
Public Health Ontario Webinar
May 22, 2013

Vanessa G. Allen MD MPH
On behalf of the gonorrhea guidelines working group
Overview

• Brief overview of *Neisseria gonorrhoeae*
  • Ontario epidemiology
  • Dwindling antibiotic options for treatment

• Guidelines for Testing and Treatment of Gonorrhea in Ontario, 2013

• Future directions
  • Parallel initiatives
  • Future approaches to the prevention and treatment of gonorrhea

• Conclusions
BRIEF OVERVIEW
OF NEISSERIA GONORRHOEAE
Gonorrhea Infections

- Etiologic agent: *Neisseria gonorrhoeae*
  - Gram-negative intracellular diplococcus
- Infects mucous membranes
- Incubation period ~ 1 – 14 days
Modes of Transmission

• Sexual activity
  • oral, vaginal, anal
• Vertical transmission

• Common sites of infection
  • Men: urethra, pharynx and rectum
  • Women: endocervix, pharynx and rectum
  • Neonates: conjunctiva

Risk Factors

• Youth <25 years of age with multiple partners
• Men who have sex with men
• Those who have had contact with a person with proven infection or a compatible syndrome
• Sex workers and their sexual partners
• Street-involved youth
• Previous gonorrhea or other STIs
Clinical Presentation

<table>
<thead>
<tr>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>vaginal discharge</td>
<td>acute urethral discomfort</td>
</tr>
<tr>
<td>dysuria</td>
<td>urethral discharge</td>
</tr>
<tr>
<td>abnormal vaginal bleeding</td>
<td>dysuria</td>
</tr>
<tr>
<td>lower abdominal pain</td>
<td>urethral itch</td>
</tr>
<tr>
<td>pain and/or bleeding during intercourse</td>
<td>testicular pain, redness, or swelling</td>
</tr>
<tr>
<td>rectal pain and discharge (if proctitis is present)</td>
<td>rectal pain and discharge (if proctitis is present)</td>
</tr>
<tr>
<td>Over 50% of cervical infection are asymptomatic</td>
<td>Over 10-15% of urethral infections are asymptomatic</td>
</tr>
</tbody>
</table>
Sequelae

• Females:
  • Pelvic inflammatory disease
  • Ectopic pregnancy
  • Chronic pelvic pain
  • Infertility
  • Arthritis
  • Disseminated gonococcal infection

• Males:
  • Epididymo-orchitis
  • Urethral strictures
  • Arthritis
  • Infertility
  • Disseminated gonococcal infection

Rates of sequelae from the pre-antibiotic era ranged from 10-24%

Sequelae are now rare
Increased Risk of HIV Transmission and Acquisition Secondary to Gonorrhea Infection

- Transmission increased by 2-5X
  - Both increased infectiousness and susceptibility
  - Increased HIV shedding with gonorrhea
    - Inflammatory mediators and target cell recruitment caused by STIs
    - OR 3.2 (Moss GB et al JID 1995), and prevalence decreased after treatment of gonorrhea
  - Increased susceptibility
    - Postulated to be due to increased local recruitment of CD4 cells

Wasserheit, J. Sexually Transmitted Diseases. 26(10), November 1999
Reported incidence of gonorrhea by year: Ontario, 2003-2012

Source: Ontario Ministry of Health and Long-Term Care, integrated Public Health Information System (iPHIS) database, extracted by Public Health Ontario March 6, 2013


Thanks to Michael Whelan
PublicHealthOntario.ca
Gonorrhea by age group among females: Ontario, 2008-2012

Source: Ontario Ministry of Health and Long-Term Care, integrated Public Health Information System (iPHIS) database, extracted by Public Health Ontario

March 6, 2013
PublicHealthOntario.ca
Gonorrhea by age group among males: Ontario, 2008-2012

Source: Ontario Ministry of Health and Long-Term Care, integrated Public Health Information System (iPHIS) database, extracted by Public Health Ontario

March 6, 2013

PublicHealthOntario.ca
Repeat gonorrhea infections

• Between 2008 and 2012, 11.2% (2,196/19,673) of cases reported at least one prior infection within the same 5-year period

<table>
<thead>
<tr>
<th>Time to repeat infection</th>
<th>Number of repeat infections</th>
<th>Percentage</th>
<th>Cumulative percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to &lt;3 months</td>
<td>359</td>
<td>16.35%</td>
<td>16.35%</td>
</tr>
<tr>
<td>3 months to &lt;6 months</td>
<td>449</td>
<td>20.45%</td>
<td>36.79%</td>
</tr>
<tr>
<td>6 month to &lt; 9 months</td>
<td>287</td>
<td>13.07%</td>
<td>49.86%</td>
</tr>
<tr>
<td>9 months to &lt;1 year</td>
<td>247</td>
<td>11.25%</td>
<td>61.11%</td>
</tr>
<tr>
<td>1 year to &lt;1.5 years</td>
<td>289</td>
<td>13.16%</td>
<td>74.27%</td>
</tr>
<tr>
<td>1.5 years or more</td>
<td>565</td>
<td>25.73%</td>
<td>100.00%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2196</strong></td>
<td><strong>100.00%</strong></td>
<td><strong>N/A</strong></td>
</tr>
</tbody>
</table>

Source: Ontario Ministry of Health and Long-Term Care, integrated Public Health Information System (iPHIS) database, extracted by Public Health Ontario March 12, 2013
DILEMMA OF DWINDLING ANTIBIOTIC OPTIONS FOR GONORRHEA

CDC Trends in Reportable Sexually Transmitted Diseases in the United States, 2007
http://www.cdc.gov/std/stats07/trends.htm
...tenfold decrease in gonorrhea incidence over the last 15 years in Canada. .... the goal of eliminating locally transmitted infection of *N. gonorrhoeae* by the year 2010 appears attainable.


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

**1938:** Penicillin first used to treat gonococcal urethritis

**1943:** Penicillin is the drug of choice (50,000 units)

**1945:** A third of *N. gonorrhoeae* resistant to sulfonamides

**1946:** Crude extract of *Penicillium notatum* used to treat gonococcal ophthalmia in infant

**1948:** Penicillin introduced

**1952:** Tetracycline introduced

**1953:** Tetracycline resistance (pen S & later in pen R)

**1955:** Spectinomycin introduced

**1956:** Spectinomycin mediated penicillin resistance described

**1959:** Spectinomycin resistance described

**1960:** Spectinomycin introduced for the treatment of *NG*

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

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

**1972:** Increasing penicillin resistance (altered PBPs), dose recommended now 4.8 million units and probenecid

**1976:** Plasmid mediated tetracycline resistance acquired

**1980:** Ceftriaxone resistance described

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

**1985:** Plasmid mediated tetracycline resistance acquired

**1988:** Quinolone resistance described in Hawaii (QRNG)

**1990:** Quinolone resistance described in Hawaii (QRNG)

**1991:** Quinolone resistance described in Hawaii (QRNG)

**1995:** Seattle outbreak of QRNG

**1996:** Increasing ciprofloxacin resistance (altered PBPs), dose recommended now 500 mg or 2 g (oral)

**1998:** Increasing ciprofloxacin resistance (altered PBPs), dose recommended now 500 mg or 2 g (oral)

**2001:** Rx failure with oral ceftriaxone in Japan

**2003:** RX failure with oral ceftriaxone in Japan

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

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

**2010:** First high level ceftriaxone resistant strain of *NG* in Japan

Sequential loss of each class of antimicrobials as effective therapy for *Neisseria gonorrhoeae*

PublicHealthOntario.ca
<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Previous recommendations</th>
<th>Date</th>
<th>Most recent recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>2008</td>
<td>cefixime 400 mg PO</td>
<td>Dec 2011</td>
<td>ceftriaxone 250 mg intramuscularly* (IM) or cefixime po 800 mg orally (PO) and azithromycin 1 gm PO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>Nov 2010</td>
<td>ceftriaxone 250 mg IM or cefixime 400 mg PO</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></td>
<td></td>
<td>and azithromycin 1 gm PO or doxycycline 100 mg PO bid X 7 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>2005</td>
<td>ceftriaxone 250mg IM or cefixime 400mg PO or spectinomycin 2g IM</td>
<td>June 2011</td>
<td>ceftriaxone 500 mg IM and azithromycin 1 gm PO</td>
</tr>
<tr>
<td>European Union</td>
<td>2009</td>
<td>ceftriaxone 250 mg IM** or cefixime 400 mg PO or spectinomycin 2 gms IM</td>
<td>2012</td>
<td>ceftriaxone 500 mg IM and azithromycin 2 gm PO</td>
</tr>
<tr>
<td>Japan</td>
<td>-</td>
<td></td>
<td>2006</td>
<td>ceftriaxone 1 gm IV</td>
</tr>
</tbody>
</table>
Proclivity of *Neisseria gonorrhoeae* to develop antibiotic resistance

- Multiple mechanisms for the development of resistance
  - Transformation with other *Neisseria* species
  - Conjugation
  - Mutations
  - Internal recombination

- Primary mechanism of cephalosporin resistance in *N. gonorrhoeae*
  - Mosaic *penA* that encodes for penicillin binding protein (PBP2)

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

"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."
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.
Gonorrhea by health unit of residence: Ontario, 2012

Source: Ontario Ministry of Health and Long-Term Care, integrated Public Health Information System (iPHIS) database, extracted by Public Health Ontario March 6, 2013
The Appropriate Route and Dose of Cephalosporin for the Treatment of *N. gonorrhoeae*

Table 3. Simulation of $t_{\text{MIC}}$ 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</th>
<th>Ceftriaxone im</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>200 mg</td>
<td>400 mg</td>
</tr>
<tr>
<td>0.008</td>
<td>29.2</td>
<td>32.6</td>
</tr>
<tr>
<td>0.015</td>
<td>25.8</td>
<td>29.2</td>
</tr>
<tr>
<td>0.03</td>
<td>22.3</td>
<td>25.7</td>
</tr>
<tr>
<td>0.06</td>
<td>18.8</td>
<td>22.2</td>
</tr>
<tr>
<td>0.125</td>
<td>15.3</td>
<td>18.8</td>
</tr>
<tr>
<td>0.25</td>
<td>11.7</td>
<td>15.3</td>
</tr>
<tr>
<td>0.5</td>
<td>7.8</td>
<td>11.7</td>
</tr>
<tr>
<td>1</td>
<td>1.4</td>
<td>7.8</td>
</tr>
<tr>
<td>2</td>
<td>0.0</td>
<td>1.4</td>
</tr>
<tr>
<td>4</td>
<td>0.0</td>
<td>0.0</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
Case Reports of Treatment Failure Associated with the Cephalosporins

Rapid Communications

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

M Unemo (magnus.unemo@orebro.se), D Golparian, G Syversen, D Vestheim, H Mol.
1. Swedish Reference Laboratory for Pathogenic Neisseria, Department of Laboratory Medicine, Microbiology, Örebro University Hospital, Örebro, Sweden
2. Department of Microbiology, Oslo University Hospital, Ullevål, Oslo, Norway
3. Olafsklinikken, Oslo University Hospital, Oslo, Norway
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:

Eurosurveillance, Volume 16, Issue 14, 07 April 2011

Rapid communications

GONORRHOEA TREATMENT FAILURES TO CEFIXIME AND AZITHROMYCIN IN ENGLAND, 2010
CA Ison (catherine.ison@hpa.org.uk), J Hussey, KN Sankar, J Evans, S Alexander
1. Sexually Transmitted Bacteria Reference Laboratory, Health Protection Agency, London, United Kingdom
2. Carlton Street Clinic, Blyth, Northumberland, United Kingdom
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.
Study of Clinical Impact of Rising Minimum Inhibitory Concentrations

Objective

- To assess the risk of clinical treatment failure of *N. gonorrhoeae* infections associated with the use of cefixime

Study Methods

- Retrospective cohort study
- May 1, 2010, and April 30, 2011
- Culture-positive *N. gonorrhoeae* infections
- A single STI clinic that routinely performs test of cure
- Treated with cefixime as recommended by Canadian (PHAC) Guidelines

Main Outcome Measure

- Cefixime treatment failure
291 Patients at study clinic had a positive culture for *Neisseria gonorrhoeae*

158 Did not return for test-of-cure visit
31 Originally had isolates with reduced susceptibility to cefixime

133 Returned for test-of-cure visit
28 Originally had isolates with reduced susceptibility to cefixime

120 Did not have a positive culture for *N gonorrhoeae* at test-of-cure visit

13 Had a positive culture for *N gonorrhoeae* at test-of-cure visit

4 Excluded (possible reexposure; originally had isolates with reduced susceptibility to cefixime)

9 Had treatment failure
7 Had isolates that originally had reduced susceptibility to cefixime
2 Had isolates that originally were susceptible to cefixime
Results

• Rate of clinical treatment failure was 6.77%
  • 95% CI, 3.14%-12.45%; 9/133

• Rate of clinical failure associated with a cefixime MIC of 0.12 μg/mL or greater was 25.0%
  • 95% CI, 10.69%-44.87%; 7/28
  • The relative risk of failure with a cefixime MIC of 0.12 μg/mL or greater was 13.13 (95% CI, 2.88-59.72; $P < .001$)
Urethral, pharyngeal and rectal sites of infection

- MSM, MSW, women
- Two cases initially treated with cefixime 800 mg
ADDITIONAL CONSIDERATIONS
The Adoption of Molecular Diagnostics for the Diagnosis of Gonorrhea

• Introduction of Nucleic Acid Amplification (NAAT)
• NAAT available as a duplex test (with chlamydia)
• 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
Gonorrhea Resistance to the Cephalosporins has not been Defined in North America: May fail therapy without lab warning of “resistance”
Is Neisseria gonorrhoeae Initiating a Future Era of Untreatable Gonorrhea?: Detailed Characterization of the First Strain with High-Level Resistance to Ceftriaxone

Makoto Ohnishi,1 Daniel Golparian,2 Ken Shimuta,1 Takeshi Saika,3 Shinji Hoshina,4 Kazuhiro Iwasaku,5 Shu-ichi Nakayama,1 Jo Kitawaki,5 and Magnus Unemo2

- Named “H041”
- From a 31 commercial sex worker
- Treated with ceftriaxone 1 gm, repeat + test considered reinfection

Concern about Untreatable Gonorrhea
GUIDELINES FOR TESTING AND TREATMENT OF GONORRHEA IN ONTARIO, 2013
• Complementary to other aspects of the PHAC STI Guidelines

• Focused on the testing, treatment, and follow-up of uncomplicated gonorrhea

• Recommendations are based on:
  • Ontario surveillance data of *N. gonorrhoeae*
  • Pharmacokinetic/pharmacodynamics modeling studies
  • Clinical efficacy data

• Recommended treatment approach is similar to the CDC, UK, EU, aimed to
  • Effectively treat gonorrhea given current trends of antimicrobial resistance
  • Delay progression of antimicrobial resistance in Ontario
Gonorrhea guidelines


Public Health Ontario's Guidelines for Testing and Treatment of Gonorrhea in Ontario provide the evidence, rationale, and recommendations to effectively diagnose and treat persons infected with N. gonorrhoea. The recommendations are based on current scientific evidence, Ontario epidemiology and antimicrobial susceptibility profiles of N. gonorrhoea, and available laboratory testing methods in Ontario. The Guidelines cover:

- Laboratory testing recommendations, including when to perform a Gram stain, bacterial culture or nucleic acid amplification testing (NAAT);
- Treatment recommendations for uncomplicated urogenital, rectal and pharyngeal N. gonorrhoea infections; and
- Recommendations for follow-up of N. gonorrhoea infections, including public health reporting, testing and treatment of sexual contacts, indications for test of cure and follow-up testing.

Gonorrhea is the second most commonly reported sexually transmitted infection in Ontario and North America. Left untreated, gonorrhea can lead to a host of complications including pelvic inflammatory disease, infertility, and blood stream infections. Cephalosporins, the last available class of antibiotics recommended for the treatment of gonorrhea, have been failing worldwide. In response to Ontario and global clinical failures, the new guidelines recommend an injectable drug (ceftriaxone), in combination with a pill (azithromycin).

- Frequently Asked Questions
- Quick Reference Guide: a two page document that highlights the testing, screening and testing recommendations in addition to symptoms and risk factors and reporting obligations.
- Online Training Module: an interactive tool to help health care professionals become more familiar with the guidelines.
- Press Release

Ontario Ministry of Health and Long-Term Care Resources:

- Patient Information Sheet
- Sexual Health and Sexually Transmitted Infections Prevention and Control Protocol, 2013

http://www.oahpp.ca/resources/gonorrhea-guideline.html
1) Quick guide
2) Interactive tool
3) Q & A
4) Complete document
5) Patient information sheet
# Testing Recommendations

<table>
<thead>
<tr>
<th>Laboratory Diagnosis</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All sexually active persons who have signs and symptoms of <em>N. gonorrhoeae</em> infection should be tested. Consideration should also be given to laboratory screening of asymptomatic persons who have risk factors for <em>N. gonorrhoeae</em>.</strong></td>
<td></td>
</tr>
<tr>
<td>The recommended screening method for asymptomatic persons is urine NAAT for males and cervical or urine NAAT for females.</td>
<td></td>
</tr>
<tr>
<td>The recommended method for testing symptomatic persons is urethral culture for males and cervical swab culture for females or urine NAAT for males and cervical NAAT for females.</td>
<td></td>
</tr>
</tbody>
</table>
Testing Recommendations for Symptomatic Patients

Gonorrhea Testing Recommendations
(for individuals presenting with symptoms and risk factors consistent with gonorrhea)

Symptomatic patients
Choose specimen site based on patient gender and history
(Include test for chlamydia)

Males
1. Urethral culture (preferred)
   or
2. Urine NAAT (if culture not locally available or acute urethral discharge)

Females
1. Cervical culture (preferred)
   or
2. Cervical NAAT

Additional rectal / pharyngeal specimens

Culture
Screening Recommendations for Asymptomatic Patients

Gonorrhea Screening Recommendations
(for individuals presenting with risk factors for gonorrhea, but without associated symptoms)

Asymptomatic patients
Choose specimen site based on patient gender and history
(Including test for chlamydia)

- **Males**
  - Urine

- **Females**
  - Urine or cervical swab

- **Additional rectal / pharyngeal specimens**
  - (indicated for all men who have sex with men, with unprotected sexual exposure at these sites)

- **NAAT**

- **Culture**
Treatment Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
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</thead>
<tbody>
<tr>
<td><strong>Treatment of Gonorrhea</strong></td>
</tr>
</tbody>
</table>

Treatment of gonorrhea with two antimicrobials is recommended on the theoretical basis that this may offer synergistic therapy, potentially improving treatment efficacy and delaying the emergence and spread of resistance in *N. gonorrhoeae*.
Treatment Recommendations and Follow-up for Gonorrhea

Positive Indications for treatment
including empiric therapy

1. First-line therapy
(recommended)
   - Ceftriaxone 250 mg IM
   - Azithromycin 1 g PO

2. Second-line therapy
(use only in cases of allergy or if first-line therapy is unavailable)
   - Cefixime 400 mg PO + azithromycin 1 g PO
     OR
   - Spectinomycin 2 g IM + azithromycin 1 g PO
     OR
   - Azithromycin 2 g PO

Has the following occurred?
- Pharyngeal/rectal infection?
- Pregnancy?
- Potential reduced susceptibility?
- Potential treatment failure?

YES

Test of cure
- Culture ≥ 4 days post treatment (preferred)
- NAAT ≥ 2 weeks post-treatment (alternative)

NO

Rescreen
- 6 months post-treatment for potential repeat infection
Follow-up Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
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<tbody>
<tr>
<td><strong>Follow-Up</strong></td>
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<tr>
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<tr>
<td></td>
</tr>
</tbody>
</table>
Recommendations for Gonorrhea Test of Cure

• First-line treatment is not used

• Those at high risk of clinical failure
  • Pharyngeal and rectal infection
  • Suspected or confirmed gonorrhea clinical treatment failure or sexual contact of a suspected or confirmed clinical failure
  • Infection with *N. gonorrhoeae* with reduced susceptibility to the cephalosporins (defined as an ceftriaxone or cefixime minimum inhibitory concentration of ≥ 0.12 μg/mL based on culture results) or sexual contact of person infected with *N. gonorrhoeae* isolate with reduced susceptibility to the cephalosporins
  • Treatment failure has occurred previously
ONGOING SURVEILLANCE OF MDR-GONORRHEA IN ONTARIO
Reporting to Health Units & PHO

- Gonorrhea treatment failures are defined as treated individuals with confirmed gonorrhea and a positive test of cure (NAAT or culture) in the absence of risk of reinfection
- Health care professionals should report any suspected or confirmed gonorrhea treatment failures to their local health unit
- The local health unit should notify PHO of the suspected or confirmed treatment failure as soon as possible to discuss any further clinical and/or public health action that may be required
Enhanced Surveillance of Treatment Failures

- Health units should work with the responsible health care practitioner to complete the PHO enhanced surveillance form for gonorrhea clinical failures.
Concerns Regarding Decreased Reliance on Culture

- Poor surveillance capacity for detecting resistance trends
- Inability to guide antibiotic therapy for clinical care
- Reduced specificity of NAAT testing
  - Leading to risk of false positives
STI Ontario Surveillance (SOS)

- A prospective surveillance system
- SOS will be completed in collaboration with 6 health unit partners based on location, population distribution, and priority populations
- SOS will initially focus on effectively monitoring the resistance patterns of *N. gonorrhoeae*
- These partners will work with PHO through increased use of culture and enhanced surveillance
Objective:

To provide aggregated and up-to-date PHO laboratory data of STIs to Boards of Health and STI clinics

Can assess rates of resistance in different HUs, percent positivity, and testing practices

Supplemented by guidelines and educational materials
ALTERNATIVE APPROACHES TO THE PREVENTION AND TREATMENT
Other Antibiotic Options for the Treatment of Gonorrhea

Parallel Increase in Ceftriaxone Resistance

Fig. 1. Ceftriaxone trends of minimum inhibitory concentrations (MICs) for Ontario Neisseria gonorrhoeae isolates tested between 2005 and 2010*

*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.
New Antimicrobials for the Treatment of Gonorrhea

- More potent drug of existing or relating classes
  - Fluoroquinolones
  - Macrolides/ fluoroketolide

- Promising 2-16 X more potent
- First step mutations in circulating strains of *N. gonorrhoeae* due to exposure to earlier classes
Effectiveness of gentamicin for gonorrhoea treatment: systematic review and meta-analysis

Deborah Dowell, Robert D Kirkcaldy

Table 2   Efficacy of single-dose gentamicin for the treatment of gonococcal urethritis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Population</th>
<th>Gentamicin dosage</th>
<th>Outcome</th>
<th>Weight in pooled analysis</th>
<th>Efficacy of gentamicin (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daly et al(^{15})</td>
<td>1997</td>
<td>Single-arm case series</td>
<td>107 Men with gonococcal urethritis in Malawi</td>
<td>240 mg IM</td>
<td>Culture on post-treatment day 7</td>
<td>27.4%</td>
<td>90.7% (84.6 to 96.8%)</td>
</tr>
<tr>
<td>Hira et al(^{16})</td>
<td>1985</td>
<td>Controlled trial, with treatment assigned to alternate consecutive patients</td>
<td>220 Men with gonococcal urethritis in Zambia</td>
<td>280 mg IM</td>
<td>Culture on post-treatment day 14</td>
<td>65.4%</td>
<td>91.4% (87.7 to 95.1%)</td>
</tr>
<tr>
<td>Lule et al(^{14})</td>
<td>1994</td>
<td>Randomised controlled trial</td>
<td>40 Men with gonococcal urethritis in Malawi</td>
<td>240 mg IM</td>
<td>Culture on post-treatment day 8–10</td>
<td>7.2%</td>
<td>95.0% (88.3% to 100.0%)</td>
</tr>
<tr>
<td>Pooled inverse weighted averages of included studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100%</td>
<td>90.7% (88.1%–94.0%)</td>
</tr>
</tbody>
</table>

IM, intramuscular.
TABLE 1. MIC using the Etest method and zone sizes with the calibrated dichotomous sensitivity disc diffusion method of *Neisseria gonorrhoeae* H041 to various antimicrobials

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Class</th>
<th>MIC Etest result in µg/ml (agar dilution result), interpretation&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>CDS (mm)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G</td>
<td>β-Lactams, penicillins</td>
<td>4, R&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td>Ampicillin</td>
<td></td>
<td>2</td>
<td>ND</td>
</tr>
<tr>
<td>Amdinocillin</td>
<td></td>
<td>&gt;256</td>
<td>ND</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td></td>
<td>0.25</td>
<td>ND</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>β-Lactam, monobactam</td>
<td>128</td>
<td>ND</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>β-Lactams, cephalosporins</td>
<td>16, R&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ND</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td></td>
<td>3</td>
<td>ND</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td></td>
<td>16, R&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ND</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td></td>
<td>8, R&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>ND</td>
</tr>
<tr>
<td>Cefixime</td>
<td></td>
<td>8 (8), R&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>ND</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td></td>
<td>4 (2), R&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>1</td>
</tr>
<tr>
<td>Cefepine</td>
<td></td>
<td>16, R&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ND</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>β-Lactams, carbapenemenes</td>
<td>0.064</td>
<td>ND</td>
</tr>
<tr>
<td>Meropenem</td>
<td></td>
<td>0.125</td>
<td>ND</td>
</tr>
<tr>
<td>Imipenem</td>
<td></td>
<td>2</td>
<td>ND</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Fluoroquinolones</td>
<td>&gt;32, R&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>1</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td></td>
<td>&gt;32</td>
<td>ND</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td></td>
<td>6</td>
<td>ND</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Macrolides</td>
<td>1, R&lt;sup&gt;b&lt;/sup&gt;</td>
<td>ND</td>
</tr>
<tr>
<td>Erythromycin</td>
<td></td>
<td>2</td>
<td>ND</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Aminoglycosides</td>
<td>4</td>
<td>ND</td>
</tr>
<tr>
<td>Kanamycin</td>
<td></td>
<td>16</td>
<td>ND</td>
</tr>
<tr>
<td>Tobramycin</td>
<td></td>
<td>6</td>
<td>ND</td>
</tr>
<tr>
<td>Spectinomycin</td>
<td>Aminocyclitol</td>
<td>16, S&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>9</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Tetracycline</td>
<td>4, R&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>Glycylcycline</td>
<td>0.5</td>
<td>ND</td>
</tr>
<tr>
<td>Trimetoprim-sulfamethoxazole</td>
<td>Folic acid antagonists</td>
<td>1</td>
<td>ND</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td></td>
<td>4</td>
<td>ND</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td></td>
<td>4</td>
<td>ND</td>
</tr>
<tr>
<td>Rifampin</td>
<td></td>
<td>0.25</td>
<td>ND</td>
</tr>
</tbody>
</table>
Ertapenem for the Treatment of Gonorrhea

Activity of Ertapenem against *N. gonorrhoea*

IG 1 MIC (micrograms per milliliter) distribution of ertapenem and ceftriaxone for clinical *Neisseria gonorrhoeae* isolates ($n = 257$) and *N. gonorrhoeae* international reference strains ($n = 17$).

Unemo M et al AAC 2012
Principles of Treating Sexually Transmitted Infections

The basic criteria for treating STIs may no longer be feasible for the treatment of gonorrhea

Combined Therapy

• 3 conflicting in vitro study of the synergy

• (cephalosporin and azithromycin)
  • Benefit
    • Furuya Ret al JIC 2006
    • Furuya R et al JIC 2013
  • No benefit
    • Pereira R et al JAC 2013

• Two studies supporting value of cephalosporin + azithromycin therapy for the treatment of pharyngeal gonorrhea infections
  • Sathia et al Int J of STD and AIDS 2007
  • Barbee LA et al CID 2013 (RR 3.98)
Synergistic Therapy for Pharyngeal Gonorrhea

Table 1  Pharyngeal clearance rates and linear regression analysis with cefixime and ceftriaxone

<table>
<thead>
<tr>
<th>Antibiotic used</th>
<th>No. of patients with TOC</th>
<th>No. with negative TOC result (%)</th>
<th>P value (95% confidence intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefixime alone</td>
<td>16</td>
<td>14 (87.6)</td>
<td>0.61 (−0.148 to 0.087)</td>
</tr>
<tr>
<td>Cefixime+doxycycline</td>
<td>15</td>
<td>11 (73.3)</td>
<td>0.015 (−0.397 to −0.044)</td>
</tr>
<tr>
<td>Cefixime+azithromycin</td>
<td>24</td>
<td>24 (100)</td>
<td>0.030 (0.018–0.335)</td>
</tr>
<tr>
<td>Ceftriaxone alone</td>
<td>17</td>
<td>15 (88.2)</td>
<td>1.0 (−0.123 to 0.123)</td>
</tr>
<tr>
<td>Ceftriaxone+doxycycline</td>
<td>11</td>
<td>10 (90.9)</td>
<td>1.0 (−0.223 to 0.223)</td>
</tr>
<tr>
<td>Ceftriaxone+azithromycin</td>
<td>5</td>
<td>5 (100)</td>
<td>0.458 (−0.184 to 0.398)</td>
</tr>
</tbody>
</table>

TOC=test of cure; Bold values indicate statistical significance
Molecular Detection of Antibiotic Resistance in Gonorrhea


Note

One-step PCR for the identification of multiple antimicrobial resistance in Neisseria gonorrhoeae

Ratana Lawung a, Rungrot Cherdtrakulkiat a, Angkana Charoenwatanachokchai b, Sunanta Nabu a, Wanvisa Suksaluk a, Virapon Prachayasittikul a,∗

a Department of Clinical Microbiology, Faculty of Medical Technology, Mahidol University, Bangkok 10700, Thailand
b Thai Bureau of AIDS, TB and STD, Department of Communicable Disease Control, Ministry of Public Health, Bangkok, Thailand
Neisseria gonorrhoeae Vaccines

• Initially explored in the early 1900’s, then again in the 1970s with little success

• Given initial promise of *N. meningitidis* serogroup B
  • New efforts for “reverse vaccinology”
CONCLUSIONS
Conclusions

• Persistent issue of antibiotic resistance in *Neisseria gonorrhoeae*
  • now threatening the effectiveness of the last available class of antimicrobials for the treatment of gonorrhea

• New guidelines for the diagnosis and treatment of gonorrhea in Ontario
  • Key to effective treatment in Ontario
  • Secondary goal is delay of ongoing resistance

• Alternative approaches to the prevention and treatment are needed
Thanks to the many collaborators, including:

- **Ontario Task Group for drug resistant NG**
  - Public Health Units
  - MOHLTC
  - Sexual Transmitted Infections Clinics

- **PHO**
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  - Dr. Colin Lee
  - Jennifer Pritchard
  - Emily Karas
  - Michael Whelan

- **Hassle Free Clinic**
  - Leo Mitterni
  - Jerry Juzkiw
  - Dr. Ed Lee
  - Clinic staff

- **PHO Laboratories**
  - Staff in STI and susceptibility laboratories
  - Dr. Roberto Melano
  - Christine Seah
  - Stephen Perusini
  - Krystal Siebert
  - Dr. Virginie Braun
  - Dr. Anu Rebbapragada
  - Lynn Towns
  - Heather Siebert
  - Stephen Lo
  - Prasad Rawte
  - Shirley Brown
  - Anne Maki
  - Dr. Don Low
THANK YOU.

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