ANTIMICROBIAL RESISTANCE AMONG BACTERIAL STIs

Presented by
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Edvard Munch - The scream (1893)
### Bacterial STIs

- **Neisseria gonorrhoeae**
  - Disease Burden: +++
  - AMR Threat: ++++

- **Treponema pallidum**
  - Disease Burden: +
  - AMR Threat: +/-

- **Mycoplasma genitalium**
  - Disease Burden: ++
  - AMR Threat: +++

- **Haemophilus ducreyi**
  - Disease Burden: +/-
  - AMR Threat: +/-

- **Chlamydia trachomatis**
  - Disease Burden: ++++
  - AMR Threat: -
Neisseria gonorrhoeae
History of Treatment & Development of Drug Resistance

*Neisseria gonorrhoeae*

Numbers relate to years that an antibiotic was in use before resistance emerged.
Penicillin for Gonorrhoea - 1943
Chromosomally-Mediated Penicillin Resistance

- Initially, only 72 mg of penicillin was required for treatment
- By mid 1950s, reports of decreased susceptibility to penicillin
- Chromosomal resistance reported in 1958

\[
\text{pen A mutations} + \text{mtr mutations} + \text{penB mutations} = 120\times \text{increase in minimum inhibitory concentration}
\]

- Lower affinity of penicillin for penicillin-binding protein 2
- Increased activity of the MtrCDE efflux pump
- Reduced entry of penicillin across outer membrane
Penicilllinase-Producing Neisseria gonorrhoeae (PPNG)

W.H.O. ACTS TO CURB A NEW STRAIN OF V.D.

By LAWRENCE K. ALTMAN Special to The New York Times

New York Times - 9 Jan 1977

Courtesy of J. Zenilman

W.H.O. ACTS TO CURB A NEW STRAIN OF V.D.

Labs to Begin Tests To Detect Type of Gonorrhea That Resists Penicillin

By LAWRENCE K. ALTMAN Special to The New York Times

GENEVA, Jan. 8—In an urgent step to prevent the development of a major international health problem, the World Health Organization has asked laboratories throughout the world to begin tests to detect a new penicillin-resistant strain of gonorrhea.

Already, the new type of venereal disease has infected Americans in at least 15 states and people in 10 other countries, and it threatens to become the dominant type among the millions of cases of gonorrhea that occur each year throughout the world.

The volume of air travel throughout the world and the limited surveillance for this organism to date means every area of the world must view this as a real or potential problem," the World Health Organization said in a statement sent to health officials in 150 countries that are members of the organization, and to thousands of scientists.

New York Times - 9 Jan 1977

Courtesy of J. Zenilman

- PPNG isolates first detected in 1976
- Two β-lactamase encoding plasmid strains: ‘Asian’ (USA) and ‘African’ (UK)


Tetracycline Resistant Gonococci

- Plasmid-mediated resistance (TRNG, Tet MIC > 10 mg/L) appeared in the Netherlands in 1985 and was reported from USA in 1986
- Dutch and US TRNG strains had different phenotypes
- Tetracycline resistance is unacceptably high at the global level

Data from Johannesburg for 210 *N. gonorrhoeae* isolates surveyed in 2008

- Dutch plasmid
- American plasmid
Spectinomycin Resistant Gonococci

- Spectinomycin used to treat PPNG in Korea from 1981
- Resistance rapidly emerged due to a single point mutation (C1192U) in 16S rRNA
- Transmission of spectinomycin resistant strains was linked to female sex work
**Quinolone Resistant *Neisseria gonorrhoeae* (QRNG)**

- Fluoroquinolones were introduced as single dose agents to treat gonorrhoea in the 1980s.

- Clinical failure of single dose 250mg ciprofloxacin was first reported in London in 1990 – failures with the 500mg dose soon followed.

- Resistance in *N. gonorrhoeae* is associated with point mutations resulting in amino acid changes in:
  
  a) the A subunit (*GyrA*) of the DNA gyrase  
  b) the *parC*-encoded subunit of topoisomerase IV
Quinolone Resistant *Neisseria gonorrhoeae*

WHO Western Pacific Region, 1998-2004

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>PPNG</td>
<td>1.1%</td>
<td>0.7%</td>
<td>0.5%</td>
</tr>
<tr>
<td>TRNG (MIC ≥ 16mg/l)</td>
<td>2.2%</td>
<td>0.7%</td>
<td>0.5%</td>
</tr>
<tr>
<td>CMRNG Pen (MIC ≥ 2mg/l)</td>
<td>2.2%</td>
<td>59.3%</td>
<td>73.3%</td>
</tr>
<tr>
<td>CMRNG Tet (MIC ≥ 2mg/l)</td>
<td>11.0%</td>
<td>53.7%</td>
<td>68.8%</td>
</tr>
<tr>
<td>QRNG Levofloxacin (MIC ≥ 1mg/l)</td>
<td>27.5%</td>
<td>53.3%</td>
<td>78.3%</td>
</tr>
<tr>
<td>Cefixime decreased susceptibility (MIC ≥ 0.5mg/l)</td>
<td>0%</td>
<td>26.0%</td>
<td>30.3%</td>
</tr>
<tr>
<td>Ceftriaxone decreased susceptibility (MIC ≥ 0.5mg/l)</td>
<td>0%</td>
<td>0%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Spectinomycin resistance (MIC ≥ 128mg/l)</td>
<td>0%</td>
<td>0.7%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Reduced Cephalosporin Susceptibility in Gonococci is Associated with Mosaic penA Genes

- penA mutations produce structural changes to penicillin binding protein (PBP2) in most gonococci with decreased cephalosporin susceptibility

- Some regions within these mosaic genes show homology to the penA genes of commensal Neisseria spp. & N. meningitidis

Mutations (blue dots) in the penA gene decrease inactivation of penicillin-binding protein 2, the primary mechanism underlying reduced susceptibility.

Other Mechanisms of Cephalosporin Resistance in Neisseria gonorrhoeae

• **penA** point mutations reduce susceptibility in isolates with non-mosaic **penA** genes, including A501V/A501T, which are close to the KTG active-site motif of PBP-2

Other mechanisms:

• Mutations affecting the **MtrCDE** efflux pump

• **penB** mutations in PorB1b (major porin)

• **ponA** mutation resulting in an altered PBP-1
Prevalence of Decreased Susceptibility to Extended Spectrum Cephalosporins in Asia-Pacific Countries, 2010

WHO WPR and SEAR Regional Surveillance

N = 9,282 N. gonorrhoeae isolates (7,024 validated by WHO EQA)
Emergence of Extensively Drug Resistant Neisseria gonorrhoeae (XDR-NG) in Central Japan, 2009

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*

H041 strain
Emergence and Transmission of XDR-NG in MSM

High-Level Cefixime- and Ceftriaxone-Resistant *Neisseria gonorrhoeae* in France: Novel penA Mosaic Allele in a Successful International Clone Causes Treatment Failure

Magnus Unemo,* Daniel Golparian,* Robert Nicholas,* Makoto Ohnishi,* Anne Gallay,† and Patrice Sednaoui*  
WHO Collaborating Centre for Gonorrhoea and Other STIs, Department of Laboratory Medicine, Microbiology, Örebro University Hospital, Örebro, Sweden; Department of Pharmacology, University of North Carolina, Chapel Hill, North Carolina, US-PH, National Institute of Infectious Diseases, Tokyo, Japan; Institut de Veille Sanitaire, Saint-Maurice, France; and Institut Alfred Fournier, Centre National de Références des Gonocoques, Paris, France

Molecular characterization of two high-level ceftriaxone-resistant *Neisseria gonorrhoeae* isolates detected in Catalonia, Spain

Jordi Cámara1, Judit Serra2, Josefin Ayats1, Teresa Bastida3, Dolors Carneric-Pont4, Antonia Andreu2 and Carmen Ardanuy1*  
1Microbiology Department, Hospital Universitari de Bellvitge-Universitat de Barcelona-IDIBELL, L’Hospitalet de Llobregat, Barcelona, Spain; 2Microbiology Department, Hospital Universitari Vall d’Hebron, Barcelona, Spain; 3Microbiology Department, ‘Esperit Sant’ Regional Hospital, Santa Coloma de Gramenet, Spain; 4Centre d’Estudis Epidemiològics sobre les Infeccions de Transmissió Sexual i Sida de Catalunya (CEEISCAT), Institut Català d’Oncologia, Badalona, Barcelona, Spain
MICROORGANISMS WITH A THREAT LEVEL OF URGENT

Clostridium difficile
Carbapenem-resistant Enterobacteriaceae
Drug-resistant Neisseria gonorrhoeae

These bacteria are immediate public health threats that require urgent and aggressive action.
Treponema pallidum
Erythromycin Resistance in *T. pallidum*

- Stamm and Bergen amplified a 692-bp region in the 23S rRNA gene of *T. pallidum* and *T. pertenue* strains.
- A point mutation (A2058G*) was present in both 23S rRNA genes of *T. pallidum* street strain 14, obtained from a patient who had failed therapy with erythromycin.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Strain</th>
<th>23S rRNA sequence in region of nucleotide position 2058*</th>
<th>Erythromycin susceptibility</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>T. pallidum</em></td>
<td>Nichols</td>
<td>TAGTTAGACGGAAGACCCCA</td>
<td>S</td>
<td>-</td>
</tr>
<tr>
<td><em>T. pallidum</em></td>
<td>Street strain 14</td>
<td>TAGTTAGACGGAAGACCCCA</td>
<td>R</td>
<td>A → G</td>
</tr>
<tr>
<td><em>T. pertenue</em></td>
<td>Gauthier</td>
<td>TAGTTAGACGGAAGACCCCA</td>
<td>S</td>
<td>-</td>
</tr>
</tbody>
</table>

* E.coli numbering
Macrolide Resistance: Rising Prevalence

• In a survey of 18 historical *T. pallidum* isolates collected between 1912-1987, only the Street 14 strain had the A2058G mutation.

• A study of 58 syphilis isolates (blood, 54; CSF, 16) cultured in rabbits and collected in the USA between 2001-2005 demonstrated that macrolide resistance increased over time.

• Risk of having a resistant strain was higher among those receiving macrolides in the previous year (RR 2.2; 95% CI, 1.1-4.4; p = 0.02).

• Similar mutations have subsequently been detected in *T. pallidum* DNA samples from syphilitic patients in other countries, e.g. Ireland, UK, Canada and Australia.
Spiramycin Resistance in *T. pallidum*

- Spiramycin, a 16-member lactone ring macrolide, was previously shown to be effective against the Street 14 strain.

- More recently, a A2059G mutation in the 23S rRNA gene was reported in a *T. pallidum* strain from a man with secondary syphilis, who failed treatment with spiramycin in the Czech Republic.

- Similar A2059G mutations have been reported from London in further cases of secondary syphilis in MSM.

Tipple C et al., Sex. Transm. Infect. 2011;87:486-488;
Low Prevalence of *T. pallidum* Macrolide Resistance in Early Syphilis in Southern Africa

**Madagascar:**

- Multi-centre Phase III RCT to assess the efficacy of single-dose oral azithromycin (2 g) vs. single-dose i.m. benzathine penicillin (2.4 MU)

- 0/141 (0%) *T. pallidum* +ve samples had the A2058G mutation

**South Africa/Lesotho:**

- A2058G mutations were detected in 1/100 (1%) *T. pallidum* +ve samples from Southern Africa

- No A2059 mutations detected
Mycoplasma genitalium
**M. genitalium: Azithromycin vs. Doxycycline**

- **Eradication rates reported from Norway and Sweden:**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Eradication Rate</th>
<th>Sample Size</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin 1g stat.</td>
<td>85% in 39 men</td>
<td>[95% CI 69-94]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>88% in 17 women</td>
<td>[95% CI 64-99]</td>
<td></td>
</tr>
<tr>
<td>Doxycycline x 9 days</td>
<td>17% in 76 men</td>
<td>[95% CI 9-27]</td>
<td></td>
</tr>
<tr>
<td>(200mg d1, 100mg d2-8)</td>
<td>37% in 27 women</td>
<td>[95% CI 19-58]</td>
<td></td>
</tr>
<tr>
<td>Azithromycin x 5 days</td>
<td>96% in 47 men</td>
<td>[95% CI 85-99]</td>
<td></td>
</tr>
<tr>
<td>(500mg d1, 250mg d2-5)</td>
<td>100% in 6 women</td>
<td>Nos. too small</td>
<td></td>
</tr>
<tr>
<td>Doxycycline x 15 days</td>
<td>66% in 3 men</td>
<td>Nos. too small</td>
<td></td>
</tr>
<tr>
<td>(100mg 12-hrly x 15d)</td>
<td>100% in 1 woman</td>
<td>No. too small</td>
<td></td>
</tr>
</tbody>
</table>

- **Prolonged azithromycin should be considered first-line therapy for M. genitalium infection - doxycycline is not appropriate treatment**
Macrolide Resistant *Mycoplasma genitalium*

- Increasing rates of treatment failure with the azithromycin 1g single-dose regimen used to treat NGU and chlamydial infections – now failures seen with the 1.5g 5 day course

- Key mutations in 23S rRNA gene at positions 2071 and 2072 (2058 and 2059, *E. coli* numbering)

- Main driver is suboptimal macrolide dosage

- The role of socio-epidemiological factors, e.g. importation of antimicrobial resistant *M. genitalium* strains or their transmission within defined sexual networks, requires further research
Moxifloxacin Resistant Mycoplasma genitalium

• Moxifloxacin 400 mg o.d. for 10 days is recommended for azithromycin-resistant M. genitalium infections

• Tagg et al. screened DNA from 186 M. genitalium positive specimens:
  o 43% of initial samples had 23S rRNA gene mutations
  o 15% of initial samples had gyrA/parC mutations

• Couldwell et al. reported the first cases of clinical and microbiological treatment failure

• Pristinamycin 1g 6-hrly x 10 days is used as salvage therapy

Couldwell DL et al., Int. J. STD AIDS 2013;24:822-828
Haemophilus ducreyi
Antimicrobial Resistance in *Haemophilus ducreyi*

**Comparison of the In Vitro Activities of Various Parenteral and Oral Antimicrobial Agents Against *Haemophilus ducreyi***

KENNETH E. ALDRIDGE, * CATHY

Department of Medicine, Louisiana State University Health science Center


table 1. In vitro activities of various antimicrobial agents against *haemophilus ducreyi*.

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>24 h</th>
<th>48 h</th>
<th>90%</th>
<th>% Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>≤0.12</td>
<td>≤0.12</td>
<td>≤0.12</td>
<td>100</td>
</tr>
<tr>
<td>Penicillin</td>
<td>≤0.12</td>
<td>≤0.12</td>
<td>≤0.12</td>
<td>100</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>≤0.12</td>
<td>≤0.12</td>
<td>≤0.12</td>
<td>100</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>≤0.12</td>
<td>≤0.12</td>
<td>≤0.12</td>
<td>100</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>≤0.25</td>
<td>4</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.25</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>100</td>
</tr>
</tbody>
</table>

**Ampicillin, penicillin, erythromycin, and clindamycin** and 90% of isolates tested, respectively. * MICs which are considered susceptible. These values are based on the manufacturer’s recommendations (2) or those of the National Committee for Clinical Laboratory Standards (9). * Susceptibility rates 24 h/48 h. A single value indicates no change in the susceptibility rate from 24 to 48 h.

No published AMR data for *H. ducreyi* for >20 years!
Aetiological Surveillance of Genital Ulcers
Johannesburg, South Africa (2007-2013)

Prevalence (%)
Chlamydia trachomatis and Antimicrobial Resistance

• Repeat or persistent chlamydial infection occurs in 10%-15% of treated women — what is the role of antimicrobial resistance?

• Potential for C. trachomatis to develop resistance has not been well studied - lack of a standardised in vitro susceptibility assay

• The correlation between in vitro susceptibility results and testing and clinical outcome is unknown

• Heterotypic resistance is observed in C. trachomatis BUT failure to isolate clinical strains that exhibit stable (homotypic) resistance to macrolides or tetracyclines

• In vitro genetically created fluoroquinolone- and rifampicin-resistant variants have been described

Wang S et al., J. Infect.. Dis. 2005;191:917-923
Conclusions

• Antimicrobial resistance in STIs is worsening with the added threat of untreatable *N. gonorrhoeae* and *M. genitalium* in the future

• The Asia-Pacific region has historically been an epicentre for the emergence and dissemination of antimicrobial resistant STIs

• Core groups (MSM, sex workers) have been implicated in the emergence/transmission of antimicrobial resistant STIs

• The early detection/treatment of STIs in core group members should be a crucial component of STI control programmes

• This requires accessible, acceptable and high quality STI services for sex workers, MSM and other key populations
Imagine a World of Untreatable STIs

Edvard Munch
The scream (1893)