in areas where T. vaginalis is highly prevalent: Metronidazole 2 gm PO x 1 dose OR Tinidazole 2 gm PO x 1 dose

In summary...

• *M. gent* seems to be an important pathogen, specifically as relates to male urethritis though we need a better understanding of role in cervicitis and upper tract disease

• Reliable test not currently available but on the horizon
  • Several large commercial labs offer (?performance)

• Current *M. gent* treatments are already failing and salvage drugs studied are not available in the U.S. (and long-standing efficacy not clear)

• A screening program is not ready for primetime...
An Interesting Twist...

• 18 yo male presents to STD clinic with a greenish drip
• Gram stain demonstrates gram negative intracellular diplococci
• NAAT-based test negative for gonorrhea

• What happened?
Increase in *Neisseria meningitidis*–Associated Urethritis Among Men at Two Sentinel Clinics — Columbus, Ohio, and Oakland County, Michigan, 2015

Jose A. Bazan, DO1,2; Amy S. Peterson, MPH3; Robert D. Kirkcaldy, MD4; Elizabeth C. Briere, MD5; Courtney Maierhofer, MPH2; Abigail Norris Turner, PhD2; Denisse B. Licon, PhD1; Nicole Parker, MPH6; Amanda Dennison, MPH7; Melissa Ervin1; Laura Johnson, MD8; Barbara Weberman6; Pamela Hackett, MD6; Xin Wang, PhD5; Cecilia B. Kretz, PhD5; A. Jeanine Abrams, PhD5; David L. Trees, PhD4; Carlos Del Rio, MD9; David S. Stephens, MD5; Yih-Ling Tzeng, PhD9; Mary DiOrio, MD7; Mysheika Williams Roberts, MD1

Columbus, OH – N=52
Oakland Co, MI – N=15

99% heterosexual

97% symptomatic urethritis

Almost all had received fellatio

Picked up through discordant test results

Treated successfully with GC treatment

No increase in invasive NM disease over this time period

MMWR June 3, 2016
A Routine Day in HRA Clinic...
Continued...

- 3 male partners over the last 6 months – HIV- and HIV+
- Stable group of partners though they may have other partners
- No known contact to an STI recently
- Of note, remainder of exam significant for a few papulosquamous lesions on the scrotum and perhaps a few (<3) erythematous macules on his flanks
How would you manage him the day of the visit?

1. Treat him with valacyclovir 1 gm PO bid x 5-10 days
2. Bicillin 2.4 MU IM x 1
3. Both 1 and 2
4. 1 and 2 plus ceftriaxone 250mg IM x 1 plus doxycycline 100mg PO bid x 7 days
5. None of the above
Insert Web Page

This app allows you to insert secure web pages starting with https:// into the slide deck. Non-secure web pages are not supported for security reasons.

Please enter the URL below.

https://api.cvent.com/polling/v1/api/polls/spvp7p8

Note: Many popular websites allow secure access. Please click on the preview button to ensure the web page is accessible.
Follow-up

- RPR 1:256
- Rectal GC and CT: both negative
- Oral GC: negative
- HSV 1 and 2 PCR: negative

- Path from biopsy: patchy immunostaining positive for *T. pallidum*
- Real time *T. pallidum* PCR (CDC): positive
Syphilis Natural History

Exposure → 30-50% → 1\(^0\) → 2\(^0\) → Latent → Lifetime Latency

- **Incubation Period**: 3-4 wks
  - Range: 3-90 days
- **1\(^0\)**
  - 2-6 wks
  - Range: 1-12 wks
  - After 2-8 weeks lesions disappear spontaneously
  - Range: up to 1 yr
- **Latent**
  - 25%
- **Tertiary**
  - 70%
  - 2-20 years

Overlap Between 1\(^0\) and 2\(^0\) can occur

Neurosyphilis can occur at any stage

**Courtesy:** Susan Philip, SF DPH
And M. Urban, URochester

ACTHIV 2018: A State-of-the-Science Conference for Frontline Health Professionals

MSM† = Gay, bisexual, and other men who have sex with men (collectively referred to as MSM); MSW† = Men who have sex with women only.

* 36 states were able to classify ≥70% of reported cases of primary and secondary syphilis as either MSM†, MSW†, or women for each year during 2012–2016.
Primary and Secondary Syphilis — Reported Cases by Sex, Sexual Behavior, and HIV Status, United States, 2016

* MSM = Gay, bisexual, and other men who have sex with men (collectively referred to as MSM); MSW = Men who have sex with women only.
Syphilis Treatment

**Primary, Secondary & Early Latent:**
- Benzathine penicillin G 2.4 million units IM x 1 dose

**Late Latent and Unknown Duration:**
- Benzathine penicillin G 7.2 million units total, given as 3 IM 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 q4hr for 10-14 days

2015 CDC STD Treatment Guidelines

*Only one dose of PCN is recommended for early syphilis in HIV-infected persons; extra doses not needed*
What would you have treated him with, if he had a history of anaphylaxis to PCN?

1. Azithromycin 2 gm PO x 1
2. Doxycycline 100 mg PO bid x 14 days
3. Ceftriaxone 2 gm IM qd x 10-14 days
4. Desensitize him!
Insert Web Page

This app allows you to insert secure web pages starting with https:// into the slide deck. Non-secure web pages are not supported for security reasons.

Please enter the URL below.

https://api.cvent.com/polling/v1/api/polls/spffzwom

Note: Many popular websites allow secure access. Please click on the preview button to ensure the web page is accessible.
Case continued....

• The patient was treated with bicillin 2.4 MU on the day of the visit
• He returns to clinic in 3 months
• He denies sexual activity since his last visit
• Repeat RPR titer = 1:64
What is your next move?

1. Check titers again in 3 months
2. Re-treat the patient with 2.4 MU bicillin
3. Perform a lumbar puncture to rule out neurosyphilis
4. Recheck the RPR to confirm that it is really 1:64
5. None of the choices above
Insert Web Page

This app allows you to insert secure web pages starting with https:// into the slide deck. Non-secure web pages are not supported for security reasons.

Please enter the URL below.

https://api.cvent.com/polling/v1/api/polls/spk4vk4

Note: Many popular websites allow secure access. Please click on the preview button to ensure the web page is accessible.
Titer

1:1  1:2  1:4  1:8  1:16

1:32  1:64  1:128  1:256  1:512
Titer

1:1  1:2  1:4  1:8  1:16  1:32  1:64  1:128  1:256  1:512
Titer

- $256/4 = 64$

ACTHIV 2018: A State-of-the-Science Conference for Frontline Health Professionals
Another example

1:1  1:2  1:4  1:8  1:16
1:32  1:64  1:128  1:256  1:512
Titers

1:1  1:2  1:4  1:8  1:16
1:32 1:64 1:128 1:256 1:512
Titers – not significant

1:1
1:2
1:4
1:8
1:16
1:32
1:64
1:128
1:256
1:512

1 dilution
Another example

1:1 1:2 1:4 1:8 1:16
1:32 1:64 1:128 1:256 1:512
Titers

1:1  1:2  1:4  1:8  1:16

1:32 1:64 1:128 1:256 1:512
Titers – significant change

1:1  1:2  1:4  1:8  1:16

1:32  1:64  1:128  1:256  1:512

2 dilutions
Response to Syphilis Therapy

- **Primary or Secondary Syphilis**\(^1\) – Fourfold or greater decline in nontreponemal serologic titers by 6-12 months follow-up
  - 15-20% of patients treated for primary or secondary will not achieve this at 1 year post-treatment\(^2,3\)

- **Latent Syphilis (Early, Late, or Unknown Duration)**\(^1\) – Fourfold or greater decline in initially high \((\geq 1:32)\) nontreponemal serologic titers by 12-24 months follow-up

Proportion of Patients with Seroreversion (Negative RPR) after a $\geq 4$-fold Decline in Nontreponemal Antibody Titers After Syphilis Treatment, According to Stage of Infection and Time After Therapy

<table>
<thead>
<tr>
<th>Stage of Syphilis</th>
<th>3 Mo</th>
<th>6 Mo</th>
<th>9 Mo</th>
<th>12 Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary (n=86)</td>
<td>9 (10.5%)</td>
<td>20 (34.9%)</td>
<td>30 (34.9%)</td>
<td>32 (37.2%)</td>
</tr>
<tr>
<td>Secondary (n=170)</td>
<td>1 (0.6%)</td>
<td>7 (4.1%)</td>
<td>10 (5.9%)</td>
<td>17 (10.0%)</td>
</tr>
<tr>
<td>Early Latent (n=77)</td>
<td>5 (6.5%)</td>
<td>5 (6.5%)</td>
<td>8 (10.4%)</td>
<td>8 (10.4%)</td>
</tr>
<tr>
<td>Total</td>
<td>15 (4.5%)</td>
<td>32 (9.6%)</td>
<td>48 (14.4%)</td>
<td>57 (17.1%)</td>
</tr>
</tbody>
</table>

Sena et al. Sex Transm Dis 2017; 44 (1): 7-11
Case

• 51yo male presents for routine HIV care
• Adherent to HIV therapy (HIV VL target not detected; CD4 770)
• elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
• Mentions rash on chest prompting urgent care visit 2 days prior to this visit
• Diagnosed with pityriasis rosea
What do you want to know next?

1. Additional details about onset and accompanying signs/symptoms
2. Grooming/product history
3. New medications
4. Sexual history
5. All of the above
Insert Web Page

This app allows you to insert secure web pages starting with https:// into the slide deck. Non-secure web pages are not supported for security reasons.

Please enter the URL below.

```
https://api.cvent.com/polling/v1/api/polls/sp-l4dz4v
```

Note: Many popular websites allow secure access. Please click on the preview button to ensure the web page is accessible.
Additional info....

- Rash started one week prior to presentation
- No fever, night sweats, vision changes
- No new products
- No new medications

- Sexual history – not obtained
- RPR drawn and dermatology referral placed
- Patient sent home
What is missing???

Besides sexual history....
Genital Exam!
The next day...

- He is seen by dermatology
- The patient is concerned that he may have syphilis. He had syphilis in the 1980’s and is afraid that he might have it again
- Exam significant for multiple papules on trunk and arms (still no genital exam)
- Biopsy performed $\rightarrow$ syphilis
- RPR $\rightarrow$ 1:64
- One week later patient returns to HIV provider for treatment
IT’S BEEN LOVELY BUT I HAVE TO SCREAM NOW
More information...

• 4 male partners/2 months
• Reports 2 painless ulcers on penis that have nearly resolved
• Exposure at oral, penile and rectal sites through sex
• Condom use intermittent
• Exam – small indurated ulcer on lateral aspect of tip of penis
• Oral GC, Rectal GC/CT, Urine GC/CT performed
• Rectal CT positive!
Take home points

- Rash = RPR
- The sexual history is important!
- The genital exam can inform patient management!
- Patients with one STI should be checked for others at all relevant anatomic sites
- If a high risk patient has lesions concerning for early syphilis, treat before they leave the clinic
  - Up to 30% of patients with primary chancre can have negative RPR
Azithro or Doxy for Rectal CT using NAAT

Kong et al (Epidemiol Infect 2016)
- Retrospective
- Treatment efficacy for azithromycin 1gm: 83.6% (95% CI 77.2-88.8)
- High pre-treatment organism load associated with repeat positivity

Gratrix et al (Sex Transm Dis 2016)
- Retrospective
- Treatment failure for azithromycin 1gm: 8.5% (95% CI 5.9-11.0)
Bottom Line

• Treatment guidelines for rectal CT have not changed in the U.S.
  • Azithromycin 1gm PO x 1 or doxycycline 100mg PO BID x 7 days for asymptomatic infection
  • Doxycycline 100mg PO BID x 21 days to cover LGV (plus treatment for gonorrhea and potentially syphilis/HSV) if proctitis symptoms

• RCT in process

What is the recommended treatment for gonorrhea?

1. Cefixime 400mg PO x 1 plus azithromycin 1gm PO x 1
2. Azithromycin 2gm PO x 1
3. Ceftriaxone 250mg PO x 1 plus azithromycin 1gm PO x 1
4. Ciprofloxacin 500mg PO x 1
5. None of the choices above
Insert Web Page

This app allows you to insert secure web pages starting with https:// into the slide deck. Non-secure web pages are not supported for security reasons.

Please enter the URL below.

https://api.cvent.com/polling/v1/api/polls/spga5h9z

Note: Many popular websites allow secure access. Please click on the preview button to ensure the web page is accessible.
Gonorrhea — Rates of Reported Cases by Region, United States, 2007–2016
ACTHIV 2018: A State-of-the-Science Conference for Frontline Health Professionals

Superintelligent Gonorrhea!
UK Man Infected With Gonorrhea With High Resistance To Antibiotics
Cluster of Hawaii Gonorrhea Isolates with Diminished Susceptibility to Multiple Antibiotics, Including Very High Azithromycin MIC and Alert-Value Ceftriaxone MIC
April-May, 2016

<table>
<thead>
<tr>
<th></th>
<th>Minimum Inhibitory Concentrations, µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>azithro*</td>
</tr>
<tr>
<td>1</td>
<td>&gt; 256</td>
</tr>
<tr>
<td>2</td>
<td>&gt; 256</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 256</td>
</tr>
<tr>
<td>4</td>
<td>&gt; 256</td>
</tr>
<tr>
<td>5</td>
<td>&gt; 256</td>
</tr>
<tr>
<td>6</td>
<td>&gt; 256</td>
</tr>
<tr>
<td>7</td>
<td>&gt; 256</td>
</tr>
</tbody>
</table>

*Hawaii State Laboratories Division  
**Seattle GISP Reference Lab
2015 STD Treatment Guidelines: Gonorrhea

• Recommended
  • Ceftriaxone 250 mg IM

  Plus (even if chlamydia test negative)

  • Azithromycin 1gm po x 1

  ** Doxycycline 100mg po BID x 7d removed from preferred

Gonorrhea Treatment Alternatives

- Cefixime 400mg orally once
  
  Plus

- Azithromycin 1gm orally once regardless of CT

In case of severe allergy:

- Gentamicin 240mg IM or 5mg/kg IM plus azithromycin 2gm orally x 1
  OR

- Gemifloxacin 320mg orally x 1 plus azithromycin 2gm orally x 1

Suspected Treatment Failure*: What do I do?

**CULTURE:** If GC culture not available, call your local health department STD controller

**RETREATMENT:** Gemifloxacin 320 mg PO + Azithromycin 2 g PO OR Gentamicin 240 mg IM + Azithromycin 2 g PO

**REPORT:** Report failure to your local or state health department within 24 hours; consult an ID specialist or call CDC (404-639-8659) for advice

**TREAT PARTNERS:** ID sex partners from preceding 60 days and treat with same regimen that patient receives

**TEST OF CURE (TOC):** Patient returns 7-14 days after retreatment for TOC culture and NAAT

*If reinfection suspected instead of treatment failure, OK to repeat treatment with ceftriaxone 250 mg IM + azithromycin 1 g PO.

Who needs a test of cure?

- Patients with pharyngeal GC treated with an alternative regimen, 14 days after tx, using either culture or NAAT
- Cases of suspected treatment failure (with culture and simultaneous NAAT)

Proportion of CT and GC infections MISSED among 3398 asymptomatic MSM if screening only urine/urethral sites, San Francisco, 2008-2009