Hold Your Applause- The Clap (Gonorrhea) in Indiana, the U.S., and Beyond
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Intended Outcome

• By the completion of this educational activity learners will increase knowledge and skills to identify appropriate treatments for patients infected with gonorrhea and understand the difference between re-infection and antimicrobial resistance.
Presenters

- Elizabeth Torrone is the team lead for surveillance in the Surveillance and Data Management Branch in the Division of STD Prevention at the Centers for Disease Control and Prevention. She received a master of science in public health and a doctoral degree in epidemiology from the University of North Carolina at Chapel Hill. She joined CDC in 2009 as an officer in the Epidemic Intelligence Service in the Division of STD Prevention. Since 2011, she has worked in STD surveillance in the Division of STD Prevention monitoring national trends in STDs and providing technical assistance to state and local project areas.

- Kimberly Workowski MD is a Professor of Medicine in the Division of Infectious Diseases at Emory University. Dr Workowski also serves as a consultant to CDC and WHO for the development of national guidelines for Sexually Transmitted Diseases, serves as the workgroup chair for the syphilis section of the HIV Prevention and Opportunistic Infection Guidelines, and serves as the co-chair of the renal section of the Hepatitis C Guidelines. Dr. Workowski provides expert assistance and technical guidance for the NIH Sexually Transmitted Infection clinical trials network scientific advisory council. Current research interests include clinical trials design and participation in clinical trials for HIV, PrEP, hepatitis C, gonorrhea, antimicrobial resistance (T vaginalis, T pallidum, N gonorrhoeae), guidelines development, and quality assessment on the clinical management of sexually transmitted infections.

- Justin Holderman comes from the frontlines of public health as a Disease Intervention Specialist for the Bell Flower Clinic, Marion County, and as the Area Manager for District 5. After completing his MPH in Epidemiology at the Fairbanks School of Public Health, he accepted the role as the Epidemiology Coordinator for the CDC ELC Grant: Strengthening US Response to Resistant Gonorrhea (SURRG). The SURRG program aims to expand gonorrhea resistance testing and surveillance with assistance from community partners, innovative DIS interviews, and social network analysis.
Gonorrhea Trends in the United States and Beyond

Elizabeth Torrone, MSPH, PhD
Lead, Surveillance & Special Studies Team

Emily Weston, MPH
Epidemiologist, Surveillance & Special Studies

Webinar for the Indiana State Department of Health’s STD Prevention Program on Gonorrhea
4/20/2017
General outline

- Gonorrhea epidemiology in the United States
  - Including some Indiana-specific data
  - Will be sharing preliminary 2016 data
- Antimicrobial resistant gonorrhea in the United States
  - Trends from the Gonococcal Isolate Surveillance Project (GISP)
  - Including some Indiana-specific data
- Antimicrobial resistant gonorrhea beyond our borders
Gonorrhea basics
Gonorrhea

- Caused by *Neisseria gonorrhoeae*
  - Gram negative diplococci
  - Described in 1879 by Albert Neisser

- Sexually transmitted
  - Urogenital, rectal, and oropharyngeal infection
Gonorrhea: Symptoms & sequelae

- Often asymptomatic
  - Can cause dysuria and discharge
  - Can lead to pelvic inflammatory disease & epididymitis
  - Disseminated infection (rarely)
- May facilitate HIV infection
- Vertical transmission
  - Conjunctivitis
Gonorrhea: Prevention & control

- Identify Infections
- Treat patient
- Treat partners

Gonorrhea: Prevention & control

Population | Screening recommendation
---|---
Women | Screen all sexually active women age ≤24 and older women who are at increased risk for infection (CDC; USPSTF: Grade B)
Heterosexual men | Screen if resources allow (CDC; USPSTF: Grade I)
Men who have sex with men | Screen at exposed anatomic sites (CDC)

Gonorrhea: Diagnosis & treatment

- **Diagnosis**
  - Nucleic acid amplification tests (NAATs)
    - Urine, vaginal, endocervical, extragenital swabs
  - Culture
    - Ability to conduct antimicrobial susceptibility tests
- **Treatable with antibiotics**
  - Dual therapy: 250 mg ceftriaxone + 1 g Azithromycin
  - Ability to develop resistance

The Emerging Threat of Untreatable Gonococcal Infection

Gail A. Bolan, M.D., P. Frederick Sparling, M.D., and Judith N. Wasserheit, M.D., M.P.H.

It is time to sound the alarm. During the past 3 years, the wily gonococcus has become less susceptible to our last line of antimicrobial defense, threatening our ability to cure gonorrhea and prevent severe sequelae.

Gonorrhea is the second most common sexually transmitted disease in the United States. Control and Prevention (CDC) are limited to third-generation ceftriaxone (0.04% of those in the GISP) had a MIC of ceftriaxone of 0.2% μg per milliliter in the first half of 2011, the proportion of GISP isolates with an elevated ceftriaxone MIC (≥0.125 μg per milliliter) has increased by a factor of 10 since 2006 (from 0.08% to 0.50%).

Gonorrhea Tops List of Scary Superbugs

Gonorrhea is the second most common sexually transmitted disease in the United States. Control and Prevention (CDC) are limited to third-generation ceftriaxone (0.04% of those in the GISP) had a MIC of ceftriaxone of 0.2% μg per milliliter in the first half of 2011, the proportion of GISP isolates with an elevated ceftriaxone MIC (≥0.125 μg per milliliter) has increased by a factor of 10 since 2006 (from 0.08% to 0.50%).

CDC: The rise of antibiotic-resistant gonorrhea “appears imminent”

The STD could soon be impossible to treat

LINDSAY ABRAMS
Combating Antibiotic-Resistant Bacteria (CARB)
Gonorrhea epidemiology in the U.S.
Gonorrhea — Rates of Reported Cases by Year, United States, 1941–2015

1976: 1,013,436 cases
2010: 309,341 cases
2015: 395,216 cases
Gonorrhea — Rates of Reported Cases by Region, United States, 2006–2015
### Gonorrhea — Rates of Reported Cases by Age Group and Sex, United States, 2015

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Rate (per 100,000 population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-14</td>
<td>19.0</td>
</tr>
<tr>
<td>15-19</td>
<td>148.0</td>
</tr>
<tr>
<td>20-24</td>
<td>79.1</td>
</tr>
<tr>
<td>25-29</td>
<td>79.1</td>
</tr>
<tr>
<td>30-34</td>
<td>148.0</td>
</tr>
<tr>
<td>35-39</td>
<td>37.6</td>
</tr>
<tr>
<td>40-44</td>
<td>15.3</td>
</tr>
<tr>
<td>45-54</td>
<td>4.1</td>
</tr>
<tr>
<td>55-64</td>
<td>0.6</td>
</tr>
<tr>
<td>65+</td>
<td>107.2</td>
</tr>
</tbody>
</table>

For Men:
- Total: 140.9
- 10-14: 244.8
- 15-19: 448.8
- 20-24: 275.2
- 25-29: 183.1
- 30-34: 108.8
- 35-39: 71.8
- 40-44: 26.8
- 45-54: 5.1

For Women:
- Total: 442.2
- 10-14: 539.1
- 15-19: 448.8
- 20-24: 275.2
- 25-29: 183.1
- 30-34: 108.8
- 35-39: 71.8
- 40-44: 26.8
- 45-54: 5.1
- 55-64: 0.6
- 65+: 107.2
Gonorrhea — Rates of Reported Cases by State, United States and Outlying Areas, 2015

NOTE: The total rate of reported cases of gonorrhea for the United States and outlying areas (Guam, Puerto Rico, and Virgin Islands) was 122.7 cases per 100,000 population.
Gonorrhea — Rates of Reported Cases by Race/Ethnicity, United States, 2011–2015

* AI/AN = American Indians/Alaska Natives; NHOPI = Native Hawaiian/Other Pacific Islanders.

Gonorrhea – Rates of Reported Cases in the United States and Indiana by Sex, 2007-2016*

*2016 data are preliminary as of 4/7/2017

<table>
<thead>
<tr>
<th>Year</th>
<th>Males</th>
<th>Females</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Dif '07-'16</td>
<td>44.4</td>
<td>-6.0</td>
<td>17.9</td>
</tr>
<tr>
<td>% Dif '15-'16</td>
<td>16.6</td>
<td>8.5</td>
<td>13.1</td>
</tr>
</tbody>
</table>
Gonorrhea – Rates of Reported Cases in the United States and Indiana by Sex, 2007-2016*

*2016 data are preliminary as of 4/7/2017
Gonorrhea: Estimated burden & cost

- 395,000 cases diagnosed and reported in 2015
  - Most diagnosed outside of the STD clinic
- Case reports underestimate burden of disease
  - ~820,000 infections occur annually
- Estimated $162 million in direct medical costs

Antimicrobial resistant gonorrhea in the U.S.
Antimicrobial Resistance (AMR) gonorrhea

- Undermines treatment success
- Heightens risk of complications
- Facilitates transmission
Timeline of Introduction of Antimicrobials and Emergence of Resistance

PPNG = penicillinase-producing *N. gonorrhoeae*
Adapted from: Goire N et al. Molecular approaches to enhance surveillance of gonococcal antimicrobial resistance. Nature Reviews Microbiology 2012
Gonococcal Isolate Surveillance Program (GISP)

- Established in 1986 to monitor trends in *N. gonorrhoeae* susceptibility to antimicrobials
  - Collaboration between CDC, clinical sites, and laboratories
  - Directly inform CDC STD Treatment Guidelines
  - Data disseminated through routine surveillance reports
GISP data collection

- 27 participating STD clinics
- Urethral specimens and epi data obtained from first 25 men with gonococcal urethritis at clinical sites each month
- Isolates are sent to regional laboratories
  - Susceptibility testing conducted by agar dilution
  - Results provided to clinical sites (not for clinical decision making)
- Epi and susceptibility data transmitted to CDC and merged for analysis
- Alert isolates and archive isolates sent to CDC
Current GISP clinical sites
What’s the difference between GISP and K8?

<table>
<thead>
<tr>
<th></th>
<th>GISP</th>
<th>Rapid Detection and Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Four word summary of project</strong></td>
<td>Sentinel surveillance for resistance</td>
<td>Population-level resistance mitigation</td>
</tr>
<tr>
<td><strong>Primary purpose</strong></td>
<td><strong>Surveillance</strong> for antibiotic susceptibility/resistance; monitor trends over time</td>
<td><strong>Rapid identification of outbreaks</strong> for immediate response; inform clinical management of patients</td>
</tr>
<tr>
<td><strong>Number of awardees</strong></td>
<td>27 clinical sites sending specimens</td>
<td>9 awardees, each of whom chose 1 city/county</td>
</tr>
<tr>
<td><strong>Participating clinics/providers</strong></td>
<td>STD Clinics</td>
<td>STD Clinics + non-STD Clinic partners (e.g., Emergency Departments, HIV care)</td>
</tr>
<tr>
<td><strong>Types of specimens sent</strong></td>
<td>Up to 25 urethral specimens each month (per site) from symptomatic men</td>
<td>Any specimens that can be cultured for GC—urethral, vaginal, oropharyngeal, rectal (male and female)</td>
</tr>
<tr>
<td><strong>AST turn-around time</strong></td>
<td>2 months</td>
<td>72 hours</td>
</tr>
</tbody>
</table>

Source: Gonococcal Isolate Surveillance Project (GISP)
Prevalence of QRNG among NG isolates, Gonococcal Isolate Surveillance Project (GISP), United States, 1990–2008
Prevalence of QRNG among NG isolates, Gonococcal Isolate Surveillance Project (GISP), United States, 1990–2008
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Prevalence of QRNG among NG isolates, Gonococcal Isolate Surveillance Project (GISP), United States, 1990–2008

2007 Treatment Guidelines
- Cefixime
- Ceftriaxone
- Ciprofloxacin
- Ofloxacin

Percentage of GISP isolates resistant to ciprofloxacin

U.S.
**Neisseria gonorrhoeae** — Distribution of Isolates with Penicillin, Tetracycline, and/or Ciprofloxacin Resistance, Gonococcal Isolate Surveillance Project (GISP), 2015

![Pie chart showing distribution of Neisseria gonorrhoeae isolates resistant to various antibiotics.](image)

### NOTE:
- **PenR** = penicillinase-producing *Neisseria gonorrhoeae* and chromosomally-mediated penicillin-resistant *N. gonorrhoeae*;
- **TetR** = chromosomally- and plasmid-mediated tetracycline-resistant *N. gonorrhoeae*;
- **QRNG** = quinolone-resistant *N. gonorrhoeae*.

*PenR* = penicillinase-producing *Neisseria gonorrhoeae* and chromosomally-mediated penicillin-resistant *N. gonorrhoeae*; *TetR* = chromosomally- and plasmid-mediated tetracycline-resistant *N. gonorrhoeae*; and *QRNG* = quinolone-resistant *N. gonorrhoeae*. 
*Neisseria gonorrhoeae* — Percentage of Isolates with Elevated Ceftriaxone Minimum Inhibitory Concentrations (MICs) (≥0.125 μg/ml) and Elevated Cefixime MICs (≥0.25 μg/ml), Gonococcal Isolate Surveillance Project (GISP), 2006–2015

Neisseria gonorrhoeae — Distribution of Ceftriaxone and Cefixime Minimum Inhibitory Concentrations (MICs) by Year, Indianapolis Gonococcal Isolate Surveillance Project (GISP), 2011–2015
*Neisseria gonorrhoeae* — Distribution of Ceftriaxone and Cefixime Minimum Inhibitory Concentrations (MICs) by Year, Indianapolis Gonococcal Isolate Surveillance Project (GISP), 2011–2015
Neisseria gonorrhoeae — Percentage of Isolates with Reduced Azithromycin Susceptibility (MIC ≥ 2.0 μg/ml), GISP, 2006–2015

Percentage

0.0
1.0
2.0
3.0
4.0


2.6%
0.2%
Neisseria gonorrhoeae — Distribution of Azithromycin Minimum Inhibitory Concentrations (MICs) by Year, Indianapolis, GISP, 2011–2015
Percentage of Isolates with (A) Reduced Azithromycin Susceptibility and (B) Reduced Ceftriaxone Susceptibility with Other Resistance Phenotypes, 2015

**A**
- **Azithromycin-RS† (n=133)**
- Tetracycline-R
- Penicillin-R
- Ciprofloxacin-R
- Ceftriaxone-RS

**B**
- **Ceftriaxone-RS† (n=14)**
- Tetracycline-R
- Penicillin-R
- Ciprofloxacin-R
- Azithromycin-RS

† Azithromycin-RS=reduced azithromycin susceptibility (MIC ≥2 µg/ml); ceftriaxone-RS=reduced ceftriaxone susceptibility (MIC ≥0.125 µg/ml)

NOTE: Resistance categories are not mutually exclusive
Cluster of *N. gonorrhoeae* isolates with high-level azithromycin resistance AND reduced ceftriaxone susceptibility, April–May, 2016

- High-level azithromycin resistance (MIC $\geq 256 \, \mu g/ml$) in 8 specimens from 7 patients
  - 4 isolates had reduced ceftriaxone susceptibility (MIC $\geq 0.125 \, \mu g/ml$)
  - All were resistant to penicillin, tetracycline, & ciprofloxacin
  - Closely related by genomic analysis
- All cases and 4/9 partners interviewed
  - All had sx resolution or tested negative

Katz A et al. STD Prevention Conference, 2016
DRUG-RESISTANT NEISSERIA GONORRHOEAE

188,600 DRUG-RESISTANT GONORRHEA INFECTIONS
11,480 REDUCED SUSCEPTIBILITY TO CEFTIXIME
3,280 REDUCED SUSCEPTIBILITY TO LEFURAXONE
2,460 REDUCED SUSCEPTIBILITY TO AZITHROMCYCIN

820,000 GONOCOCCAL INFECTIONS PER YEAR

This bacteria is an immediate public-health threat that requires urgent and aggressive action.

THREAT LEVEL: URGENT
Emergence of ceftriaxone-resistant N. gonorrhoeae could impose direct medical costs of over $400 million over the next 10 years.
Antimicrobial resistant gonorrhea beyond our borders
Global Warning Signs

- 1st cephalosporin treatment failure reported in Japan (2001)
  - Additional treatment failures reported throughout Asia and Western Pacific (2002-2007)
  - All reported increasing cephalosporin MICs → *early warning for potential resistance*

- First highly ceftriaxone-resistant strain identified in Japan (2009)
  - Associated with ceftriaxone treatment failure (pharyngeal); ceftriaxone MIC 2 µg/ml, cefixime MIC 8 µg/ml

- Over time, Europe & U.S. have been reporting increasing cephalosporin MICs (2010-2014)
  - Cefixime (oral cephalosporin) treatment failures noted in Europe & Canada

- Second high-level ceftriaxone resistant strain reported in France & Spain (2011)
  - Ceftriaxone MIC 1-2 µg/ml
Countries reporting elevated MICs to cefixime and/or ceftriaxone, 2009-2013

Proportion of *N. gonorrhoeae* resistant to Azithromycin in reported countries, 2009-2013

Systematic AMR GC Surveillance Globally

- Single Country
  - United Kingdom Gonococcal Resistance to Antimicrobial Surveillance (GRASP)
  - Australian Gonococcal Surveillance Programme (AGSP)

- Multi-country
  - European Centre for Disease Prevention and Control (ECDC)
    - Gonococcal Antimicrobial Susceptibility Surveillance in Europe (Euro-GASP)
  - World Health Organization (WHO)
    - Gonococcal Antimicrobial Susceptibility Programme (GASP)
Global AMR GC Surveillance

Similarities
- Collection of demographic and clinical data linked to isolate*
- Standardized lab methodology within each program*
- Routine quality assurance testing
- Trend data published
  - Annually to every other year
- Data inform treatment guidelines

Differences
- Sampling strategy
- Collection of behavioral data
- Lab methodology varies between programs
- Resistance profiles

*Exception: GASP
Enhanced Gonococcal Antimicrobial Surveillance Program (EGASP)

- The Enhanced Gonococcal Antimicrobial Susceptibility Program is a collaboration between WHO and CDC
- Objectives:
  - to improve the quality, comparability, and timeliness of gonococcal antimicrobial susceptibility data by establishing standardized sentinel surveillance for gonococcal susceptibility in selected countries
- Implementation
  - Thailand: late 2015
  - Western Pacific country is next!
Neisseria gonorrhoeae — Distribution of Ceftriaxone and Cefixime Minimum Inhibitory Concentrations (MICs), EGASP Thailand, 11/2015-10/2016 (N=590)

Ceftriaxone

- 98.6% ≤0.016
- 1.5% 0.032
- 0.5% 0.064
- 0.3% 0.125
- 0.2% 0.25
- 0.8% 0.5
- 2.7% 1
- 19.5% 2
- 54.1% 4
- 21.7% 8
- 0% 16
- 0% ≥32

Cefixime

- 98.6% ≤0.016
- 0.8% 0.032
- 0.2% 0.064
- 0.3% 0.125
- 0% 0.25
- 0% 0.5
- 0% 1
- 0% 2
- 0% 4
- 0% 8
- 0% 16
- 0% 32
- 0% 64
- 0% 128
- 0% ≥256
### Early EGASP Data Summary, 11/2015-10/2016

<table>
<thead>
<tr>
<th>Description</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of EGASP specimens collected</td>
<td>1102</td>
<td>-</td>
</tr>
<tr>
<td>Number of EGASP specimens gram stain positive</td>
<td>565</td>
<td>51.3%</td>
</tr>
<tr>
<td>Number of EGASP specimens culture positive (for NG)</td>
<td>591</td>
<td>53.6%</td>
</tr>
<tr>
<td>Number of isolates with Antimicrobial Susceptibility Test (AST) Results</td>
<td>590</td>
<td>99.8%</td>
</tr>
<tr>
<td>Number of isolates contaminated/non-viable</td>
<td>1</td>
<td>0.2%</td>
</tr>
</tbody>
</table>
Gonorrhea is common in the U.S.

- Rates of reported cases are increasing
- Screening and prompt, effective treatment can help prevent sequelae

Resistance is urgent threat

- Dual therapy still highly effective
- Declining cephalosporin and azithromycin susceptibility threatens last recommended gonorrhea treatment
Conclusions (cont)

- National and global AMR GC surveillance is critical
  - Epidemiological and laboratory data help to better understand the populations at highest risk
  - Standardized global surveillance of AMR gonorrhea will help better monitor trends
- New antimicrobials & innovative prevention and control strategies are urgently needed
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