N. Gonorrhoeae with High-Level Azithromycin Resistance

2019 Indiana Infectious Disease Summit

Justin Holderman, MPH
November 20, 2019
• Gonorrhea 101
• STD Surveillance
• Antibiotic Resistance
• What’s a SURRG?
• Findings in Indianapolis
• Know your role!
Gonorrhea 101

- 2nd most common notifiable disease
- Often asymptomatic
- Symptoms, when present
  - Discharge
  - Dysuria (pain when urinating)
  - Disseminated infection (DGI)
- Untreated risks
  - Infertility/Sterility
  - Pelvic Inflammatory Disease (PID)
  - Increases HIV transmission/acquisition
Screening Recommendations pt. 1

Women <25 (older if at risk)*

- First prenatal care visit
- Third trimester if still at elevated risk

Pregnant women <25 (older if at risk)*

* Those with a new sex partner, >1 sex partner, a sex partner with concurrent partners, or a sex partner who has an STD, inconsistent condom use among persons not in mutually monogamous relationships, previous or coexisting STD, and exchanging sex for money or drugs
Screening Recommendations pt. 2

**Sexually active MSM**
- At least annually at sites of contact (regardless of condom use)
- More frequently if at increased risk*

**People with HIV**
- At first HIV evaluation, then at least annually

**People on HIV PrEP**
- At initiation, semi-annually

* multiple anonymous partners and substance abuse
Gonorrhea Case Management

• Case Definitions
  – (+) Nucleic Acid Amplification Test (NAAT) OR
  – Isolation of *N. gonorrhoeae* via culture

• Treatment
  – 250 mg Ceftriaxone + 1g Azithromycin

• Partner Services
  – Expedited Partner Therapy (EPT)
  – Disease Intervention Specialists (DIS)
- Gonorrhea 101
- STD Surveillance
- Antibiotic Resistance
- What’s a SURRG?
- Findings in Indianapolis
- Know your role!
STD Rates are Rising!

The State of STDs in the United States in 2018

STDs surge for the fifth straight year, reaching an all-time high.

- 1.8 million cases of Chlamydia (19% rate increase since 2014)
- 583,405 cases of Gonorrhea (63% rate increase since 2014)
- 115,045 cases of Syphilis (71% rate increase of infectious Syphilis since 2014)
- 1,306 cases of Syphilis among newborns (185% rate increase since 2014)

Learn more at: www.cdc.gov/std/
Rates of Reported Gonorrhea Cases by Year, U.S., 1941-2018

* Per 100,000.
• 53.3% increase in reported gonorrhea cases since 2015

• In 2018, gonorrhea was highest among African-American, non-Hispanic men (25%)

• Leveling off?
Estimated* Rates of Reported Gonorrhea Cases by MSM, MSW, and Women, STD Surveillance Network (SSuN)†

* Estimates based on interviews among a random sample of reported cases of gonorrhea (n=21,417); cases weighted for analysis. Data not available for 2014; 2013–2015 trend interpolated; trends lines overlap for MSW and women in this figure.
† Sites include Baltimore, Philadelphia, New York City, Washington State, San Francisco, and California (excluding San Francisco).
‡ Per 100,000.

• Gonorrhea 101
• STD Surveillance
• Antibiotic Resistance
• What’s a SURRG?
• Findings in Indianapolis
• Know your role!
Super Gonorrhea Is Spreading: What's Oral Sex Got To Do With It

News story
Two cases of resistant gonorrhoea diagnosed in the UK

Public Health England is reminding people of the importance of practising safer sex and seeking help if they are worried they may have an STI.

UK man's super-gonorrhoea cured — but now two Australians have it

Updated 20 Apr 2018, 11:47pm
AR Threat Report 2019

Drug-Resistant Neisseria Gonorrhoeae

Threat Level URGENT

- 550,000 Estimated drug-resistant infections each year
- 1.14M Total new infections each year
- $133.4M Annual discounted lifetime direct medical costs
Gonorrhea Treatment History

Distribution of Primary Antimicrobial Drugs Used to Treat Gonorrhea

Percentage of Isolates with Elevated MICs, Gonococcal Isolate Surveillance Project (GISP), United States

![Graph showing percentage of isolates with elevated MICs by year for Azithromycin, Cefixime, and Ceftriaxone.]
Percentage of Urethral Isolates with Elevated MIC by Sex of Sex Partners, GISP

A. Azithromycin

B. Ceftriaxone

* Elevated Azithromycin MIC: $\geq 2.0 \mu g/mL$.
† Elevated Ceftriaxone MIC: $\geq 0.125 \mu g/mL$.

ACRONYMS: MSM = Gay, bisexual, and other men who have sex with men; MSW = Men who have sex with women only.
• Gonorrhea 101
• STD Surveillance
• Antibiotic Resistance
• What’s a SURRG?
• Findings in Indianapolis
• Know your role!
SURRG Goals

1. Increase local lab capacity for antimicrobial susceptibility testing (AST)
2. Expand the culture criteria for patients receiving AST
3. Intensify DIS investigations to develop a better understanding of GC transmission
Expand Laboratory Capacity

- Specimens from the local STD clinic and four non-STD clinic partner sites
- Sampling ~14% of the local morbidity
- AST done within ~ 5-day turnaround
- Result transmitted directly to providers
- Building a laboratory safety net for outbreak responses
Screening Criteria
Expand testing to include:

• Women
• Extra-Genital Sites
• Sex Partners

*Symptoms include discharge, lesions, strong burning

A good candidate for SURRG!
Understanding Networks

How do disease spread within a group?

• Screening sexual partners and social contacts
• Identify persons or places of interest
• Complete phylogenetic analysis
• Evaluate the two methods of detailing disease transmission for a better solution
• Gonorrhea 101
• STD Surveillance
• Antibiotic Resistance
• What’s a SURRG?

• Findings in Indianapolis

• Know your role!
Antimicrobial Susceptibility of *N. gonorrhoeae* Isolates to Azithromycin, May 2017-December 2018, N=874

**Azithromycin Susceptibility MIC Breakpoints**
- Susceptible: < 2µg/ml
- Reduced Susceptibility: 2-128 µg/ml
- High Level Resistance: ≥ 256 µg/ml
Distribution of Azithromycin MICs by Etest

**Azithromycin Susceptibility MIC Breakpoints**
- Susceptible: < 2µg/ml
- Reduced Susceptibility: 2-128 µg/ml
- High Level Resistance: ≥ 256 µg/ml
### Isolates Identified with Reduced Azithromycin Susceptibility or High-Level Azithromycin Resistance, May 2017–Dec 2018

<table>
<thead>
<tr>
<th>Month of Sample Collection</th>
<th>Reduced Susceptibility (2-128 µg/ml)</th>
<th>High-Level Resistance (≥ 256 µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>May 2017</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>June 2017</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>July 2017</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Aug 2017</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Sept 2017</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Oct 2017</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Nov 2017</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Dec 2017</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Jan 2018</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Feb 2018</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Mar 2018</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Apr 2018</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>May 2018</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>June 2018</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>July 2018</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Aug 2018</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Sept 2018</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Oct 2018</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Nov 2018</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Dec 2018</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>
### Patients with High-Level Resistance to Azithromycin

- All isolates came from patients visiting the local STD clinic
- Patients received CDC-recommended treatment
- Most isolates were urethral samples (79%)
- Most returned for a test of cure and were negative
- Limited travel and previous antibiotic use

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Reduced AZI Susceptibility N=46</th>
<th>High-Level AZI Resistance N=12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>43 (94.5%)</td>
<td>12 (100%)</td>
</tr>
<tr>
<td>Female</td>
<td>3 (6.5%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Median Age</strong></td>
<td>32 (20-50)</td>
<td>28.5 (20-46)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>28 (60.9%)</td>
<td>2 (16.7%)</td>
</tr>
<tr>
<td>White</td>
<td>15 (32.6%)</td>
<td>9 (75%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (2.2%)</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>2 (4.3%)</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td><strong>Orientation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterosexual</td>
<td>29 (63.0%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Gay, Bisexual, and other Men who have Sex with Men (MSM)</td>
<td>17 (37.0%)</td>
<td>9 (75%)</td>
</tr>
<tr>
<td><strong>Previous GC Infection</strong></td>
<td>14 (30.4%)</td>
<td>7 (58.3%)</td>
</tr>
<tr>
<td>Chlamydia Coinfection</td>
<td>6 (13.0%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>HIV+</td>
<td>1 (2.2%)</td>
<td>0</td>
</tr>
</tbody>
</table>
## DIS Investigation Outcomes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Reduced Susceptibility N= 46 N (%)</th>
<th>High Level Resistance N= 12 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partner Services</td>
<td></td>
<td></td>
</tr>
<tr>
<td># Partners</td>
<td>120</td>
<td>36</td>
</tr>
<tr>
<td># Named Partners</td>
<td>26 (21.7%)</td>
<td>11 (30.1%)</td>
</tr>
<tr>
<td># Partners +GC</td>
<td>10 (38.5%)</td>
<td>6 (54.5%)</td>
</tr>
<tr>
<td>&gt;3 Partners</td>
<td>9 (19.6%)</td>
<td>5 (41.7%)</td>
</tr>
<tr>
<td>Test of Cure</td>
<td>17 (37.0%)</td>
<td>9 (75%)</td>
</tr>
<tr>
<td>Anonymous Partners</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20 (43.5%)</td>
<td>6 (50%)</td>
</tr>
<tr>
<td>No</td>
<td>26 (56.5%)</td>
<td>6 (50%)</td>
</tr>
<tr>
<td>Phone App Use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13 (28.3%)</td>
<td>5 (41.7%)</td>
</tr>
<tr>
<td>No</td>
<td>33 (71.7%)</td>
<td>7 (58.3%)</td>
</tr>
</tbody>
</table>

- Those with resistance were more likely to:
  - Have more partners
  - Have anonymous partners
  - Use of phone apps to meet partners
- Minimal connections between cases
Local Sexual and Social Networks

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>HL AZI-R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+Ng NAAT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Testing/ Unable to Locate</td>
<td></td>
<td>Unnamed P1/ Anonymous P1</td>
</tr>
</tbody>
</table>

- A visual representation of local sexual and social networks, with different icons and colors representing various statuses and groups.
Phylogenetic Analysis of High-Level Resistance Isolates from Indiana

- Whole genome sequencing identified a novel combination of mutations
  - Mosaic mtrR and 23S A2059G
  - Cau, et. al (2019)
- Most likely a locally acquired
- The red clade shows the resistant isolates are incredibly similar
  - This tight clustering would suggest transmission within a shared sexual network
In Summary

• 14 isolates were collected with high-level azithromycin resistance
• This was primarily seen in white MSM
• A clear distinction between those with resistance and others
• Limited partner information hindered disease intervention activities
• Incorporating WGS into STD intervention may help expand what partner services entails
Update!!

• 1 more isolate with Azithromycin resistance found
• 1 isolates was found to have reduced susceptibility to both cephalosporins
• Our reduced susceptibility numbers have begun to spike
  – ~20% of sampled isolates in recent months
• More isolates are set for WGS to identify how it can better be used in conjunction with DIS investigations
• Gonorrhea 101
• STD Surveillance
• Antibiotic Resistance
• What’s a SURRG?
• Findings in Indianapolis

• Know your role!
How do **YOU** participate?

1. Understand the risks of untreated STDs
2. Work with your DIS
3. Encourage your patients to test at extra-genital sites
4. Make sure patients take *all* of their meds; **Don’t share**!
5. Engage in partner services, either through EPT or DIS
Special Thanks

**Marion County Public Health Department**
- Dr. Christine Heumann
- Ashley Sherrow
- Rose Finney

**Indiana State Department of Health**
- Mackie Rios
- Julia Lay
- Kara Vogelzang
- Jamie Black
- Caitlin Conrad
- Jeremy Turner

**Centers for Disease Control and Prevention**
- Karen Schlanger
- Dr. Sancta St. Cyr
- Cau Pham
- Dr. Robert (Bob) Kirkcaldy

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
Thank you!

Contact Information

Justin Holderman, MPH
SURRG Epidemiologist
317-233-7749
juholderman@isdh.in.gov