Update on Gonorrhea

May 22, 2019
Lunch and Learns

The HIV/STD/TB/Hepatitis Program and the Dakotas AIDS Education and Training Center (DAETC) conduct monthly Lunch and Learn Webinars for health care professionals in North and South Dakota.

Each month a new topic will be held from 12:00 p.m. to 1:00 p.m. CST on the fourth Wednesday of the month.
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https://www.ndhealth.gov/hiv/Provider/

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Update on Gonorrhea

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Public Health – Seattle & King County HIV/STD Program

May 22, 2019
DISCLOSURES

• I have received research support from Hologic.

• There will be graphic images in this talk.
Outline

• Sites of Infection & Clinical Syndromes
• Epidemiology
• Screening & Diagnostics
• Antimicrobial Resistance
• Recommended Treatment
• Partner Therapy
Urethritis and Epididymitis

• Urethral infection in men is typically symptomatic

• Incubation ~5 days
Cervicitis and Pelvic Inflammatory Disease

- Cervical infections are often (≥ 50%) asymptomatic
- PID
- Perihepatitis
Anorectal Infection and Proctitis

• **Most** anorectal infections are asymptomatic

• **Proctitis**
  • Pain
  • Itching/Irritation
  • Painful bowel mvmts
  • Rectal discharge
Pharyngeal infections

• Virtually always asymptomatic

• Source of transmission (asymptomatic reservoir)

• Important treatment consideration in MSM
  • Generally lower tissue penetration of antibiotics compared to genitals and rectum

• Possible source of antimicrobial resistance development (commensal Neisseriaeae)
Clinical Syndromes: Ocular gonorrhea

Ophthalmia neonatorum

Needs systemic therapy, not drops!

Gonococcal conjunctivitis
Clinical Syndromes: Disseminated Gonococcal Infection

Triad of:
Tenosynovitis
Arthritis
Polyarthralgia
Epidemiology
NOTE: The total rate of reported cases of gonorrhea for the United States and outlying areas (including Guam, Puerto Rico, and the Virgin Islands) was 170.3 per 100,000 population. See Section A1.11 in the Appendix for more information on interpreting reported rates in the outlying areas.

ACRONYMS: GU = Guam; PR = Puerto Rico; VI = Virgin Islands.
Gonorrhea — Rates of Reported Cases by Age Group and Sex, United States, 2017
Gonorrhea — Rates of Reported Cases by Race and Hispanic Ethnicity, United States, 2013–2017

NOTE: Not all US jurisdictions reported cases in OMB-compliant Race categories in 2017. This may minimally under- or overestimate rates for Asians, NHOPI, or Multirace individuals. For completeness, data in this figure include cases reported from all jurisdictions. See Section A1.5 in the Appendix for information on reporting STD case data for race and Hispanic ethnicity.

ACRONYMS: AI/AN = American Indians/Alaska Natives; NHOPI = Native Hawaiians/Other Pacific Islanders; OMB = Office of Management and Budget.
Gonorrhea infections increased 41.8% in 2018

Gonorrhea, North Dakota
2014-2018

Source: NDDoH Division of Disease Control
55% of gonorrhea infections were female

Gonorrhea case count by gender, North Dakota 2018

Source: NDDoH Division of Disease Control
66% increase of gonorrhea infections between 30-44 years old

Gonorrhea, North Dakota 2018

Source: NDDoH Division of Disease Control
American Indian/Alaskan Natives had the highest rate of gonorrhea in 2018.

Gonorrhea rates by race, North Dakota 2014-2018

Source: NDDoH Division of Disease Control
Sioux County reported the highest gonorrhea rate in 2018 – 1416 cases per 100,000.
Diagnosis and Testing
Gonorrhea: Diagnostic Testing

- Nucleic acid amplification tests (NAAT) recommended for men & women
- Optimal specimen: first-catch urine in men and vaginal swabs in women
- NAAT optimal for rectal and pharyngeal testing; not FDA approved but commercially available & validation protocols available
- Cannot perform drug resistance testing on NAAT (need culture if concern)

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6302a1.htm?s_cid=rr6302a1_w
Diagnosis of Gonorrhea

• **Gram Stain:**
  • >95% sensitive and specific with male urethral discharge
  • Not sensitive or specific enough for endocervical, vaginal, rectal or pharyngeal

• **Culture:**
  • Can use any body fluid
  • Allows for antimicrobial susceptibility testing
CDC STD Screening Guidelines for Women

• Sexually active adolescents <25 years of age
  • Routine chlamydia and gonorrhea screening
  • Others STDs and HIV based on risk

• Women ≥25 years of age
  • STD/HIV testing based on risk
    • New sex partner, more than one sex partner, a sex partner with concurrent partners, sex partner with an STI

Vaginal, endocervical or urine
Case

• 24 yo MSM; 4 sex partners ≤2 months.
• He is versatile – reports both receptive and insertive anal intercourse, and performs and receives oral sex.
• Occasionally uses condoms.
• He wants an *complete* “STD Check”
• Currently asymptomatic
Which tests do you do?

A) HIV & syphilis
B) GC at urethra and rectum
C) CT at urethra and rectum
D) GC and CT at throat
E) All of the above
Extragenital CT/GC in MSM in the STD Surveillance Network, 2010-2012

Patton, Clinical Infectious Diseases 2014
Importance of extra-genital gonorrhea

• Most GC in MSM is extragenital

• Transmission
  • 30% of symptomatic gonococcal urethritis is attributable to oropharyngeal exposure

• HIV Transmission
  • Potentiate acquisition, even after controlling for sexual behaviors

• Treatment differentials
  • Pharyngeal GC
    • Ceftriaxone > Cefixime

STI Self-Testing Program

Posters available in English and Spanish
Email aradford@uw.edu for free posters for your clinic
How often to screen MSM?

• STD Guidelines are relatively non-specific
  • “More frequent STD screening” 3–6-month intervals is indicated for MSM, if high risk

• King County guidelines
  • “High-risk” once every 3 months
    • Bacterial STD in past year
    • Methamphetamine or popper use in past year
    • HIV serodiscordant sex partners in past year
    • 10 or more sex partners in past year
  • All other sexually active MSM: yearly
  • Taking PrEP: Every 3 months
Antimicrobial Resistance & Treatment
HISTORICAL PERSPECTIVE: Recommended Gonococcal Treatments

- **1940s**: Penicillin & Tetracycline
- **1980**: Ceftriaxone
- **1990**: Cipro / Cefixime
- **2000**: Azithro / Dual Tx
- **2010**: Cipro
- **2015**: Cefixime
- **>2020s**: Doxy / Azithro 2g

*PCN DOSE INCREASES*

Drugs removed from recommended therapy
Trends in the Prevalence of Quinolone Resistant *Neisseria gonorrhoeae* in China and the U.S.

Yue-Ping Yin, Chinese National STD Control Program
CDC 2008 GISP Report
Percent of GC isolates with ciprofloxacin resistance, 2014

CDC defines alert value MIC to Cefixime as ≥0.25 µg/mL and Ceftriaxone ≥0.125 µg/mL.

Percent of GC isolates with ceftriaxone/cefixime resistance, 2014

Percentage of azithromycin (AZM)-resistant NG in the United States and Seattle-King County from 2010-2018

- U.S. 2017: 4.4%

United States
Seattle -- King County

Proportion of Isolates with Azithromycin MIC ≥2 mcg/mL

- 2010: 0.4%
- 2011: 0.5%
- 2012: 0.6%
- 2013: 0.7%
- 2014: 1.8%
- 2015: 2.9%
- 2016: 3.7%
- 2017: 5.7%
- 2018: 8.8%
Percent of GC isolates with azithromycin resistance, 2014

Man has 'world's worst' super-gonorrhoea

By James Gallagher
Health and science correspondent, BBC News

28 March 2018

A man in the UK has caught the world's "worst-ever" case of super-gonorrhoea.

Multi-drug resistant gonorrhoea detected in Australia
What is first-line recommended treatment for gonorrhea?

1. Depends on anatomic site
2. Ceftriaxone 250mg or cefixime 400mg PLUS Azithromycin 1g
3. Ceftriaxone 250mg + Azithromycin 1g orally
4. Gentamicin 240mg + 2g Azithromycin
5. Ciprofloxacin 500mg
UPDATED GONORRHEA TREATMENT GUIDELINES COMING BY 2020!

Stay Tuned!
Why Dual Therapy?

- To treat concomitant chlamydial infections
  - Historical and epidemiological basis
- To prevent development of resistance
  - Theoretical, based on experience with other organisms (e.g. tuberculosis)
- Possible clinical synergy for pharyngeal GC with two drugs $^{1,2}$

2. Barbee et al CID 2013
Case

You are about to administer ceftriaxone to a 26 year old man with milky penile discharge and gram-negative intracellular diplococci on Gram stain.

His chart says he has a penicillin allergy.

Now what?
Allergies vs. Drug reactions

<table>
<thead>
<tr>
<th>Allergy</th>
<th>Drug Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylaxis</td>
<td>Mild rash, delayed GI upset</td>
</tr>
<tr>
<td>Immediate hives</td>
<td>OK TO CHALLENGE</td>
</tr>
<tr>
<td>Angioedema, bronchospasm</td>
<td></td>
</tr>
<tr>
<td>DO NOT RECHALLENGE</td>
<td></td>
</tr>
</tbody>
</table>

• Of those reporting penicillin allergy, only 10-15% are positive by skin testing

• Negligible or no cross-reactivity between penicillin and 3rd gen cephalosporins, like ceftriaxone

• Many with cephalosporin allergy can tolerate an alternative class of cephalosporin (ie, cephalexin – ceftriaxone)

CDC 2015 STD Tx Guidelines [www.cdc.gov/std/treatment](http://www.cdc.gov/std/treatment)
Romano et al, *J Allergy Clin Immunol*, 2015 Sep;136(3)
Case, continued

• He remembers getting immediate, severe hives after taking ceftriaxone last year

• Now what?
2015 Updated Gonorrhea Treatment Guidelines

**CEPHALOSPORIN ALLERGY RECOMMENDED THERAPY**

**Gentamicin**
240 mg IM x 1

**OR**

Gemifloxacin
320 mg PO x 1

**Azithromycin**
2 g PO x 1

**NOTES:**
- Urogenital infections only
- If used for pharyngeal infections, perform TOC (culture >3 days and NAAT >14 days).
### CDC-funded study: AZM 2g plus either gemifloxacin or gentamicin

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>Effectiveness*</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemifloxacin 320mg + AZM 2g</td>
<td>199</td>
<td><strong>99.5%</strong> (LB 95% CI: 97.6%)</td>
<td>37% nausea, 23% diarrhea, 11% abd pain/vomiting, 7.7% vomited &lt;1 hour</td>
</tr>
<tr>
<td>Gentamicin 240mg + AZM 2g</td>
<td>202</td>
<td><strong>100%</strong> (LB 95% CI: 98.5%)</td>
<td>28% nausea, 19% diarrhea, 7% abd pain/vomiting, 3.3% vomited &lt;1 hour</td>
</tr>
</tbody>
</table>

*For uncomplicated urogenital infections

**Not powered for extra-genital infections, but Gemi/AZM cured 15/15 pharyngeal and 5/5 rectal, and Gent/AZM cured 10/10 pharyngeal and 1/1 rectal GC infections.
Neisseria gonorrhoeae — Distribution of Gentamicin Minimum Inhibitory Concentrations (MICs) by Year, Gonococcal Isolate Surveillance Project (GISP), 2015–2017
Back to the case...

You have treated him with azithromycin 2 g + gentamicin 240mg IM.

The day after he is treated, the lab calls and says his pharyngeal swab is now positive for GC.
What now?

A) Repeat azithromycin 2 gm PO + gentamicin 240mg IM

B) Desensitize and give ceftriaxone 250 mg IM + AZM 2g

C) Levofloxacin 500 mg PO

D) Ask him to return for test of cure NAAT in 2 weeks
Follow-up after Gonorrhea Diagnosis

1) Counseling: No sex for 7 days after treatment

2) Treat partners! – 30-70% infected
   • if exposed within last 60 days, or if >60 days, most recent partner

3) Report infection to Public Health Authority

4) Retest 3 months → 10-40% reinfection

5) Test for HIV

6) Pharyngeal GC treated with alternative regimen should return for test of cure

7) Persistent symptoms → Culture and susceptibility testing
Suspected Treatment Failure

• Symptomatic >3-5 days after treatment & no sexual contact

• Positive TOC (culture >72 hours or NAAT > 14 days) & no sexual contact

• Positive culture 30-60 days post treatment & elevated cephalosporin MICs

• Consult STD Expert at Seattle STD PTC via the CCN
Gonorrhea Treatment: What’s coming?

• Will dual treatment be continued?
• Will we increase the dose of ceftriaxone?
• Will we use single dose DOT? Or will we need multi-dose & multi-day regimens?
• Will we have multiple first-line agents?
# Gonorrhea Treatment Around the World

<table>
<thead>
<tr>
<th>Country</th>
<th>Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Kingdom*</td>
<td>Ceftriaxone 1g x1</td>
<td>If you have susceptibility data prior to treatment, AND it’s susceptible to cipro → use cipro 500mg</td>
</tr>
<tr>
<td>Australia &amp; Europe</td>
<td>Ceftriaxone 500mg x1 Plus Azithromycin 2g</td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>Ceftriaxone 1g</td>
<td></td>
</tr>
</tbody>
</table>

*New guidelines as of January 2019!
Hope for the Future?

2 novel drugs with recently completed Phase 2 trials with favorable results

Single-Dose Zoliflodacin (ETX0914) for Treatment of Urogenital Gonorrhea

Stephanie N. Taylor, M.D., Jeanne Marrazzo, M.D., M.P.H.,
Byron E. Batteiger, M.D., Edward W. Hook, III, M.D., Arlene C. Seña, M.D., M.P.H.,
Jill Long, M.D., M.P.H., Michael R. Wierzbicki, Ph.D., Hannah Kwak, M.H.S.,
Shaconda M. Johnson, B.S.P.H., Kenneth Lawrence, Pharm.D.,
and John Mueller, Ph.D.

Gepotidacin for the Treatment of Uncomplicated Urogenital Gonorrhea: A Phase 2, Randomized, Dose-Ranging, Single-Oral Dose Evaluation

Stephanie N. Taylor, David H. Morris, Ann K. Avery, Kimberly A. Workowski, Byron E. Batteiger, Courtney A. Tiffany, Caroline R. Perry, Aparna Raychaudhuri, Nicole E. Scangarella-Oman, Mohammad Hossain, and Etienne F. Dumont

1Section of Infectious Disease, Louisiana State University Health Sciences Center, New Orleans; 2Desert AIDS Project, Palm Springs, California; 3Department of Medicine, Division of Infectious Diseases, MetroHealth Medical Center, Cleveland, Ohio; 4Department of Medicine, Division of Infectious Diseases, Emory University Department of Medicine, Atlanta, Georgia; 5Department of Medicine, Division of Infectious Diseases, Indiana University School of Medicine, Indianapolis; and 6R&D, GlaxoSmithKline, Collegeville, Pennsylvania
Partner Therapy
Case

• 22 yo woman with two regular male sex partners tests positive for gonorrhea on vaginal NAAT.

• You treat her in your office with IM ceftriaxone plus azithro x 1.
What should you do for her partners?

A) Offer cefixime plus azithromycin as expedited partner therapy (EPT)

B) Do not offer EPT – they need ceftriaxone

C) Defer to the public health department for partner treatment
What?! You just talked about the need for ceftriaxone

- GC isolates with reduced susceptibility to cephalosporins remain exceedingly uncommon
- Reinfection in persons with previously diagnosed gonorrhea is high
  - Strongest risk factor for acquisition is past history
- Health department does not contact all partners (varies by jurisdiction)
The Effectiveness of Expedited Partner Treatment on Re-Infection Rates

Expedited Partner Therapy (EPT)

• Appropriate for heterosexual patients with GC/CT whose partners’ treatment cannot be ensured or is unlikely

• NOT recommended MSM due to risk of undiagnosed HIV (and syphilis); and higher rates of AMR

EPT for Gonorrhea:
cephixime 400mg PO x 1 AND azithromycin 1g PO x 1
Summary

• Screen for gonorrhea in
  • Sexually active women <25 years of age
  • Sexually active MSM - don’t forget the throat and rectum

• NAATs superior to culture for both GC and CT
  • But, need to maintain culture capability for antimicrobial susceptibility testing

• Treat GC with Ceftriaxone 250 mg + AZM 1 g

• EPT for heterosexuals

• Retesting at 3 months for all
Find it in the Q+A Section of the CDC STD Guidelines!

2015 Sexually Transmitted Diseases Treatment Guidelines

Sexually Transmitted Diseases > Treatment > 2015 STD Treatment Guidelines > Questions and Answers

Gonorrhea | Questions & Answers | 2015 STD Treatment Guidelines

General management

Question: Is ceftriaxone 250 mg intramuscularly, plus doxycycline 100 mg orally twice a day for seven days, considered inadequate for the treatment of gonorrhea?

Due to the high proportion (>20%) of Gonococcal Isolate Surveillance Project (GISP) isolates with tetracycline (i.e., doxycycline) resistance and the results of two observational studies which showed inferiority of cephalosporins plus doxycycline (Barbee et al. and Sathia et al.), azithromycin is the preferred second agent to accompany ceftriaxone. All individuals treated for gonorrhea should receive two drugs, both to ensure clinical cure and to prevent the development of resistance. Persons treated with an alternative regimen for pharyngeal gonorrhea, should receive a test of cure three to four weeks after treatment.

Dual Therapy

Question: What is the purpose of dual treatment for gonorrhea and what is the appropriate timing for administering the medications?
https://www.std.uw.edu/
Additional Resources for Clinicians

• CDC 2015 STD Treatment Guidelines
  https://www.cdc.gov/std/tg2015/default.htm

• National Network of STD/HIV Prevention Training Centers
  www.nnptc.org

• Public Health – Seattle & King County HIV/STD Program

• CDC Division of STD Prevention
  www.cdc.gov/std/training
Thank you!

Lindley Barbee, MD MPH
lbarbee@u.washington.edu
• Thank You to Our Speaker!
  • Lindley Barbee, MD MPH

• CEU: [www.ndhealth.gov/HIV/Provider](http://www.ndhealth.gov/HIV/Provider)

• Next Lunch and Learn: June 26th at 12pm CT

• Register Now for the 2019 ND HIV.STD.TB.Viral Hepatitis Symposium: [https://www.ndhealth.gov/HIV/Symposium/](https://www.ndhealth.gov/HIV/Symposium/)