Management of *Neisseria gonorrhoeae* in Adults

Evidence informing BASHH/BHIVA Guidelines 2018

Dr Tariq Sadiq
4th Joint Conference of BHIVA with BASHH
Edinburgh, 2018
Statement of Competing Interests

• Research Funding: NIHR, MRC, Wellcome Trust and Innovate UK, (SBRI 2015, 2017).

• Applied Diagnostic Research and Evaluation Unit (ADREU) has received funding from Alere, TwistDx, Cepheid, Atlas genetics, SpeedDx, Mologic, Revolugen and Sekisui.

• I have received consultancy from Roche and Phillips
- **Neisseria gonorrhoeae** (and STIs) - causes serious reproductive health sequelae, particularly vulnerable populations.

- **Sequential failure of monotherapy**
- NOT PROOF THAT CEFTRIAXONE MONOTHERAPY WILL FAIL

- **Ceftriaxone** only available antibiotic left for **empirical therapy**. Disappointing Gentamycin results from GtoG. *(Ross et al, ISSTDR 2017)*

- Preventing loss of ceftriaxone as empirical therapy a priority

- No widespread emergence of ceftriaxone resistance in UK *(Ceftriaxone MIC creep in the UK (Town et al STIs 2016))*
Global Risk of Ceftriaxone Resistance
GASP sentinel surveillance sites in China 2015.
Ceftriaxone Resistance = >0.125mg/L (0.25-0.5)

n=1242

- Ceftriaxone 1g monotherapy has **not prevented emergence of ceftriaxone resistance** where it has been used.
Monte Carlo simulations for ceftriaxone free drug concentrations (Chisholm et al. JAC 2010)

Assumption:

$f_T_{>MIC}$ Ceftriaxone 20-24 hours for effective treatment

$f_T_{>MIC}$ of various monotherapy regimens in hours

<table>
<thead>
<tr>
<th>MIC mg/L</th>
<th>250mg</th>
<th>500mg</th>
<th>1g</th>
</tr>
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<tbody>
<tr>
<td>0.125</td>
<td>24.3</td>
<td>32.8</td>
<td>41.3</td>
</tr>
<tr>
<td></td>
<td>(10.5 - 52.5)</td>
<td></td>
<td>(19.6 - 83.3)</td>
</tr>
<tr>
<td>0.25</td>
<td>15.6</td>
<td>24.3</td>
<td>32.8</td>
</tr>
<tr>
<td></td>
<td>(5 - 34.3)</td>
<td></td>
<td>(15.4 - 65.8)</td>
</tr>
<tr>
<td>0.5</td>
<td>6.6</td>
<td>15.6</td>
<td>24.3</td>
</tr>
<tr>
<td></td>
<td>(0.0 - 19.8)</td>
<td></td>
<td>(11.1 - 49.8)</td>
</tr>
</tbody>
</table>
MDR-NG in Europe and N. America

Ceftriaxone-Resistant Neisseria gonorrhoeae, Canada, 2017

Brigitte Letefbre, Irene Martin, Walter Demczuk, Lucie Deshaies, Stéphanie Michaud, Annie-Claude Labbé, Marie-Claude Beaudoin, Jean Longtin

We identified a ceftriaxone-resistant Neisseria gonorrhoeae isolate in a patient in Canada. This isolate carried the penA-60 allele, which differs substantially from its closest relative, mosaic penA X031 (80% nucleotide identity). Epidemiologically, the isolate was confirmed to be penA-60.

Journal of Antimicrobial Chemotherapy

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

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Journal of Antimicrobial Chemotherapy

Clinical Infectious Diseases

Cluster of Neisseria gonorrhoeae Isolates With High-Level Azithromycin Resistance and Decreased Ceftriaxone Susceptibility, Hawaii, 2016

Alina R. Katz,1,2 Alan L. Kenney,1 Robert G. Kolaczuk,1,3,4,6 Christiane White,1,3,4,6 Hoonjung B. Soge,3 John P. Pappas,2,7,8 Elena N. Korvitz2

1Department of Public Health Sciences, 2Center for Tobacco Control Research and Education, 3School of Public Health, 4University of Hawai‘i, 5Department of Dermatology, 6Department of Internal Medicine, 7Department of Laboratory Medicine & Pathology, and 8John A. Burns School of Medicine, University of Hawai‘i, Honolulu, Hawaii

Clinical Infectious Diseases

Futility Dual Antimicrobial Therapy in Treatment of Gonorrhea

By James O’Doherty

BBC News

Man has ‘world’s worst’ super-gonorrhoea

Health

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16 March 2018

News

Health and science correspondent, BBC News

On day 98, St. George’s was treated in a pharyngeal sample on the nuclease and amplification test and culture. The patient received a single dose of ceftriaxone at a dose of 1 g intramuscularly plus azithromycin at a dose of 2 g orally. At the test of cure on day 112, the pharyngeal specimen was negative (according to the nuclease and amplification test). Initial treatment specimens were unsuitable for further analysis.

The N. gonorrhoeae strain was identified in a pharyngeal sample on the nuclease and amplification test and culture. The patient received a single dose of ceftriaxone at a dose of 1 g intramuscularly plus azithromycin at a dose of 2 g orally. At the test of cure on day 98, the pharyngeal specimen was negative (according to the nuclease and amplification test). Initial treatment specimens were unsuitable for further analysis.
Azithromycin

- Azithromycin 1g inadequate if ceftriaxone treatment failure (Ross et al ISSTDR 2017).

- Azithromycin 2g:
  
is an effective dose. *(Bignel Garley STIs 2010)*

  resistance threatens dual therapy
  HLAzR –sustained but still limited? *(Fifer et al LID 2018)*

  in NG unlikely to contribute to macrolide resistance in **NG** except.........Long half life of azithromycin and re-infection (Horner, personal omm.)

  ...probably not other STIs (?syphilis).

Toxicity of long 2g azithromycin dose. *(Kirkaldy et al CID 2015; Handsfield 1994)*
Treatment options considered

**Dual Therapy**
- Ceftriaxone 500mg / Azithromycin 1G  X X
- Ceftriaxone 500mg / Azithromycin 2G*  √ √
- Ceftriaxone 1G / Azithromycin 2G*  √ X
  (*with light snack and anti-emetics)

**Monotherapy:**
- Ceftriaxone 1G only  √ X

**Not Considered:**
- Ceftriaxone 1g / Azithromycin 1g
- Ceftriaxone 500mg monotherapy
- Ceftriaxone 250mg containing regimens
## Current Management Guidelines and Proposed changes

<table>
<thead>
<tr>
<th></th>
<th>Recommended Treatment</th>
<th>Proposed change</th>
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<tbody>
<tr>
<td>CDC (2015)</td>
<td>Ceftriaxone 250mg + Azithromycin 1g</td>
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<tr>
<td>European (2012)</td>
<td>Ceftriaxone 500mg + Azithromycin 2g</td>
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<tr>
<td>Australian (2018)</td>
<td>Ceftriaxone 500mg + Azithromycin 1g</td>
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<tr>
<td>WHO (2016)</td>
<td>Ceftriaxone 250mg + Azithromycin 1g</td>
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</tr>
<tr>
<td>UK (2011)</td>
<td>Ceftriaxone 500mg + Azithromycin 1g</td>
<td>Provisional-Not Final</td>
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<tr>
<td></td>
<td></td>
<td>Ceftriaxone 500mg +</td>
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<tr>
<td></td>
<td></td>
<td>Azithromycin 2g</td>
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</tbody>
</table>
Other Considerations

- Anti-emetics and food – really??

- Ciprofloxacin usage if phenotypic and later genotypic results available. (as mono or part of dual therapy) *(Pond et al 2015)*

- Commercial genotypic laboratory assay available August 2018 (SpeedDx)/. PoC Test ?2020 (Atlas-St George’s)

- Treating for chlamydia infection – 2g Azithromycin/ When should we add doxycycline

- Is azithromycin 2g adequate for *M. genitalium* infection

- Transgender considerations for testing
Gonorrhoea Guidelines Committee

Tariq Sadiq, Helen Fifer, John Saunders, Suneeta Soni, Mark Fitzgerald,

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