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Management of *Neisseria gonorrhoeae* in Adults

Evidence informing BASHH/BHIVA Guidelines 2018

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

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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

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Background

- ***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*))

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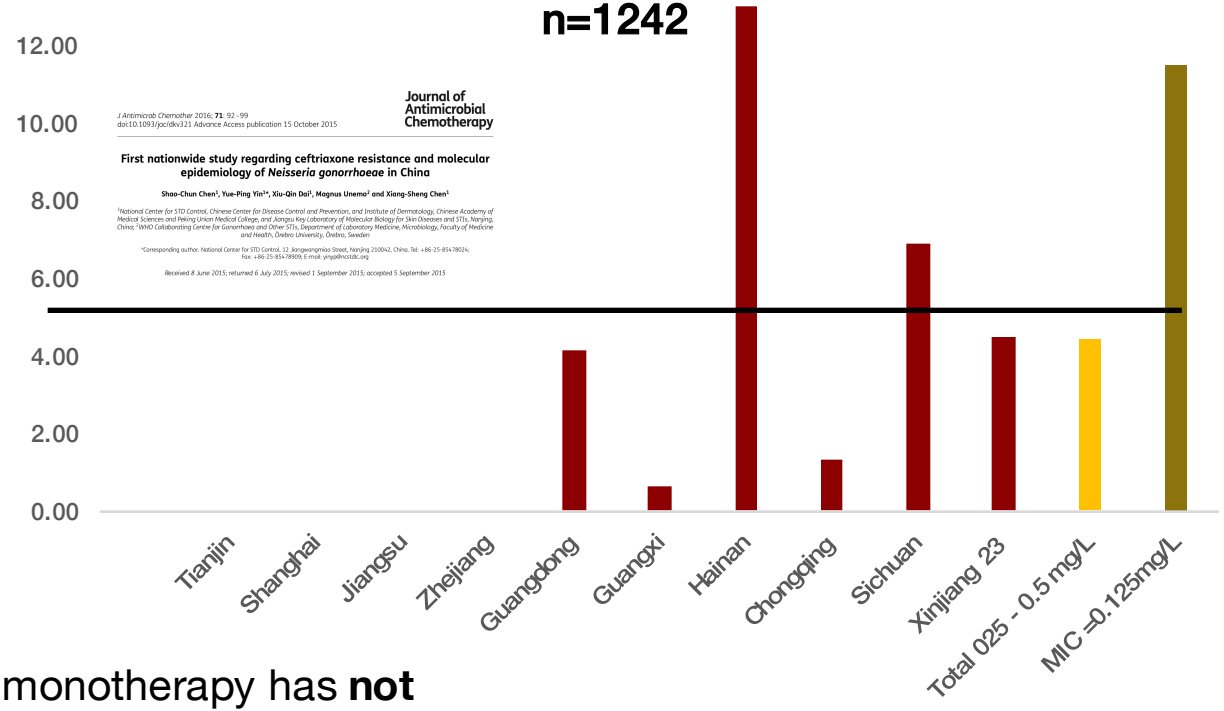
Global Risk of Ceftriaxone Resistance
GASP sentinel surveillance sites in China 2015.
Ceftriaxone Resistance = >0.125mg/L (0.25-0.5)
n=1242



J Antimicrob Chemother 2016; **71**: 92 – 99
doi:10.1093/jac/dkv321 Advance Access publication 15 October 2015

Journal of Antimicrobial Chemotherapy

First nationwide study regarding ceftriaxone resistance and molecular epidemiology of *Neisseria gonorrhoeae* in China

Shao-Chun Chen[1], Yue-Ping Yin[1*], Xiu-Qin Dai[1], Magnus Unemo[2] and Xiang-Sheng Chen[1]

[1]*National Center for STD Control, Chinese Center for Disease Control and Prevention, and Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union Medical College, and Jiangsu Key Laboratory of Molecular Biology for Skin Diseases and STIs, Nanjing, China;* [2]*WHO Collaborating Centre for Gonorrhoea and Other STIs, Department of Laboratory Medicine, Microbiology, Faculty of Medicine and Health, Örebro University, Örebro, Sweden*

*Corresponding author. National Center for STD Control, 12 Jiangwangmiao Street, Nanjing 210042, China. Tel: +86-25-85478024; Fax: +86-25-85478909; E-mail: yinyp@ncstd8.org

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- Ceftriaxone 1g monotherapy has **not prevented emergence of ceftriaxone resistance** where it has been used.

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Monte Carlo simulations for ceftriaxone free drug concentrations *(Chisholm et al JAC 2010)*

Assumption:
$fT_{>MIC}$ Ceftriaxone 20-24 hours for effective treatment

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

	CEFTRIAXONE IM		
MIC mg/L	250mg	500mg	1g
0.125	24.3 (10.5 - 52.5)	32.8	41.3 (19.6 - 83.3)
0.25	15.6 (5 - 34.3)	24.3	32.8 (15.4 - 65.8)
0.5	6.6 (0.0 - 19.8)	15.6	24.3 (11.1 - 49.8)

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MDR-NG in Europe and N. America

Ceftriaxone-Resistant *Neisseria gonorrhoeae*, Canada, 2017

Brigitte Lefebvre, 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* XXVII (80% nucleotide identity). Epidemio-

(recommended therapy according to Québec STI Treatment Guidelines) (*8*). Because the patient was from a low-prevalence population, the healthcare provider decided to perform a genital gonorrhea culture. The culture was positive for *N. gonorrhoeae* (no. GC063564/47707), thus confirming the positive NAAT result.

Because antimicrobial susceptibility testing (Etest, bioMérieux, Marcy l'Etoile, France) demonstrated non-susceptibility of the isolate to ceftriaxone and cefixime but

J Antimicrob Chemother 2012; **67**: 1858–1860
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Journal of Antimicrobial Chemotherapy

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

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

Alan R. Katz,[1,2] Alan Y. Komeya,[2] Robert D. Kirkcaldy,[3] A. Christian Whelen,[1,4] Olusegun O. Soge,[5] John R. Papp,[3] Ellen N. Kersh,[3] Glenn M. Wasserman,[1,2] Normar

[1]Department of Public Health Sciences, Control and Prevention, Atlanta, GA; [4]Sta Washington, Seattle

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DOI: 10.1056/NEJMc1514294

Molecular characterization of two high-level ceftriaxon *Neisseria gonorrhoeae* isolates detected in Catalonia

Jordi Cámara[1], Judit Serra[2], Josefina Ayats[1], Teresa Bastida[3], Dolors Carnicer-Pont[4], A and Carmen Ardanuy[1]*

[1]*Microbiology Department, Hospital Universitari de Bellvitge-Universitat de Barcelona-IDIBELL, L'Hospitalet Spain;* [2]*Microbiology Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain;* [3]*Microbiology Departme Hospital, Santa Coloma de Gramenet, Spain;* [4]*Centre d'Estudis Epidemiològics sobre les Infeccions de Trans Catalunya (CEEISCAT), Institut Català d'Oncologia, Badalona, Barcelona, Spain*

*Corresponding author. Tel: +34932607930; Fax: +34932607547; E-mail: c.ardanuy@bellvitgehosp

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Health

Man has 'world's worst' super-gonorrhoea

By James Gallagher
Health and science correspondent, BBC News

28 March 2018 · Share

Failure of Dual Antimicrobial Therapy in Treatment of Gonorrhea

TO THE EDITOR: Resistance to all antimicrobial agents has developed in some *Neisseria gonorrhoeae* strains. Dual antimicrobial therapy (ceftriaxone plus azithromycin) is a recommended first-line empirical treatment in many countries.[1-3] We describe treatment failure with dual therapy in a patient with gonorrhea.

In December 2014, a heterosexual man presented to a sexual health clinic in the United Kingdom with a 2-week history of urogenital symptoms (Table 1). Ten days previously, he had returned from Japan, where his Japanese female partner had been treated for gonorrhea. He reported having no other recent sexual partners.

On day 98, *N. gonorrhoeae* was detected in a pharyngeal sample on the nucleic acid amplification test and culture. The patient received one dose of ceftriaxone at a dose of 1 g intramuscularly plus azithromycin at a dose of 2 g orally.[3] At the test of cure on day 112, the pharyngeal specimen was negative (according to the nucleic acid amplification test). Initial pretreatment specimens were unavailable for further analysis.

The *N. gonorrhoeae* species was verified with the use of the Phadebact Monoclonal GC Test and matrix-assisted laser desorption ionization–time of flight mass spectrometry. Antimicrobial susceptibility testing with the use of Etest

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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)

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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

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Current Management Guidelines and Proposed changes

	Recommended Treatment	Proposed change
CDC (2015)	Ceftriaxone 250mg + Azithromycin 1g	
European (2012)	Ceftriaxone 500mg + Azithromycin 2g	
Australian (2018)	Ceftriaxone 500mg + Azithromycin 1g	
WHO (2016)	Ceftriaxone 250mg + Azithromycin 1g	
UK (2011)	Ceftriaxone 500mg + Azithromycin 1g	**Provisional-Not Final** Ceftriaxone 500mg + Azithromycin 2g

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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

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Gonorrhoea Guidelines Committee

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

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