Disclosure

- I do not have any financial interest or affiliation with any organization that would influence the content of this presentation
Objectives

- Understand current trends in *Neisseria gonorrhoeae* antimicrobial susceptibilities

- Comprehend public health and clinical implications of gonococcal cephalosporin susceptibility trends
Overview

- Gonorrhea
- Resistance and treatment
- Surveillance of gonococcal resistance
- Emerging threat of cephalosporin resistance
- Conclusions
Gonorrhea

- One of the oldest known human diseases
  - Named by Galen (2nd century) ~ “flow of semen”

- Caused by *Neisseria gonorrhoeae*

- 2nd most commonly reported notifiable infection

- Can be asymptomatic

- Can cause
  - Pelvic inflammatory disease (PID)
  - Ectopic pregnancy
  - Infertility

- May facilitate HIV transmission
Gonorrhea Rates, United States, 1941–2011

Rate (100,000 population)
Neisseria gonorrhoeae (NG) Treatment

- Prompt antimicrobial treatment limits sequelae, prevents transmission
  - Detection & treatment is cornerstone of NG control

- Antimicrobial resistance
  - Undermines treatment success
  - Heightens risk of complications
  - Facilitates transmission (*by lengthening infectious period*)
Treatment of Gonorrhea in the Pre-Antimicrobial Era

- Patent Medicines
- Intraurethral irrigation
  - Mercurochrome
  - Nitric acid
  - Silver nitrate
- Mechanical removal of strictures
  - Sounds
  - Dilators

Baumann F. Gonorrhea: Its Diagnosis and Treatment. D. Appleton & Co. 1910
Antimicrobial Treatment of Gonorrhea

- **1930s**
  - **Sulfonamide therapy introduced**
    - Prontosil found to be effective
    - *N. gonorrhoeae* rapidly developed resistance within several years (~30% resistance)
Antimicrobial Treatment of Gonorrhea

1930s
- Sulfonamide therapy introduced

1940s
- Penicillin proved effective
  - Becomes treatment of choice
Antimicrobial Treatment of Gonorrhea

- **1930s**
  - Sulfonamide therapy introduced

- **1940s**
  - Penicillin proved effective

- **1970s**
  - Incremental penicillin resistance
    - Penicillin dosage increased
    - Probenecid added to extend half-life
Antimicrobial Treatment of Gonorrhea

- **1930s**: Sulfonamide therapy introduced
- **1940s**: Penicillin proved effective
- **1970s**: Incremental penicillin resistance
- **1980s**: High-level penicillin resistance (penicillinase-producing NG [PPNG])
  - Emerged in SE Asia and West Africa
  - Spread globally
Treatment Options after Emergence of PPNG

- **Spectinomycin**
  - No longer available in US

1980s—new antimicrobials became available

- **Fluoroquinolones**
  - Ciprofloxacin
  - Levofloxacin

- **Third-generation cephalosporins**
  - Ceftriaxone (injectable)
  - Cefixime (oral)
The Gonococcal Isolate Surveillance Project (GISP)

- CDC-supported US sentinel surveillance since 1987
- Monitors trends in *N. gonorrhoeae* susceptibility to antimicrobials

**Methods**

- Urethral isolates obtained from first 25 men per clinical site each month
- Susceptibility testing conducted by regional laboratories
  - Minimum inhibitory concentrations (MICs) by agar dilution
- Confirmatory testing by CDC
- Limited demographic & clinical data
Gonococcal Isolate Surveillance Project — United States, 2012

Source: Gonococcal Isolate Surveillance Project
Measuring Antimicrobial Susceptibility

- **Agar dilution**
  - Grow bacteria on plates with varying antimicrobial concentrations
  - Requires culture
  - Gold standard but labor-intensive (done at reference laboratories)
  - Provides minimum inhibitory concentration (MIC) – lowest antimicrobial concentration that inhibits bacterial growth in lab
    - Low MICs ~ susceptible
    - High MICs ~ resistant

- **Disc diffusion (Kirby-Bauer)**

- **Etest**
Measuring Antimicrobial Susceptibility

- **Agar dilution**
  - Gold standard
  - Labor-intensive
  - Done at reference laboratories
  - Provides minimum inhibitory concentration (MIC) – lowest antimicrobial concentration that inhibits bacterial growth in lab

- **Disc diffusion (Kirby-Bauer)**

- **Etest**
Disc Diffusion (Kirby-Bauer)

Dead bacteria

Live bacteria
Disc Diffusion (Kirby-Bauer)

Results as diameter (in millimeters)

Dead bacteria

Live bacteria
Measuring Antimicrobial Susceptibility

- **Agar dilution**
  - Gold standard
  - Labor-intensive
  - Done at reference laboratories
  - Provides minimum inhibitory concentration (MIC) – lowest antimicrobial concentration that inhibits bacterial growth in lab

- **Disc diffusion (Kirby-Bauer)**

- **Étest**
  - Provides MIC

bioMérieux Clinical Diagnostics

Dead bacteria

Live bacteria
CDC STD Treatment Guidelines, 2002

- Cefixime 400 mg *(oral, single dose)*
- Ceftriaxone 125 mg *(injectable, single dose)*
- Ciprofloxacin 500 mg *(oral, single dose)*
- Ofloxacin 400 mg *(oral, single dose)*
- Levofloxacin 250 mg *(oral, single dose)*

If chlamydia is not ruled out:
- Azithromycin 1 g or
- Doxycycline 100 mg BID x 1 week


GISP, Gonococcal Isolate Surveillance Project, 1990–2007
Resistant isolates have ciprofloxacin MICs ≥1 µg/ml
Ciprofloxacin Resistance in *N. gonorrhoeae*, by Gender of Sex Partner, United States, 1999-2007

GISP, Gonococcal Isolate Surveillance Project, 1990–2007
Resistant isolates have ciprofloxacin MICs ≥1 µg/ml
MSM, men who have sex with men
MSW, men who have sex exclusively with women
CDC STD Treatment Guidelines, 2007

- Cefixime 400 mg po
- Ceftriaxone 125 mg IM
- Ciprofloxacin 500 mg po
- Ofloxacin 400 mg po
- Levofloxacin 250 mg po

& If CT is not ruled out
  - Azithro 1 g or
  - Doxycycline 100 mg BID x 1 week

Cephalosporins are only remaining class
Global Emergence of Resistance to Cephalosporins

- First reported oral cephalosporin treatment failure – Japan (2001)
- Additional treatment failures with oral cephalosporins (east Asia)
- Increasing cephalosporin MICs – *early warning for potential resistance*
  - Japan
  - China
  - Australia
Increasing oral cephalosporin MICs (late 2000s)
- Europe
- Canada

2009 – 1st high-level ceftriaxone resistant isolate (H041) from pharynx of CSW (Japan)
- Cured, H041 has not since been detected

Ceftriaxone-resistant isolates found in MSM in France, Spain
- All were cured

Treatment failures with cefixime among MSM identified in Toronto
Proportion of GISP Isolates with Elevated Cefixime MICs (≥0.25 μg/ml), United States, 2000–2011

Source: Gonococcal Isolate Surveillance Project
Proportion of GISP isolates with Elevated Cefixime MICs (≥0.25 μg/ml) by Region, 2006–2011

Source: Gonococcal Isolate Surveillance Project
Proportion of GISP isolates with Elevated Cefixime MICs (≥0.25 μg/ml) by Gender of Sex Partner, US, 2006–2011

* Preliminary (Jan-June)
MSM = Men who have sex with men; MSW = Men who have sex exclusively with women

Source: Gonococcal Isolate Surveillance Project
Other Resistance in Isolates with Elevated Cefixime MICs, 2011–2012*

* Preliminary Jan-June
PenR=penicillin-resistant; QRNG = quinolone-resistant; TetR = tetracycline-resistant

Source: Gonococcal Isolate Surveillance Project
The chart shows the percentage of isolates with elevated ceftriaxone MICs (≥0.125 µg/ml) from 2008 to 2011.

- **2008**: Preliminary (Jan-June)
- **2009**: 0.2%
- **2010**: 0.4%
- **2011**: 0.8%

*Source: Gonococcal Isolate Surveillance Project*
Proportion of Isolates with Elevated Cefixime MICs ($\geq 0.25 \mu g/ml$), Chicago, 2006–2012*

Cefixime AST not conducted

* Preliminary (Jan-June)

Source: Gonococcal Isolate Surveillance Project
Proportion of Isolates with Elevated Cefixime MICs (≥0.25 μg/ml) by Sex of Sex Partner, Chicago, 2006–2012*

- **MSM** = Men who have sex with men; **MSW** = Men who have sex exclusively with women

* Preliminary (Jan-June)

Source: Gonococcal Isolate Surveillance Project

- MSM n=56
- MSW n=240
- MSM n=56
- MSW n=179
- MSM n=53
- MSW n=71
- MSM n=58
- MSW n=198
- MSM n=39
- MSW n=97
Updated GC Treatment Guidelines, 2012

- **Recommended**
  - Ceftriaxone 250 mg IM **PLUS**
  - Azithro 1 g or Doxycycline

- **Alternatives**
  - Cefixime 400 mg **PLUS** Azithro/Doxy **OR**
  - Azithromycin 2 g

- **PLUS**
  - Test of cure
New Systemic Antibacterial Agents Approved by the FDA, 1983–2007

Number of New Antimicrobial Agents Approved

1983-1987: 16
1988-1992: 14
1993-1997: 10
1998-2002: 6
2003-2007: 4


Source: Gonococcal Isolate Surveillance Project (GISP)
Gonococcus Antimicrobial Susceptibility Testing

Dicker et al. STD 2004;31(5):259-264
Dicker et al. STD 2007; 34(1):41-46
Azithromycin Susceptibility

- In 2011, 0.3% isolates had elevated azithromycin MICs (≥2.0 µg/ml)
  - No clear temporal trends
- Macrolide resistance can emerge rapidly
- Have seen small number with reduced susceptibility/resistance in the US
  - San Diego: cluster of isolates from MSM with MICs 8–16
  - Hawaii: highly azithromycin-resistant infection (MIC > 512)
  - Portland: treatment failure after 2 g monotherapy (MICs 1, 8)

CDC. MMWR 2011
Katz AR et al. CID 2012
Soe O et al STD 2012
Yet, some recent cause for optimism
Recent developments

- No reported treatment failures yet in US
- Strains with elevated cephalosporin MICs do not appear to be more virulent or transmissible
- Heightened awareness
  - Media coverage (2011–present)
  - High level of awareness by public health STD programs
  - Increasing interest by drug developers
- GAIN Act (2012)
  - *N. gonorrhoeae* might be qualifying pathogen
GC Dual Therapy Clinical Trial for Salvage Therapy
(NCT00926796)

- NIAID/NIH and CDC collaboration
- Investigating efficacy of 2 combinations for treatment of uncomplicated urogenital gonorrhea
  - Gentamicin 240 mg IM and Azithromycin 2 g po
  - Gemifloxacin 320 mg po and Azithromycin 2 g po

- Four clinical sites
  - San Francisco, CA
  - Birmingham, AL
  - Pittsburgh, PA
  - Los Angeles, CA

- Enrollment completed; data being analyzed
Proportion of GISP isolates with Elevated Cefixime MICs (≥0.25 μg/ml), 2006–2012*

* Preliminary (Jan-June)

Source: Gonococcal Isolate Surveillance Project
Where do we go from here? (Short-term)

- **Surveillance**
  - GISP
  - Local GC detection & reporting
  - Enhanced local surveillance for GC AMR?
  - Clinician vigilance & reporting

- **Ability of labs to culture for GC**

- **Program preparedness and response**

- **Basic gonorrhea control**

- **Ensure appropriate clinical management**
Where do we go from here? ( Longer-term)

- New antimicrobials or combinations
- New diagnostic approaches
  - Molecular detection of resistance determinants?
  - POC tests?
- Exploration of genome sequencing
- Vaccine?
Conclusions

- Emerging threat of cephalosporin-resistance *N. gonorrhoeae*
- Ceph RNG would severely complicate treatment
- Spread of resistance might be slowed by
  - Aggressive treatment
  - Prompt programmatic response
  - Driving down GC morbidity
- Local efforts are critical
- Preparedness now can enhance response later
- New treatment options urgently needed
Acknowledgements

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- Alesia Harvey
- Gail Bolan
- Kevin Pettus
- Samera Bowers
- Steve Shapiro

GISP Clinical Sites
- Englewood and Lakeview clinics

GISP PIs
- Ned Hook
- Olusegun (S.O.) Soge
- King Holmes
- Carlos del Rio
- Susan Harrington
- Susan Tanksley & Grace Kubin
Resources

www.cdc.gov/std

- CDC Cephalosporin-Resistant *Neisseria gonorrhoeae* Public Health Response Plan
- Updated gonorrhea treatment guidelines (MMWR, 2012)
- STD Surveillance Report, 2011 (contains aggregate GISP data)
- GISP home page (www.cdc.gov/std/gisp)
  - Annual site-specific profiles
For more information please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA 30333
Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov  Web: http://www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
### Percentage of Isolates with Elevated MICs or Resistance by Sex of Sex Partner, 2005–2010

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<thead>
<tr>
<th>Antibiotic</th>
<th>MSM n=8,117</th>
<th>MSW n=26,483</th>
<th>$\rho$</th>
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<tbody>
<tr>
<td>Ceftriaxone*</td>
<td>0.4</td>
<td>0.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cefixime**</td>
<td>1.7</td>
<td>0.2</td>
<td>&lt;0.01</td>
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<tr>
<td>Azithromycin†</td>
<td>0.9</td>
<td>0.2</td>
<td>&lt;0.01</td>
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<tr>
<td>Tetracycline†</td>
<td>37.5</td>
<td>13.3</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* $\geq 0.125 \, \mu g/ml$

** $\geq 0.25 \, \mu g/ml$

† $\geq 2.0 \, \mu g/ml$

Kirkcaldy RD et al. Annals Internal Medicine 2013