Emergence et impact clinique de la résistance aux antibiotiques chez *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, les mycoplasmes

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WHO 2012: 357 million new cases for curable non viral STIs in adults

- **Chlamydia** 131 million
- **Gonorrhea** 78 million
- **Syphilis** 5.6 million

**Emerging STI pathogen:** *Mycoplasma genitalium*, exceedingly prevalent

**Emergence of antimicrobial resistance (AMR)** in these bacterial STIs → reduced treatment options and STIs control!

**Focus on bacterial STIs:** *C. trachomatis, M. genitalium* and *N. gonorrhoeae*
**Chlamydia trachomatis**

- **Obligate intracellular bacterium**
- **Recommended treatment** *(WHO guidelines 2016, IUSTI Europe 2015, MMWR Recommend Rep 2015)*
  - Uncomplicated urogenital infections
    - **1st-line:** azithromycin 1g orally in a single dose or doxycycline 100 mg orally twice daily for 7 days
  - Alternative regimens: tetracycline or erythromycin or fluoroquinolone (ofloxacin or levofloxacin)
  - Rectal infections
    - doxycycline 100 mg orally twice daily for 7 days
  - Lymphogranuloma venereum (LGV)
    - doxycycline 100 mg twice daily for 21 days
Chlamydia trachomatis

- Acquired AMR in patients: very rare
  - Macrolide resistance described among 4 C. trachomatis clinical strains
  - No tetracycline resistance described among C. trachomatis clinical strains but resistance described in a porcine species
  - No fluoroquinolone resistance described among C. trachomatis clinical strains but in vitro-resistant mutants selected after exposition to subinhibitory concentrations of FQs

Chlamydia trachomatis

- Clinical failure in 10% patients
  - In vivo evidence of chlamydial persistence (aberrant forms) -> failure to respond to antibiotic treatment
  - Heterotypic resistance described in C. trachomatis (1-10% population expressed resistance): slower growth, entry into a stress response
  - Anatomical sites like the gastrointestinal site protected from antibiotics -> reservoir
  - Lack of treatment compliance, post-treatment reinfection

Sandoz and Rockey, Future Microbiol 2010
Mycoplasma genitalium

- **Tetracyclines**: low eradication rate for *M. genitalium* clinically
  - Microbiological cure rate 22-45%
  - No acquired resistance described, reason?

- **Recommended treatment for uncomplicated *M. genitalium* infections**
  - Azithromycin 500 mg (day 1), then 250 mg (days 2-5)
**Mycoplasma genitalium**

- **Metanalysis on the efficacy of AZM for Mg treatment**

![Graph showing efficacy of AZM against M. genitalium declines](source)

- **Clinical acquired resistance to macrolides**
  - by mutations in the macrolide target (23S rRNA)
  - most likely caused by azithromycin 1g single dose
Prevalence of macrolide resistance in *M. genitalium*

Consequence on NGU European guidelines (IUSTI 2016)

Clinical diagnosis of NGU

Doxycycline 100 mg bid for 7 days
Diagnostic testing for gonorrhoea, chlamydia and M. genitalium

C. trachomatis or no identified
Macrolide-S M. genitalium
Macrolide-R M. genitalium pathogen

No additional testing or treatment in absence of persistent urethritis
Azithromycin 1.5g for 5 days
Moxifloxacin 400 mg for 7-10 days
Mycoplasma genitalium

• **Recommended treatment for complicated and macrolide-resistant *M. genitalium* infections**
  - Moxifloxacin 400 mg od 7-10 days (Jensen et al. JEADV 2016)

• **Emergence of clinical acquired resistance to MXF**
  - by mutations in the FQ target (topoisomerase IV)
  - both *in vitro* and clinical resistance
  - ranging from 4.5% (UK) to 47% (Japan)

Jensen and Bradshaw BMC Infect Dis 2015, Jensen and Unemo Nature Rev Urol 2017
Prevalence of fluoroquinolone resistance in *M. genitalium*

**Neisseria gonorrhoeae**

- Emergence and spread of antimicrobial resistance in *N. gonorrhoeae*
  - Horizontal gene transfer and subsequent recombination
  - Asymptomatic carriage in extragenital site for MSM
  - Inadequate monitoring of *in vitro* antimicrobial resistance, pharmacokinetics and pharmacodynamics and clinical efficacy of antimicrobials

Unemo and Shafer, Clin Microbiol Rev 2014
Neisseria gonorrhoeae

History of discovery and recommended antimicrobials, evolution of resistance in \textit{N. gonorrhoeae} since 1930

Unemo and Shafer, Clin Microbiol Rev 2014
Neisseria gonorrhoeae

- **Empirical 1st-line treatment for uncomplicated gonorrhoea (WHO, Europe, USA)**
  
  Dual antimicrobial therapy: ceftriaxone 250-500 mg + azithromycin 1–2 g

- **Treatment failures with ESCs**
  
  - XDR isolates (superbugs) with high-level resistance to all ESCs and other antimicrobials available: 3 isolates described in Japan, France, Spain
  
  - 1st treatment failure to the recommended dual therapy published in 2016 in the UK

**N. gonorrhoeae**

- **Internationals failures of dual therapy for** *N. gonorrhoeae*

<table>
<thead>
<tr>
<th>Location</th>
<th>CTX / AZI Dose</th>
<th>MIC mg/L</th>
<th>Ng-MAST ST</th>
<th>Year</th>
<th>Country</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharyngeal*</td>
<td>500 mg /1g</td>
<td>0.25</td>
<td>ST12133</td>
<td>2014</td>
<td>Sweden</td>
<td>Fifer, 2016</td>
</tr>
</tbody>
</table>

**Table:**

<table>
<thead>
<tr>
<th>Type of healthcare clinic (day of presentation)</th>
<th>Symptoms (signs)</th>
<th>Diagnostic test</th>
<th>MIC (mg/L)</th>
<th>NG-MAST</th>
<th>Treatment (day administered)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary (1)</td>
<td>Urethral discharge, dysuria, pharyngeal pain (inflammation of 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>
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<tr>
<td>STI (12)</td>
<td>(Inflammation in pharynx)</td>
<td>Culture (pharyngeal)</td>
<td>Microscopy and culture (urethral) PCR (urine)</td>
<td>2 0.125</td>
<td>Ceftriaxone One dose of 250 mg, intramuscular administration (day 26)</td>
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<tr>
<td>STI (36)</td>
<td>(Inflammation in pharynx)</td>
<td>Culture (pharyngeal)</td>
<td>NA</td>
<td>2 0.125</td>
<td>Ceftriaxone One dose of 500 mg, intramuscular administration (day 43)</td>
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<tr>
<td>STI (50)</td>
<td>(Inflammation in pharynx)</td>
<td>Culture (pharyngeal)</td>
<td>NA</td>
<td>2 0.25</td>
<td>Ceftriaxone One dose of 1 g, intravenous administration (day 71)</td>
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<tr>
<td>STI (85 and 92)</td>
<td>(—)</td>
<td>NA</td>
<td>Culture (pharyngeal)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Neisseria gonorrhoeae

- WHO global GASP, Euro-GASP and national GASP in USA, UK
  - global action plans
  - Quality-assured surveillance of gonococcal AMR and gonorrhea treatment failures

ECDC 2012
Number of countries in different WHO regions reporting gonococcal isolates with resistance to azithromycin and ciprofloxacin, and decreased susceptibility or resistance to ESCs (cefixime and/or ceftriaxone), 2009-2014

<table>
<thead>
<tr>
<th>Resistance of gonococcal isolates to antimicrobials</th>
<th>Africa</th>
<th>Americas</th>
<th>WHO regions</th>
<th>Eastern Mediterranean</th>
<th>Europe</th>
<th>Southeast Asia</th>
<th>Western Pacific</th>
<th>Total</th>
<th>Countries (%) reporting resistance/decreased susceptibility</th>
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<tbody>
<tr>
<td><strong>ESCs</strong></td>
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<tr>
<td>Countries reporting</td>
<td>9</td>
<td>16</td>
<td>3</td>
<td>27</td>
<td>6</td>
<td>16</td>
<td>73</td>
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<tr>
<td>≥5% resistance</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>15</td>
<td>4</td>
<td>6</td>
<td>26</td>
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<tr>
<td>&lt;5% resistance</td>
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<td>0</td>
<td>0</td>
<td>8</td>
<td>1</td>
<td>8</td>
<td>25</td>
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<tr>
<td>Full susceptibility</td>
<td>6</td>
<td>10</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>26</td>
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<tr>
<td><strong>Azithromycin</strong></td>
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<tr>
<td>≥5% resistance</td>
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<td></td>
<td></td>
<td>51</td>
<td>(65%)</td>
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<tr>
<td>&lt;5% resistance</td>
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<td>Full susceptibility</td>
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<td><strong>Ciprofloxacin</strong></td>
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<tr>
<td>Countries reporting</td>
<td>8</td>
<td>16</td>
<td>1</td>
<td>26</td>
<td>6</td>
<td>15</td>
<td>72</td>
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<tr>
<td>&gt;90% resistance</td>
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<td>1</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>14</td>
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<tr>
<td>≥5% resistance</td>
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<td>14</td>
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<td>23</td>
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<td>7</td>
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<tr>
<td>&lt;5% resistance</td>
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<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>4</td>
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<tr>
<td>Full susceptibility</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
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</table>

* Resistance level at which WHO recommends that the use of an antimicrobial in empiric treatment is discontinued.

* An arbitrary resistance level was included to show that the resistance levels to ciprofloxacin are extremely high in many parts of the world, particularly in the WHO Southeast Asian Region and Western Pacific Region.

ESC, Extended-spectrum cephalosporins; WHO, World Health Organization

Percentage (%) of isolates with decreased susceptibility or resistance to extended-spectrum cephalosporin (ESC) (cefixime and/or ceftriaxone) according to the 2014 WHO-GASP data.

**Neisseria gonorrhoeae**

- **Main mechanisms of resistance to ESCs:**

  - Mosaic PBP2 gene
  - Hyperexpression of the MtrCDE efflux pump

Neisseria gonorrhoeae

- **Azithromycin resistance:** 2% - 8%

<table>
<thead>
<tr>
<th>Region</th>
<th>Rate</th>
<th>Region</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>EURO-GASP 2014 (n=1066)</td>
<td>7.9%</td>
<td>Australia 2015</td>
<td>2.6%</td>
</tr>
<tr>
<td>21 countries</td>
<td></td>
<td>United States GISP 2014</td>
<td>2.5%</td>
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<tr>
<td>(n=5093), 27 sites</td>
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</table>

High-level resistance mainly caused by mutations in the macrolide target (23S rRNA gene)

- **Fluoroquinolone resistance:** 30% - 50%

Mutations in the FQ enzyme targets (DNA gyrase) leading to high MIC increases

- **Tetracycline resistance >** 50%

High-level resistance mainly caused by the *tet(M)* gene carried on a mobile element (Tn916 on a plasmid)

Percentage (%) of isolates with resistance to azithromycin according to the 2014 WHO-GASP data

Percentage (%) of isolates with resistance to ciprofloxacin according to the 2014 WHO-GASP data

Conclusion

• AMR in STIs: 2 distinct situations
  – *N. gonorrhoeae* and *M. genitalium* evolving into so called superbugs -> untreatable ??
    (Jensen and Unemo Nature Rev Urol 2017)
  – By contrast *C. trachomatis* remains susceptible to many antimicrobials

• **Combination therapy:** *N. gonorrhoeae, M. genitalium?*

• **Rapid molecular AMR testing** for simultaneous detection of *N. gonorrhoeae* and *M. genitalium* and their AMR should be developed -> immediate diagnosis, AMR surveillance and personalized treatment

• **Future treatment needed**

*The Lancet Infectious Diseases Commission
STIs: challenge ahead, Unemo et al, Lancet Infect Dis, 2017;17:e235-79*
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