The Threat of Multidrug Resistant *Neisseria gonorrhoeae*

Peel Public Health Symposium
Sex, Drugs, and....

Vanessa Allen, MD MPH
October 16, 2012
The threat of multidrug resistant gonorrhea

"We're sitting on the edge of a worldwide crisis," says Manjula Lusti-Narasimhan, of WHO's department of reproductive health and research. "There's a general complacency around sexually transmitted infections in general, and this doesn't have the same political or social pressure as HIV. That's because gonorrhea has been so easily curable so far, but in the future, that won't be the case."

http://www.usnews.com/news/articles/2012/06/06/world-health-organization-warns-gonorrhea-could-join-hiv-as-uncurable-
Three Primary Challenges for the Treatment of *N. gonorrhoeae*

1) **Antibiotic resistance**
   - Imminent risk of losing cephalosporins (cefixime and ceftriaxone)
   - This is the last reliable class of antibiotics for the treatment of *N. gonorrhoeae*

2) **Change in diagnostic testing for *N. gonorrhoeae* from culture to molecular testing**
   - Otherwise called nucleic acid amplification testing (NAAT)
   - In 2010, 24.8% were diagnosed by culture at PHO (74.2% NAAT)
   - No susceptibility data available for non-culture specimens

3) **Asymptomatic reservoirs of *N. gonorrhoeae* infection**
   - Pharyngeal infection particularly difficult to treat with antibiotics
   - Prompting a recommendation for dual therapy when pharyngeal infection is being considered in CDC 2010 guidelines
ANTIBIOTIC RESISTANT
NEISSERIA GONORRHOEAE
History of antimicrobial resistance in *Neisseria gonorrhoeae*

1930: Crude extract of *Penicillium notatum* used to treat gonococcal ophthalmia in infant

1936: Sulfonamides introduced for the treatment of gonorrhea

1943: Penicillin first used to treat gonococcal urethritis

1945: A third of NG resistant to sulfa. Penicillin is the drug of choice (50,000 units)

1948: >90% resistant to sulfa. Penicillin is the drug of choice (50,000 units)

1950: >90% resistant to sulfa

1952: Tetracycline introduced

1952-1953: Spectinomycin developed for the treatment of NG

1960: Spectinomycin introduced for the treatment of NG

1960: >90% resistant to penicillin

1967: Spectinomycin resistance (pen S & later in 1981 in pen R)

1970: Increasing penicillin resistance (altered PBPs), dose recommended now 4.8 million units and probenicid

1972: Increasing penicillin resistance described in Hawaii (QRNG)

1976: Plasmid-mediated tetracycline resistance acquired

1980: Plasmid-mediated tetracycline resistance described

1984: Large outbreak of penicillin resistance NG in North Carolina, penicillin no longer recommended

1985: Plasmid-mediated tetracycline resistance acquired

1986: Plasmid-mediated tetracycline resistance acquired

1991: Quinolone resistance described in Hawaii (QRNG)

1995: Seattle outbreak of QRNG

1999: Rx failure with oral cephalosporin in Japan

2001: Rx failure with oral cephalosporin in Japan

2002-2007: Series of US recommendations regarding when ciprofloxacin cannot be used empirically

2009: First high level ceftriaxone resistant strain of NG in Japan

Sequential loss of each class of antimicrobials as effective therapy for *Neisseria gonorrhoeae*
Proclivity of *Neisseria gonorrhoeae* to develop antibiotic resistance

1) Transformation with *Neisseria* species
2) Conjugation
3) Mutations and internal recombination

Followed by:
- Selection of drug resistant clones when exposed to sub-therapeutic concentrations of antibiotics

- Cephalosporin resistance in *N. gonorrhoeae*
  - Mosaic *penA* that encodes for penicillin binding protein (PBP2)

Reduced Susceptibility of *N. gonorrhoeae* to Cephalosporins in Ontario

Reduced susceptibility to cefixime defined as $\geq 0.125$ mg/L was 8.7% among unique patient isolates in Ontario from May 1, 2010 to April 30, 2011.

*2010 isolates are still being tested, data is preliminary

Percentages were calculated using the total number of viable Ontario isolates (resistant and susceptible isolates) tested by NML as the denominator.
What is the appropriate route and dose of cephalosporin for the treatment of *N. gonorrhoeae*?

Table 3. Simulation of $T_{>MIC}$ values (h) for various cefixime and ceftriaxone regimens based on mean pharmacokinetic parameter values

<table>
<thead>
<tr>
<th>MIC mg/L</th>
<th>Cefixime po 200 mg</th>
<th>Cefixime po 400 mg</th>
<th>Cefixime po 2×200 mg, 6 h apart</th>
<th>Cefixime po 2×400 mg 6 h apart</th>
<th>Ceftriaxone im 125 mg</th>
<th>Ceftriaxone im 250 mg</th>
<th>Ceftriaxone im 500 mg</th>
<th>Ceftriaxone im 1 g</th>
<th>Ceftriaxone im 2 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.008</td>
<td>29.2</td>
<td>32.6</td>
<td>36.5</td>
<td>39.9</td>
<td>50.3</td>
<td>58.7</td>
<td>67.2</td>
<td>75.6</td>
<td>84.1</td>
</tr>
<tr>
<td>0.015</td>
<td>25.8</td>
<td>29.2</td>
<td>33.1</td>
<td>36.5</td>
<td>41.8</td>
<td>50.3</td>
<td>58.7</td>
<td>67.2</td>
<td>75.6</td>
</tr>
<tr>
<td>0.03</td>
<td>22.3</td>
<td>25.7</td>
<td>29.5</td>
<td>32.9</td>
<td>32.9</td>
<td>41.4</td>
<td>49.9</td>
<td>58.3</td>
<td>65.8</td>
</tr>
<tr>
<td>0.06</td>
<td>18.8</td>
<td>22.2</td>
<td>26.1</td>
<td>29.5</td>
<td>24.3</td>
<td>32.8</td>
<td>41.3</td>
<td>49.8</td>
<td>58.2</td>
</tr>
<tr>
<td>0.125</td>
<td>15.3</td>
<td>18.8</td>
<td>22.6</td>
<td>26.1</td>
<td>15.6</td>
<td>24.3</td>
<td>32.8</td>
<td>41.3</td>
<td>49.8</td>
</tr>
<tr>
<td>0.25</td>
<td>11.7</td>
<td>15.3</td>
<td>19.0</td>
<td>22.6</td>
<td>6.6</td>
<td>15.6</td>
<td>24.3</td>
<td>32.8</td>
<td>41.3</td>
</tr>
<tr>
<td>0.5</td>
<td>7.8</td>
<td>11.7</td>
<td>15.2</td>
<td>19.0</td>
<td>0.0</td>
<td>6.6</td>
<td>15.6</td>
<td>24.3</td>
<td>32.8</td>
</tr>
<tr>
<td>1</td>
<td>1.4</td>
<td>7.8</td>
<td>7.1</td>
<td>15.2</td>
<td>0.0</td>
<td>0.0</td>
<td>6.6</td>
<td>15.6</td>
<td>24.3</td>
</tr>
<tr>
<td>2</td>
<td>0.0</td>
<td>1.4</td>
<td>0.0</td>
<td>7.1</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>6.6</td>
<td>15.6</td>
</tr>
<tr>
<td>4</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>6.6</td>
<td>15.6</td>
</tr>
</tbody>
</table>

Dark shading <10 h above MIC, light shading 10–20 h above MIC, no shading >20 h above MIC.

Chisolm SA et al. JAC Aug 2010
Clinical Failures seen in Europe...

Rapid Communications

Two cases of verified clinical failures using internationally recommended first-line cefixime for gonorrhoea treatment, Norway, 2010

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4. Division of Infectious Disease Control, Norwegian Institute of Public Health, Oslo
5. Faculty of Medicine, University of Oslo, Oslo, Norway

Citation style for this article:

Nine clinical failures in Ontario in a single clinic in Ontario that performs test of cure

Eurosurveillance, Volume 16, Issue 14, 07 April 2011

Rapid communications

GONORRHOEA TREATMENT FAILURES TO CEFIXIME AND AZITHROMYCIN IN ENGLAND, 2010

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1. Sexually Transmitted Bacteria Reference Laboratory, Health Protection Agency, London, United Kingdom
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3. New Croft Centre, Newcastle upon Tyne, United Kingdom
4. Health Protection Agency North East, Newcastle General Hospital, Newcastle upon Tyne, United Kingdom


Date of submission: 14 March 2011

Successful treatment of gonorrhoea is the mainstay of public health control. Cefixime and ceftriaxone, highly active third generation cephalosporins, are today the recommended first-line agents in most countries and azithromycin is a second-line agent. However, there is increasing evidence of decreasing susceptibility and emergence of therapeutic failures. In this report two cases of clinical failure to cefixime are described, one of which additionally shows failure to azithromycin and selection of a less susceptible strain during treatment.
# International gonorrhea treatment recommendations

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Previous recommendations</th>
<th>Year</th>
<th>Most recent recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Canada</strong></td>
<td>2008</td>
<td>cefixime 400 mg PO</td>
<td>Dec 2011</td>
<td>ceftriaxone 250 mg IM or cefixime po 800 mg PO and azithromycin 1 gm PO</td>
</tr>
<tr>
<td>USA</td>
<td>Nov 2010</td>
<td>ceftriaxone 250 mg IM or cefixime 400 mg PO and azithromycin 1 gm PO or doxycycline 100 mg PO bid X 7 days</td>
<td>Aug 2012</td>
<td>ceftriaxone 250 mg IM and azithromycin 1 gm PO or doxycycline 100 mg PO bid X 7 days</td>
</tr>
<tr>
<td><strong>UK</strong></td>
<td>2005</td>
<td>ceftriaxone 250mg IM or cefixime 400mg PO or spectinomycin* 2g</td>
<td>June 2011</td>
<td>ceftriaxone 500 mg IM and azithromycin 1gm PO</td>
</tr>
<tr>
<td>World Health</td>
<td>2003</td>
<td>ciprofloxacin 500 mg PO or cefixime 400 mg PO or ceftriaxone 125 mg IM or spectinomycin 2 gms IM</td>
<td>2005</td>
<td>cefixime 400 mg PO or ceftriaxone 125 mg IM</td>
</tr>
<tr>
<td>Organization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Japan</strong></td>
<td>-</td>
<td></td>
<td>2006</td>
<td>ceftriaxone 1 gm IV</td>
</tr>
</tbody>
</table>
CHANGE IN DIAGNOSTIC METHODS FOR NEISSERIA GONORRHOEAE
Impact of Changing Diagnostic Methods

Decreased submissions for culture of *N. gonorrhoeae*

- Introduction of Nucleic Acid Amplification (NAAT)
- NAAT available as a duplex (with Chlamydia) and monoplex tests
  - Recommendation in the US to screen all women aged 15-26 for asymptomatic infection
- Ease of collection and transportation/storage requirements
  - Urine and vaginal collection sites in addition to urethral and cervical
- Increased sensitivity (with concurrent loss of specificity)
  - ~95% for NAAT vs 85-95% for culture
- But, antimicrobial testing is not possible for NAAT specimens
Lack of routine test of cure

- Public Health Agency of Canada recommends test of cure in the following circumstances

  **Follow-up**
  - Repeat screening of individuals with gonorrhea after 6 months is recommended.

  - Follow-up testing by culture is essential if any of the following exist:
    - Quinolones were administered for treatment and there was no previous antimicrobial testing done.
    - Treatment failure has occurred previously.
    - Antimicrobial resistance to therapy is documented.
    - Compliance is uncertain.
    - There is re-exposure to an untreated partner.
    - There is concern over a false-positive non-culture test result.
    - Infection occurs during pregnancy.
    - PID or disseminated gonococcal infection is diagnosed.
    - Patient is a child.

- Recommended on a routine basis in 2011 UK guidelines
- For alternative treatments in CDC guidelines (2012)


CDC MMWR Aug 9, 2012 [http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6131a3.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6131a3.htm)
PHARYNGEAL RESERVOIRS OF NEISSERIA GONORRHOEAE
Anatomical reservoirs of *Neisseria gonorrhoeae*

~33% of all *N. gonorrhoeae* infections would be missed if tested only urethral site.
Persistence of *N. gonorrhoeae* in pharyngeal tract despite treatment

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pathogen</th>
<th>Antibiotic therapy</th>
<th>TOC 1</th>
<th>TOC 2</th>
<th>Different susceptibility on TOC</th>
<th>Concurrent <em>N. gonorrhoeae</em> or <em>C. trachomatis</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>N. gonorrhoeae</em></td>
<td>Cefixime, 400 mg</td>
<td>+</td>
<td>ND</td>
<td>No</td>
<td>Urethral <em>C. trachomatis</em></td>
</tr>
<tr>
<td>2b</td>
<td><em>N. gonorrhoeae</em></td>
<td>Cefixime, 400 mg</td>
<td>+</td>
<td>–</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td><em>N. gonorrhoeae</em></td>
<td>Cefixime, 400 mg</td>
<td>+</td>
<td>–</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td><em>N. gonorrhoeae</em></td>
<td>Ofloxacin, 400 mg</td>
<td>+</td>
<td>–</td>
<td>No</td>
<td>Rectal <em>N. gonorrhoeae</em> and <em>C. trachomatis</em></td>
</tr>
<tr>
<td>5</td>
<td><em>N. gonorrhoeae</em></td>
<td>Cefixime, 400 mg</td>
<td>+</td>
<td>ND</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td><em>N. gonorrhoeae</em></td>
<td>Cefixime, 800 mg</td>
<td>+</td>
<td>–</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td><em>N. gonorrhoeae</em></td>
<td>Cefixime, 800 mg</td>
<td>+</td>
<td>–</td>
<td>No</td>
<td>Urethral <em>C. trachomatis</em></td>
</tr>
<tr>
<td>8</td>
<td><em>N. gonorrhoeae</em></td>
<td>Cefixime, 800 mg</td>
<td>+</td>
<td>–</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>9b</td>
<td><em>N. gonorrhoeae</em></td>
<td>Cefixime, 400 mg</td>
<td>+</td>
<td>–</td>
<td>No</td>
<td>Rectal <em>N. gonorrhoeae</em></td>
</tr>
<tr>
<td>10</td>
<td><em>N. gonorrhoeae</em></td>
<td>Cefixime, 400 mg</td>
<td>+</td>
<td>+</td>
<td>NAAT only</td>
<td>Rectal <em>N. gonorrhoeae</em>, urethral <em>N. gonorrhoeae</em></td>
</tr>
<tr>
<td>11</td>
<td><em>N. gonorrhoeae</em></td>
<td>Cefixime, 400 mg</td>
<td>+</td>
<td>–</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td><em>C. trachomatis</em></td>
<td>Azithromycin, 1 g</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td><em>C. trachomatis</em></td>
<td>Azithromycin, 1 g</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>No</td>
</tr>
<tr>
<td>14</td>
<td><em>C. trachomatis</em></td>
<td>Doxycycline, 100 mg</td>
<td>+</td>
<td>+</td>
<td>NAAT only</td>
<td>Rectal <em>N. gonorrhoeae</em>, urethral <em>N. gonorrhoeae, rectal C. trachomatis</em></td>
</tr>
</tbody>
</table>

**NOTE.** –, negative; +, positive; NAAT, nucleic acid amplification test; ND, second course of treatment and second TOC not performed.

a Azithromycin (1 g) given empirically.
b Typing with *N. gonorrhoeae* multiantigen sequence typing.

Ota et al. CID 2009
Rapid Communications

Ceftriaxone treatment failure of pharyngeal gonorrhoea verified by international recommendations, Sweden, July 2010

M Unemo (magnus.unemo@orebro.se)
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2. Department of Dermatology and Venereology, Kårlsjukhuset, Skövde, Sweden

### Table
Details of verified clinical failure of one case of Neisseria gonorrhoeae pharyngeal infection using internationally recommended first-line ceftriaxone treatment of gonorrhoea, Sweden, 2010

<table>
<thead>
<tr>
<th>Type of healthcare clinic (day of presentation)</th>
<th>Symptoms (signs)</th>
<th>Diagnostic test (type of sample)</th>
<th>MIC (mg/L)</th>
<th>NG-MAST&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Treatment (day administered)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary (1)</td>
<td>Urethral discharge, dysuria, pharyngeal pain (inflammation in urethra and pharynx)</td>
<td>PCR (urine)</td>
<td>NA</td>
<td>NA</td>
<td>Amoxicillin Two daily doses of 750 mg, for 10 days, oral administration (first administered on day 1)</td>
</tr>
<tr>
<td>STI (12)</td>
<td>(Inflammation in pharynx)</td>
<td>Culture (pharyngeal)</td>
<td>Microscopy and culture (urothral) PCR (urine)</td>
<td>2</td>
<td>0.125</td>
</tr>
<tr>
<td>STI (36)</td>
<td>(Inflammation in pharynx)</td>
<td>Culture (pharyngeal)</td>
<td>NA</td>
<td>2</td>
<td>0.125</td>
</tr>
<tr>
<td>STI (50)</td>
<td>(Inflammation in pharynx)</td>
<td>Culture (pharyngeal)</td>
<td>NA</td>
<td>2</td>
<td>0.75</td>
</tr>
<tr>
<td>STI (85 and 92)</td>
<td>(−)</td>
<td>Culture (pharyngeal)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
WHERE ARE WE NOW?
Incidence of gonorrhea in Ontario 2001-2011

24.8

31.1
Current initiatives to address MDR *N. gonorrhoeae*

- **International (2012)**
  - World Health Organization action plan
  - CDC action plan
- **National**
  - Revision of guidelines for prevention, surveillance, diagnosis, and treatment
  - PHAC letter Dec 2011
  - CDC’s revision August 2012
- **Provincial**
  - Introduction of Ontario guidelines
  - Ontario STI sentinel surveillance program
Conclusions

• Persistent issue of antibiotic resistance now threatening the effectiveness of the cephalosporins, the last available class of antimicrobials

• Clinical failures reported, and preliminary data supports association with MICs now considered to be susceptible by CLSI

• Shift in diagnostic methodologies impairs the identification of individuals at risk of clinical failure

• Pharyngeal sites may be an important reservoir for ongoing transmission of resistant strains

• New strategies needed for effective treatment Now and in the future
THANK YOU.
DO YOU HAVE ANY QUESTIONS?