Four treatment failures of pharyngeal gonorrhoea with ceftriaxone (500 mg) or cefotaxime (500 mg), Sweden, 2013 and 2014

D Golparian[1], A K Ohlsson[2], H Janson[3], P Lidbrink[4], T Richtner[5], O Ekelund[3], H Fredlund[1], M Unemo (magnus.unemo@orebroll.se)[1]
1. World Health Organization Collaborating Centre for Gonorrhoea and other Sexually Transmitted Infections, Swedish Reference Laboratory for Pathogenic Neisseria, Department of Laboratory Medicine, Microbiology, Örebro University Hospital, Örebro, Sweden
2. Department of Clinical Microbiology, Karolinska University Hospital, Stockholm, Sweden
3. Department of Clinical Microbiology, Central Hospital, Växjö, Sweden
4. Department of Dermatovenereology, Karolinska University Hospital, Stockholm, Sweden
5. Department of Dermatology, Karolinska Institutet at Södersjukhuset, Stockholm, Sweden

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We describe four cases in Sweden of verified treatment failures of pharyngeal gonorrhoea with ceftriaxone (500 mg; n=3) or cefotaxime (500 mg; n=1) monotherapy. All the ceftriaxone treatment failures were caused by the internationally spreading multidrug-resistant gonococcal NG-MAST genogroup 1407 clone. Increased awareness of treatment failures is crucial particularly when antimicrobial monotherapy is used. Frequent test of cure and appropriate verification/falsification of suspected treatment failures, as well as implementation of recommended dual antimicrobial therapy are imperative.

This report describes four failures to treat pharyngeal gonorrhoea with ceftriaxone (500 mg; n=3) or cefotaxime (500 mg; n=1) in Sweden in 2013 and 2014.

Neisseria gonorrhoeae has developed resistance to all antimicrobials previously used as first-line treatment for gonorrhoea [1-4]. Clinical resistance is now emerging to the extended-spectrum cephalosporins (ESCs), i.e. cefixime (oral) and the more potent ceftriaxone (injectable). Many treatment failures with cefixime have been verified in Japan, Europe, Canada and South Africa. No failure to treat urogenital gonorrhoea with ceftriaxone (250 mg–1 g), the last remaining option for first-line empiric antimicrobial monotherapy, has been detected as yet. However, some few failures to treat pharyngeal gonorrhoea with ceftriaxone have been verified in Japan (n=1), Australia (n=3), Sweden (n=1) and Slovenia (n=1) [4-10]. In recent years, extensively drug-resistant (XDR) gonococcal strains with high-level ceftriaxone resistance were also reported from Japan, France and Spain [2,9-11].

Case descriptions

From February to May 2013, three cases of suspected failure to treat pharyngeal gonorrhoea with ceftriaxone 500 mg intramuscularly were reported from two clinics for sexually transmitted infections (STIs) in Sweden (Table). All three patients reported having had unprotected oral and vaginal sex with heterosexual contacts in Stockholm. Case A was a woman in her 30s, with pharyngeal symptoms including pharyngitis. Cases B and C, both in their 50s, were asymptomatic. Pharyngeal and urogenital samples were taken and all patients had a positive gonococcal pharyngeal culture. Furthermore, the urogenital samples from the Cases B and C were positive in a nucleic acid amplification test (NAAT) (BD ProbeTec GC Qx Amplified DNA Assay, Becton Dickinson). All three patients were administered a single dose of 500 mg ceftriaxone intramuscularly (Day 1). When returning for follow-up after seven to 22 days, all patients were asymptomatic but had persistent positive gonococcal pharyngeal cultures. All urogenital samples were negative. Finally, all three patients were successfully treated with a single dose of 1 g ceftriaxone intramuscularly between Day 7 and 27, which was confirmed at follow-up visits with negative pharyngeal cultures between Day 22 and 48 (Table).

In May 2014, one case of suspected failure to treat pharyngeal gonorrhoea with cefotaxime 500 mg intramuscularly was reported from an STI clinic in Karlskrona, Sweden. This patient (Case D), a man in his 30s, attended the clinic because he had had unprotected oral and vaginal sex with a woman diagnosed with gonorrhoea. On Day 1, the patient was asymptomatic and sampled from the pharynx, urethra, and rectum. The pharyngeal sample was positive for gonococci in culture and he was treated with a single dose of 500 mg cefotaxime intramuscularly. At the follow-up visit

Table

Details of three verified ceftriaxone and one verified cefotaxime treatment failure of *Neisseria gonorrhoeae* pharyngeal infection, Sweden, 2013–2014*

	Case A[a]		Case B[a]		Case C[a]		Case D[a]	
Sex	Female		Male		Female		Male	
Age (years)	30ties		50ties		50ties		30ties	
Sexual orientation	Heterosexual							
Place of exposure	Stockholm, Sweden						Karlshamn, Sweden	
Healthcare clinic	STI clinics (n=2), Stockholm, Sweden						STI clinic, Karlskrona, Sweden	
Visit	Day 1	Day 7	Day 1	Day 13	Day 1	Day 22	Day 1	Day 7
Symptoms	Pharyngitis	None	None		None		None	
Positive diagnostics	GC culture (pharynx)		GC culture (pharynx), NAAT (urogenital)	GC culture (pharynx)	GC culture (pharynx), NAAT (urogenital)	GC culture (pharynx)	GC culture (pharynx)	
Negative diagnostics	GC culture (urogenital), NAAT (urogenital)		GC culture (urogenital)	GC culture (urogenital), NAAT (urogenital)	GC culture (urogenital)	GC culture (urogenital), NAAT (urogenital)	GC culture (urogenital/rectal), NAAT (urogenital/rectal)	
Characteristics of cultured isolates								
MIC ceftriaxone (mg/L)	0.125	0.125	0.064	0.125	0.064	0.064	0.25	0.125
MIC cefixime (mg/L)	0.25	0.25	0.125	0.25	0.25	0.125	NA	NA
MIC azithromycin (mg/L)	1	1	1	2	2	2	0.25	0.25
MIC cefotaxime (mg/L)	0.25	0.25	0.5	0.5	0.25	0.25	0.5	0.5
NG-MAST ST (genogroup)	ST4706[b] (1407)	ST4706[b] (1407)	ST3149[b] (1407)	ST3149[b] (1407)	ST3149[b] (1407)	ST3149[b] (1407)	ST4539 (NA)	ST4539 (NA)
Treatment	Ceftriaxone 500 mg IM	Ceftriaxone 1 g IM[c,d]	Ceftriaxone 500 mg IM	Ceftriaxone 1 g IM[c,d]	Ceftriaxone 500 mg IM	Ceftriaxone 1 g IM[c,d]	Cefotaxime 500 mg IM	Ceftriaxone 250 mg IM + Azithromycin 1g p.o.[c,d]

GC: *Neisseria gonorrhoeae*; MIC: minimum inhibitory concentration; NAAT: nucleic acid amplification test; NA: not assessed; NG-MAST: *N. gonorrhoeae* multi-antigen sequence typing; ST: sequence type; IM: intramuscularly; p.o.: per os

[a] All four patients repeatedly reassured that they had not had any unprotected sexual contacts between the ceftriaxone/cefotaxime treatment and test of cure. Cases B and C were sexual contacts.

[b] Belonged to the internationally spreading multidrug-resistant gonococcal NG-MAST genogroup 1407 clone, which has caused many treatment failures with extended-spectrum cephalosporins [4-6,9,13].

[c] Successful final treatment on Day 7 (Case A), Day 21 (Case B), Day 27 (Case C), and Day 14 (Case D).

[c] Negative test-of-cure culture on Day 22 and Day 32 (Case A), Day 35 (Case B), Day 41 and Day 48 (Case C), and Day 26 (Case D).

(Day 7), the patient was still asymptomatic, however, a pharyngeal sample remained positive in culture. The patient was treated with a single dose of 250 mg ceftriaxone intramuscularly plus a single oral dose of 1 g azithromycin (day 14). On Day 26, the patient returned for test of cure and the pharyngeal culture was negative for gonococci (Table).

Characterisation of *N. gonorrhoeae* isolates

The pre- and post-treatment gonococcal isolates were species-confirmed by sugar utilisation test, Phadebact Monoclonal GC Test (Pharmacia Diagnostics) and MaldiTOF MS (Bruker Daltonics). The paired isolates from each case were indistinguishable using *N. gonorrhoeae* multi-antigen sequence typing (NG-MAST [12]) and the isolates from Cases A, B and C belonged to the NG-MAST genogroup 1407 clone [4,13] (Table). Using Etest (AB bioMérieux), the isolates from Cases A, B and C (ceftriaxone treatment failures) showed elevated minimum inhibitory concentrations (MICs), i.e. 0.064–0.125 mg/L, which is equal to the European resistance breakpoint (>0.125 mg/L) [14]. In Case D (cefotaxime treatment failure), according to the European resistance breakpoints [14], the paired isolates were resistant to cefotaxime (MIC: 0.5 mg/L) and the pre-treatment isolate also to ceftriaxone (MIC: 0.25 mg/L) (Table).

Sequencing of ESC resistance determinants [1,3,4,6,9,10,15] showed that all the paired isolates belonging to Cases A, B and C contained the *penA* mosaic allele XXXIV, which has been correlated with NG-MAST genogroup 1407, decreased susceptibility or resistance to ESCs and ESC treatment failures [1,4-6,9,11]. The isolates from Case D contained the *penA* mosaic allele XIII [10]. In addition, all isolates contained *mtrR* and *penB* alterations that further increase the ESC MICs [1,3-6,9-11,15].

Discussion

This paper reports four cases of verified pharyngeal gonorrhoea treatment failure in Sweden using injectable ESCs, i.e. ceftriaxone (n=3) and cefotaxime (n=1). The failures were verified in accordance with international recommendations [2,4], i.e. clinical records were obtained, reinfection was excluded, pre- and post-treatment isolates were identical using highly discriminatory molecular epidemiological typing, and the isolates had elevated ESC MICs and well recognised ESC resistance determinants. Reinfection was considered to be excluded as much as possible for all cases. Accordingly, all patients were strongly advised to abstain from any sexual contacts before their follow-up visit and all four patients repeatedly assured that they had not had any unprotected sexual contacts between the ceftriaxone/cefotaxime treatment and test of cure. Furthermore, Case D was infected by a casual sexual contact.

In the current emergent situation of fear that gonorrhoea may become untreatable [1-3,10], recommendations of using dual antimicrobial therapy (mainly ceftriaxone plus azithromycin) have been introduced in the United States [16] and Europe [17]. No appropriate well-designed international study has yet assessed the implementation of dual antimicrobial therapy. However, as observed by the authors in many international projects the implementation of these guidelines appears suboptimal in several European countries and monotherapy with ceftriaxone remains frequently used.

No failure to treat urogenital gonorrhoea with ceftriaxone (250 mg–1 g) monotherapy has been verified to date. However, the observed initial accumulation of failures treating pharyngeal gonorrhoea was not unexpected, because these infections are substantially harder to eradicate with most antimicrobials than urogenital gonorrhoea [1-4,6,18]. As shown in the present study, ceftriaxone 500 mg monotherapy can be sufficient to eradicate urogenital gonorrhoea but not the concomitant pharyngeal gonorrhoea in the same patient. The pharyngeal gonorrhoea of the patients was instead successfully treated with 1 g ceftriaxone monotherapy or 250 mg ceftriaxone plus 1 g azithromycin. Unfortunately, 1 g ceftriaxone monotherapy may only provide a short-term solution [1,2,4,19,20] judging from the failure to treat the pharyngeal gonorrhoea caused by the first gonococcal XDR strain with 1 g ceftriaxone [10], ceftriaxone MICs of all the identified gonococcal XDR strains [9-11], emergence of ceftriaxone resistance and its anticipated trend, and pharmacodynamic/pharmacokinetic simulations showing that the benefits of increasing the ceftriaxone dose from 500 mg to 1 g are limited when taking into account the high ceftriaxone MICs detected recent years [19]. Consequently, dual antimicrobial therapy, e.g. 500 mg ceftriaxone intramuscularly plus 2 g azithromycin orally, as recommended by the European gonorrhoea guideline [17], should ideally be implemented. It remains unknown if ceftriaxone and azithromycin act synergistically in vivo. However, most importantly, there are no indications, in vitro or in vivo, that they act antagonistically. According to a review from 2010, 99% of urogenital and 98% of pharyngeal gonorrhoea cases may be treatable with 2 g azithromycin monotherapy [21]. Consequently, nearly all gonorrhoea cases (ceftriaxone-resistant or not) are treatable with even 2 g azithromycin monotherapy. Nevertheless, azithromycin monotherapy is not recommended due to the spread of gonococcal strains with high-level resistance to azithromycin and the anticipated rapid selection of azithromycin resistance [1,17,20].

All ceftriaxone treatment failures in the present study (Cases A, B and C) were caused by the internationally spreading multidrug-resistant gonococcal NG-MAST genogroup 1407 clone, which has caused many ESC treatment failures internationally [4-6,9,15]. However, the cefotaxime treatment failure was caused by the unrelated NG-MAST ST4539, which shows that clinical resistance to injectable ESCs is emerging also in other gonococcal clones.

In conclusion, increased awareness of treatment failures particularly with antimicrobial monotherapy, improved implementation of recommended dual antimicrobial therapy (e.g. 500 mg ceftriaxone plus 2 g azithromycin [17]), frequent test of cure (ideally for all cases, and at least for all cases of pharyngeal gonorrhoea), and appropriate verification/falsification of suspected treatment failures (including subsequent tracing of sexual contacts of the index case with the treatment failure) are essential internationally. An enhanced focus on pharyngeal gonorrhoea is also crucial, with increased sampling and prevention, e.g. promotion of condom use also when practising oral sex. Ultimately, novel options for effective treatment of gonorrhoea are imperative.

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Conflict of interest

None declared.

Authors' contributions

MU, AKO, PL, TR, and HF designed and initiated this surveillance of treatment failures. DG, AKO, HJ, OE and MU performed and analysed all the laboratory work. PL, TR, HJ and OE collected clinical information. DG wrote the first draft of the paper and all co-authors were involved in finalising the paper.

*Erratum

The table was corrected and replaced on 12 August 2014.

References

1. Unemo M, Shafer WM. Antimicrobial resistance in Neisseria gonorrhoeae in the 21st century: past, evolution and future. Clin Microbiol Rev. 2014;27(3):587-613. http://dx.doi.org/10.1128/CMR.00010-14
2. Tapsall JW, Ndowa F, Lewis DA, Unemo M. Meeting the public health challenge of multidrug- and extensively drug-resistant Neisseria gonorrhoeae. Expert Rev Anti Infect Ther. 2009;7(7):821-34. http://dx.doi.org/10.1586/eri.09.63
3. Lewis DA. The gonococcus fights back: is this time a knock out? Sex Transm Infect. 2010;86(6):415-21. http://dx.doi.org/10.1136/sti.2010.042648
4. Unemo M, Nicholas RA. Emergence of multidrug-resistant, extensively drug-resistant and untreatable gonorrhea. Future Microbiol. 2012;7(12):1401-22. http://dx.doi.org/10.2217/fmb.12.117
5. Allen VG, Mitterni L, Seah C, Rebbapragada A, Martin IE, Lee C, et al. Neisseria gonorrhoeae treatment failure and susceptibility to cefixime in Toronto, Canada. JAMA. 2013;309(2):163-70. http://dx.doi.org/10.1001/jama.2012.176575
6. Lewis DA, Sriruttan C, Müller EE, Golparian D, Gumede L, Fick D, et al. Phenotypic and genetic characterization of the first two cases of extended-spectrum cephalosporin resistant Neisseria gonorrhoeae infection in South Africa and association with cefixime treatment failure. J Antimicrobial Chemother. 2013;68(6):1267-70. http://dx.doi.org/10.1093/jac/dkt034
7. Read PJ, Limnios EA, McNulty A, Whiley D, Lahra LM. One confirmed and one suspected case of pharyngeal gonorrhoea treatment failure following 500 mg ceftriaxone in Sydney, Australia. Sex Health. 2013;10(5):460-2. http://dx.doi.org/10.1071/SH13077
8. Chen YM, Stevens K, Tideman R, Zaia A, Tomita T, Fairley CK, et al. Failure of ceftriaxone 500 mg to eradicate pharyngeal gonorrhoea, Australia. J Antimicrob Chemother. 2013;68(6):1445-7. http://dx.doi.org/10.1093/jac/dkt017
9. Unemo M, Golparian D, Nicholas R, Ohnishi M, Gallay A, Sednaoui P. High-level cefixime- and ceftriaxone-resistant Neisseria gonorrhoeae in France: novel penA mosaic allele in a successful international clone causes treatment failure. Antimicrob Agents Chemother. 2012;56(3):1273-80. http://dx.doi.org/10.1128/AAC.05760-11
10. Ohnishi M, Golparian D, Shimuta K, Saika T, Hoshina S, Iwasaku K, et al. Is Neisseria gonorrhoeae initiating a future era of untreatable gonorrhea?: detailed characterization of the first strain with high-level resistance to ceftriaxone. Antimicrob Agents Chemother. 2011;55(7):3538-45. http://dx.doi.org/10.1128/AAC.00325-11
11. Cámara J, Serra J, Ayats J, Bastida T, Carnicer-Pont D, Andreu A, et al. Molecular characterization of two high-level ceftriaxone-resistant Neisseria gonorrhoeae isolates detected in Catalonia, Spain. J Antimicrob Chemother. 2012;67(8):1858-60. http://dx.doi.org/10.1093/jac/dks162
12. Martin IM, Ison CA, Aanensen DM, Fenton KA, Spratt BG. Rapid sequence-based identification of gonococcal transmission clusters in a large metropolitan area. J Infect Dis. 2004;189(8):1497-505. http://dx.doi.org/10.1086/383047
13. Chisholm SA, Unemo M, Quaye N, Johansson E, Cole MJ, Ison CA, et al. Molecular epidemiological typing within the European Gonococcal Antimicrobial Resistance Surveillance Programme reveals predominance of a multidrug-resistant clone. Euro Surveill. 2013;18(3):pii=20358.
14. European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoint tables for interpretation of MICs and zone diameters. Version 4.0. Basel: European Society of Clinical Microbiology and Infectious Diseases; 1 Jan 2014. Available from: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/Breakpoint_table_v_4.0.pdf
15. Zhao S, Duncan M, Tomberg J, Davies C, Unemo M, Nicholas R. Genetics of chromosomally mediated intermediate resistance to ceftriaxone and cefixime in Neisseria gonorrhoeae. Antimicrob Agents Chemother. 2009;53(9):3744-51. http://dx.doi.org/10.1128/AAC.00304-09
16. Centers for Disease Control and Prevention (CDC). Update to CDC's Sexually Transmitted Diseases Treatment Guidelines, 2010: Oral cephalosporins no longer a recommended treatment for gonococcal infections. MMWR Morb Mortal Wkly Rep. 2012;61(31):590-4.
17. Bignell C, Unemo M, European STI Guidelines Editorial Board. 2012 European guideline on the diagnosis and treatment of gonorrhoea in adults. Int J STD AIDS. 2013;24(2):85-92. http://dx.doi.org/10.1177/0956462412472837
18. Moran JS. Treating uncomplicated Neisseria gonorrhoeae infections: is the anatomic site of infection important? Sex Transm Dis. 1995;22(1):39-47. http://dx.doi.org/10.1097/00007435-199501000-00007
19. Chisholm SA, Mouton JW, Lewis DA, Nichols T, Ison CA, Livermore DM. Cephalosporin MIC creep among gonococci: time for a pharmacodynamics rethink? J Antimicrob Chemother. 2010;65(10):2141-8. http://dx.doi.org/10.1093/jac/dkq289
20. Ison CA, Deal C, Unemo M. Current and future treatment options for gonorrhoea. Sex Transm Infect. 2013;89(Suppl 4):iv52–6. http://dx.doi.org/10.1136/sextrans-2012-050913
21. Bignell C, Garley J. Azithromycin in the treatment of infection with Neisseria gonorrhoeae. Sex Transm Infect. 2010;86(6):422-6. http://dx.doi.org/10.1136/sti.2010.044586