

9 evaluable 1000 mg patients enrolled to date, gonococcal eradication rates have been 100% (9/9) for urethral/cervical, pharyngeal (2/2), and rectal (1/1) infections. Susceptibility data from 25 isolates show the median MIC (range) for solithromycin was 0.06 µg/mL (0.015–0.125) and for azithromycin was 0.125 µg/mL (0.06–0.5).

Solithromycin was generally well-tolerated with mild dose-related gastrointestinal AEs (68%; 28/41). The most common AE was mild diarrhoea, occurring in 61% (17/28) of patients receiving the 1200 mg dose and 15% (2/13) of patients receiving the 1000 mg dose.

Conclusions A single dose of 1200 or 1000 mg solithromycin appears to be well-tolerated and effective in eradicating *N. gonorrhoeae*.

002.6 AZITHROMYCIN VERSUS DOXYCYCLINE FOR THE TREATMENT OF GENITAL CHLAMYDIA INFECTION - A META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS

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J Hocking, ¹F Kong, ^{1,2}L Vodstrcil, ³R Guy, ⁴M Chen, ^{1,4}C Fairley, ⁴C Bradshaw, ^{2,5}S Tabrizi. ¹University of Melbourne, Carlton, Australia; ²Murdoch Children's Research Institute, Flemington, Australia; ³Kirby Institute, Sydney, Australia; ⁴Melbourne Sexual Health Centre, Carlton, Australia; ⁵Royal Women's Hospital, Flemington, Australia

Introduction There has been considerable debate questioning the efficacy of azithromycin for the treatment of genital chlamydia. We conducted a meta-analysis to compare the efficacy of 1 gramme azithromycin with 100mg doxycycline twice daily for seven days for the treatment of genital chlamydia infection.

Methods Medline, PubMed, Embase and the Cochrane Controlled Trials Register were searched till end 2012. Inclusion criteria included (1) randomised controlled trial of azithromycin versus doxycycline for the treatment of urethral or cervical chlamydia, and; (2) evaluation of microbial cure within 3 months of treatment. Type of diagnostic test, duration of follow up, gender, patient status (all symptomatic versus both symptomatic/asymptomatic) and microbial cure were extracted. The primary outcome was difference in efficacy (doxycycline efficacy minus azithromycin efficacy) at final follow up. Meta-analysis calculated a pooled efficacy for each treatment and the difference in efficacy between treatments.

Results Of 692 references identified, 23 trials met the inclusion criteria. 1065 individuals were treated with azithromycin and 850 with doxycycline; all studies reported efficacy within 6 weeks follow-up. Pooled cure rates were 96.2%(95% CI: 94.2%, 98.3%) for azithromycin and 98.1%(95% CI: 96.6%, 99.7%) for doxycycline. The pooled efficacy difference was 1.9%(95% CI: 0.4%, 3.4%) showing a small but significant difference in favour of doxycycline; there was negligible heterogeneity between studies ($I^2 = 1.9%$, $p = 0.44$). There was no difference in efficacy in men (3.8%; 95% CI: -1.2%, 8.8%) or women (-0.9%; 95% CI: -5.3%, 3.6%). When stratified by type of test, efficacy was significantly higher for doxycycline in culture-based studies (1.8%; 95% CI: 0.4%, 3.3%), but not in NAAT-based studies (5.5%; 95% CI: -2.1%, 13.1%). Efficacy was higher for doxycycline in symptomatic men (6.3%; 95% CI: 3.0%, 12.3%), but not in symptomatic women (-4.5%; 95% CI: -14.9%, 5.9%).

Conclusion These results suggest that doxycycline may be more effective than azithromycin for the treatment of urethral or cervical chlamydia infection, especially in symptomatic men.

0.03 - Neisseria gonorrhoeae resistance: Superbug ante portas?

003.1 RISK FACTORS FOR ANTIMICROBIAL RESISTANT NEISSERIA GONORRHOEAE IN EUROPE

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M J Cole, ²G Spiteri, ¹K Town, ³M Unemo, ⁴S Hoffmann, ²M van de Laar, ¹C Ison. ¹Health Protection Agency, London, UK; ²European Centre for Disease Prevention and Control, Stockholm, Sweden; ³Örebro University Hospital, Örebro, Sweden; ⁴Statens Serum Institut, Copenhagen, Denmark

Introduction The European Centre for Disease Prevention and Control is responsible for the enhanced surveillance of sexually transmitted infections and co-ordinates the European gonococcal antimicrobial surveillance programme (Euro-GASP) in the European Union and the European Economic Area. Linked patient and antimicrobial susceptibility data from Euro-GASP allows those at risk of acquiring antimicrobial resistant *Neisseria gonorrhoeae* to be identified.

Methods Seventeen countries in 2009 and 21 countries in 2010 and 2011 submitted gonococcal isolates to Euro-GASP, which were tested by Etest or agar dilution for cefixime, ceftriaxone, ciprofloxacin, azithromycin, spectinomycin and gentamicin. Additional patient data linked to the gonococcal isolates susceptibility profiles was collected. All three years antimicrobial susceptibility data and linked patient data were combined. Patient variables associated with resistance were established using a univariate and multivariable analyses of odds ratios. Geometric means for ceftriaxone and cefixime MICs were calculated.

Results A total of 5034 gonococcal isolates were tested in Euro-GASP from 2009 to 2011. In the multivariable analysis heterosexuals (males only for ciprofloxacin), older patients and those without a concurrent chlamydia infection remained significantly more likely to be infected with isolates displaying cefixime decreased susceptibility and ciprofloxacin resistance. The geometric mean of cefixime and ceftriaxone MICs decreased from 2009 to 2011, most significantly for MSM; MSM had lower geometric means than heterosexuals in 2011. A bimodal MIC distribution of a 'more susceptible' and 'less susceptible' gonococcal population appears to be emerging alongside this geometric mean decrease.

Conclusion This Euro-GASP data suggests that the burden of gonococcal antimicrobial resistance is more prevalent among heterosexuals and decreasing in MSM. This study shows the importance of collecting and analysing patient data along with susceptibility data, however improved data numbers and representativeness is required before any focused treatments or public health intervention strategies are initiated.

Abstract 003.1 Table 1 Patient risk factors for antimicrobial resistance (OR, 95% CI from multivariable analysis)

	Cefixime decreased susceptibility	Ciprofloxacin resistance
MSM	1	1
Male heterosexuals	2.39 (1.58–3.61)*	1.49 (1.21–1.83)*
Female	2.75 (1.68–4.5)*	1.04 (0.8–1.34)
< 25 years	1	1
≥ 25 years	2.07 (1.36–3.13)*	1.67 (1.37–2.05)*
Chlamydia - yes	1	1
Chlamydia - no	1.87(1.1–3.16)*	2.2 (1.74–2.8)*

*P value < 0.05 (from the Pearson Chi²-test)

003.2 ANTIMICROBIAL RESISTANCE OF NEISSERIA GONORRHOEAE IN THE EUROPEAN UNION: RESPONSE TO THE THREAT OF MULTIDRUG RESISTANT GONORRHOEA

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G Spiteri, ²M Cole, ³M Unemo, ⁴S Hoffmann, ²C Ison, ¹M van de Laar. ¹European Centre for Disease Prevention and Control, Stockholm, Sweden; ²Health Protection Agency, London, UK; ³Swedish Reference Laboratory for Pathogenic Neisseria, Örebro, Sweden; ⁴Statens Serum Institut, Copenhagen, Denmark

Background Increasing reports of *Neisseria gonorrhoeae in vitro* decreased susceptibility and resistance, and treatment failures with third generation cephalosporins are of major concern as these drugs are the last remaining options for effective antimicrobial therapy in many settings.

Methods The European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP), a sentinel surveillance programme funded by the European Centre for Disease Prevention and Control since 2009, monitors antimicrobial susceptibility patterns across the European Union (EU/EEA). Participating laboratories performed susceptibility testing by Etest or agar dilution breakpoint method, or sent isolates to reference laboratories in Denmark, Sweden or the United Kingdom for testing. Euro-GASP validated proficiency and result accuracy through an external quality assessment scheme.

Results In 2011, 1902 isolates from 21 countries were collected and tested. The percentage of tested isolates with decreased susceptibility to cefixime (8.0%) remained stable compared to 2010 (8.7%), but was still significantly higher than in 2009 (5.1%, $p < 0.01$). Isolates with decreased susceptibility to cefixime were reported from 17 countries in 2011, the same as in 2010; however three countries reported such isolates for the first time in 2011. For the first time, ten isolates with decreased susceptibility to ceftriaxone were reported from two countries. Rates of ciprofloxacin (49%) and azithromycin (5.3%) resistance remained high. Minimum inhibitory concentration of gentamicin remained low (MIC₅₀: 4 mg/L; MIC₉₀: 8 mg/L).

Conclusions Although the rapid increase and spread of decreased susceptibility to cefixime in 2010 has not continued, the detection of isolates with decreased susceptibility to ceftriaxone is concerning. ECDC has published a response plan which aims to strengthen surveillance of gonococcal antimicrobial susceptibility in the EU/EEA; ensure that capacity for culture and susceptibility testing is maintained; establish a system for collection and verification of data on clinical treatment failure; and to recommend public health actions at national and European level.

003.3 MAXIMISING THE EFFICIENCY OF GONORRHOEA TREATMENT BY TARGETING THE USE OF PREVIOUS FIRST LINE THERAPIES TO SUSCEPTIBLE PATIENTS

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K Town, ¹C Obi, ²S Chisholm, ¹G Hughes, ²C A Ison. ¹HIV/STI Department, Health Protection Agency, London, UK; ²Sexually Transmitted Bacteria Reference Unit, Health Protection Agency, London, UK

Background Gonorrhoea treatment guidelines change when less than 95% of the infected population is successfully treated with the recommended antimicrobial. Isolates with decreased susceptibility to ceftriaxone, the current recommended therapy, have been identified and if treatment failure becomes problematic there are no new antimicrobials approved. However, *Neisseria gonorrhoeae* remains susceptible to penicillin, ciprofloxacin and cefixime in at least two thirds of patients (82%, 68%, and 98% respectively) so it may be possible to target previously recommended antimicrobials to specific population sub-groups.

Methods Descriptive data from the Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) were analysed for trends in penicillin, ciprofloxacin and cefixime susceptibility across patient sub-groups. Patient characteristics associated with antimicrobial susceptibility were identified using univariate and multivariable analyses. All analyses were performed separately for heterosexuals and men who have sex with men (MSM).

Results Heterosexual patients whose infection was susceptible to penicillin, ciprofloxacin or cefixime were of black ethnicity, penicillin: 94%, adjusted odds ratio (OR) 3.52 (95% confidence interval (CI) 2.62–4.72), ciprofloxacin: 92%, OR 5.35 (CI 4.08–7.0), cefixime: 99%,

OR 3.62 (CI 1.91–6.84), or with concurrent chlamydia infection (penicillin: 94%, 2.34, 1.75–3.13, ciprofloxacin: 92%, 3.37, 2.59–4.38, cefixime: 99%, 2.32, 1.23–4.39). Additionally isolates susceptible to penicillin were found in patients aged 13–24 years (92%, 3.54, 2.63–4.77) or without symptoms (92%, 1.75, 1.28–2.4). All isolates from heterosexuals were fully susceptible to cefixime. In all sub-groups of the MSM population the proportion of isolates susceptible to penicillin, ciprofloxacin or cefixime was below 90%.

Conclusion The efficiency of gonorrhoea treatment could be maximised by targeting the use of previous first line therapies to specific heterosexual population sub-groups if the treatment threshold is reduced to 90%. Treatment of any MSM with penicillin, ciprofloxacin or cefixime would not be appropriate, as the proportion susceptible to these antimicrobials is much less than for the heterosexual population.

003.4 GENOMIC EPIDEMIOLOGY OF NEISSERIA GONORRHOEA WITH REDUCED SUSCEPTIBILITY TO CEFIXIME IN THE UNITED STATES

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^{1,2}Y H Grad, ³R Kirkcaldy, ³D Trees, ⁴J Dordel, ¹E Goldstein, ³H Weinstock, ⁴J Parkhill, ¹W P Hanage, ⁴S Bentley, ^{1,5}M Lipsitch. ¹Center for Communicable Disease Dynamics, Department of Epidemiology, Harvard School of Public Health, Boston, MA, United States; ²Division of Infectious Diseases, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States; ³Division of STD Prevention, Centers for Disease Control and Prevention, Atlanta, GA, United States; ⁴Wellcome Trust Sanger Institute, Hinxton, UK; ⁵Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, MA, United States

Background Genome sequencing of pathogens has yielded insights into transmission networks and the spread of antibiotic resistance. Here, we report a large-scale genomic epidemiology study of *Neisseria gonorrhoeae* to investigate the emergence and spread of isolates with reduced susceptibility to cephalosporins.

Methods We sequenced the genomes of 242 gonococcal isolates collected by CDC's Gonococcal Isolate Surveillance Program (GISP). These isolates comprise all 141 isolates from GISP in 2009–10 with reduced susceptibility to cefixime (cef^{RS}; cefixime MICs $\geq 0.25 \mu\text{g/ml}$) and 141 susceptible isolates matched by location, collection date, and sexual orientation of the infected individual. We assessed diversity and association of genes known to contribute to antibiotic resistance, correlated location and phylogenetic clustering to determine sexual networks, and characterised the extent of recombination.

Results Phylogenetic analysis of single nucleotide polymorphisms (SNPs) within the core genome (34959 SNPs) demonstrates that most cef^{RS} isolates in the US fall into two distinct lineages. We identify several independent acquisitions of a mosaic *penA* allele, including evidence of a partial mosaic in an isolate with cef^{RS} and of reversion to an allele conferring cephalosporin susceptibility. Correlating the phylogeny with sexual orientation and geographic location provides evidence for clones circulating in sexual networks, some of which appear geographically restricted and others widespread. Analysis of predicted recombinant regions shows evidence of exchange with other *Neisseria* spp., consistent with prior observations of interspecies mosaicism.

Conclusions Cef^{RS} isolates in the US predominantly derive from two lineages that share the same mosaic *penA* sequence, and reflect sexual networks at local and regional scales. Additionally, we quantify the extent of recombination and the correlation of selected alleles with resistance phenotypes. Genomic methods offer detailed insights into the spread of resistant infections, with potential for enhanced surveillance and improved diagnostics.

003.5 RECENT INCREASES IN GONORRHOEA IN EUROPE

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G Spiteri, K Haar, O Sftescu, M van de Laar. European Centre for Disease Prevention and Control, Stockholm, Sweden