

Two cases of verified clinical failures using internationally recommended first-line cefixime for gonorrhoea treatment, Norway, 2010

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Citation style for this article:

Unemo M, Golparian D, Syversen G, Vestrheim DF, Moi H. Two cases of verified clinical failures using internationally recommended first-line cefixime for gonorrhoea treatment, Norway, 2010. *Euro Surveill.* 2010;15(47):pii=19721. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19721>

Article published on 25 November 2010

Neisseria gonorrhoeae has developed resistance to most of the available therapeutic antimicrobials. The susceptibility to extended-spectrum cephalosporins, the last remaining first-line treatment option, is decreasing globally. This report describes the first two cases outside Japan of verified gonorrhoea clinical failures using internationally recommended first-line cefixime treatment. Enhanced awareness and more frequent follow-up examination, test-of-cure and appropriate verification/falsification of presumed clinical treatment failures, involving several clinical and laboratory parameters should be strongly emphasised worldwide.

Introduction

Gonorrhoea remains a public health problem worldwide. The prevalence of antimicrobial resistance (AMR) in *Neisseria gonorrhoeae* is high to all antimicrobials previously used as first-line treatments [1,2]. The susceptibility to the extended-spectrum cephalosporins (ESCs) ceftriaxone (injectable) and cefixime (oral), i.e. to the current internationally recommended first-line and last remaining treatment options, is decreasing worldwide [1,2]. Using ceftriaxone, no treatment failure has yet been reported. However, cefixime standard treatment (one oral dose of 400 mg) is the most common treatment in many countries due to the simple oral, single-dose regimen and its affordability. Verified treatment failures have so far only been reported in Japan [3]. Nevertheless in many cases, these failures may not be recognised because many of the gonorrhoea patients are also treated with azithromycin for suspected concomitant chlamydial infection [1,4], and/or because follow-up examinations and test-of-cure are rare [1]. In a recent review describing the latest World Health Organization (WHO) global initiatives to meet the public health challenge posed by the emergence of untreatable gonorrhoea, among others the ideal criteria for verification of gonorrhoea treatment failures are

described. These involve several clinical and laboratory parameters [1].

This report describes the first two cases outside Japan of verified treatment failures of gonorrhoea using internationally recommended first-line treatment cefixime.

Case reports

Case 1

In July 2010 a Norwegian heterosexual man in his 30s presented to a hospital in Norway with purulent urethral discharge and dysuria (day 1). Urethritis and the presence of intracellular diplococci in polymorphonuclear lymphocytes were confirmed after methylene-blue staining of a urethral smear, and the patient was given one oral dose of cefixime (400 mg). *N. gonorrhoeae* was also cultured from an additional urethral sample, and *N. gonorrhoeae*-specific DNA was detected in a urine sample using an in house PCR for the *porA* pseudogene [5]. On day 21, the patient returned with persisting symptoms, and microscopy, culture (urethral sample) and PCR (urine sample) remained positive for *N. gonorrhoeae*. The patient reported no sexual contacts between treatment and test-of-cure. He was then administered one dose of ceftriaxone (500 mg) intramuscularly (IM). On day 29, follow-up examination showed that the symptoms had resolved, and microscopy, culture (urethral sample), and PCR (urine sample) were negative for *N. gonorrhoeae*.

Case 2

In August 2010 another Norwegian heterosexual in his 30s presented to the same hospital in Norway with similar symptoms and initial laboratory findings as case one and was treated with one oral dose of cefixime (400 mg). On day 11, he returned with persisting, although milder, symptoms. Microscopy, culture (urethral sample) and PCR (urine sample) were still positive for *N. gonorrhoeae*. The patient reported no sexual contacts between treatment and test-of-cure. He was

administered one dose of ceftriaxone 500 mg IM. On day 26, follow-up examination showed that the symptoms had resolved, and PCR (urine sample) was negative for *N. gonorrhoeae*.

Characterisation of *N. gonorrhoeae* isolates (before and after treatment)

All *N. gonorrhoeae* isolates were species-confirmed by sugar utilisation test, Phadebact Monoclonal GC Test (Pharmacia Diagnostics), and a *porA* pseudogene [5]. The characterisation of the isolates is summarised in the Table.

In both cases the pre- and post-treatment isolates were indistinguishable using full-length *porB* gene sequencing (identical sequence) and *N. gonorrhoeae* multiantigen sequence typing (NG-MAST; ST1407), performed as previously described [6]. Using Etest, the paired isolates displayed a cefixime minimum inhibitory concentration (MIC) of 0.5 mg/L and 0.25/0.5 mg/L in case 1 and 2, respectively, and indistinguishable antibiograms (beta-lactamase negative, ceftriaxone: 0.125 mg/L, ciprofloxacin: >32 mg/L, azithromycin: 0.5 mg/L, spectinomycin: 12 mg/L, and ampicillin: 1-4 mg/L). According to the breakpoints stated by the Committee on Antimicrobial Susceptibility Testing (EUCAST), these isolates were considered resistant to cefixime (MIC > 0.12 mg/L). Sequencing of resistance determinants for ESCs (*penA*, *mtrR* and *porB1b* alterations) was performed as previously described [7]. All four isolates from the two cases contained an identical *penA* mosaic allele, which had previously been correlated to treatment failures in Japan, and *mtrR* and *penB* resistance determinants that enhance the MICs for ESC further (Table) [8,9].

Discussion and conclusion

This report describes the first two cases outside Japan – with no known links to Japan – of verified clinical treatment failures of urogenital gonorrhoea using standard first-line cefixime treatment, i.e. one dose of 400 mg. The treatment failures were strictly verified using several clinical and laboratory parameters in full accordance to WHO criteria [1,10], i.e. a detailed clinical history was recorded, re-exposure and reinfection was ruled out, the pre-treatment and post-treatment isolates were phenotypically and genetically indistinguishable by highly discriminatory molecular epidemiological typing methods, the MICs of cefixime were substantially enhanced (in vitro-resistance according to current breakpoints), and the isolates contained genetic resistance determinants causing the enhanced cefixime MICs. According to Monte Carlo simulations, a 400 mg dose of cefixime results in median times of free cefixime above the MIC (fT_{MIC}) of only 14.9 h (12.3-18.3 h) and 11.4 h (9.0-14.2 h) for the detected MICs of 0.25 mg/L and 0.5 mg/L, respectively [4]. Accordingly, these levels of cefixime MICs are high enough to cause treatment failures. Most worrying, the gonococcal isolates from the present treatment failures were identified as ST1407, which is a multi-resistant strain that, together with its evolving subtypes, has been shown to circulate in many countries worldwide [11].

In conclusion, cases of clinical failures of urogenital gonorrhoea using the internationally recommended first-line treatment cefixime have now also occurred outside Japan. Besides the two cases identified in Norway (with places of exposure in the Philippines and Spain/Norway), similar rare cases are likely to be identified elsewhere. Accordingly, an enhanced awareness of the existence of failures using cefixime for gonorrhoea treatment needs to be strongly emphasised worldwide as well as the need for more frequent follow-up examination, test-of-cure and appropriate verification/falsification of presumed clinical treatment

TABLE

Characteristics of two *Neisseria gonorrhoeae* cases of verified clinical failure using internationally recommended first-line cefixime treatment, Norway, 2010

Age (years) / Sex	Possible place of exposure	Treatment	Diagnostics (pre-treatment/post-treatment isolate)	MIC (mg/L)		NG-MAST	<i>penA</i> allele ^a	<i>mtrR</i> ^b	<i>penB</i> ^c	
				Cefixime	Ceftriaxone				G120K	A121N
37/male	Philippines	Cefixime 400 mg ⁻¹ oral dose	Microscopy, culture, PCR	0.5	0.125	ST1407	Mosaic	A-del in promoter	G120K	A121N
			Microscopy, culture, PCR	0.5	0.125	ST1407	Mosaic	A-del in promoter	G120K	A121N
31/male	Spain/Norway	Cefixime 400 mg ⁻¹ oral dose	Microscopy, culture, PCR	0.25	0.125	ST1407	Mosaic	A-del in promoter	G120K	A121N
			Microscopy, culture, PCR	0.5	0.125	ST1407	Mosaic	A-del in promoter	G120K	A121N

MIC: minimum inhibitory concentration; NG-MAST: *Neisseria gonorrhoeae* multiantigen sequence typing; PCR: polymerase chain reaction; ST: sequence type.

^a *penA* mosaic allele encodes the mosaic penicillin-binding protein 2 (PBP2), which causes decreased susceptibility to extended-spectrum cephalosporins.

^b A-del in promoter: characteristic single nucleotide (A) deletion in the inverted repeat of the promoter region of *mtrR* that causes overexpression of the MtrCDE efflux pump, which results in a further decreased susceptibility to extended-spectrum cephalosporins.

^c *penB*: alterations of amino acids 120 and 121 in the porin PorB1b that cause a decreased intake of extended-spectrum cephalosporins and, accordingly, a further decreased susceptibility to extended-spectrum cephalosporins.

failures. Pharyngeal gonorrhoea poses an additional challenge as it is often asymptomatic, more difficult to eradicate, and may act as a reservoir for emergence of resistance [1]. Accordingly, it is important to collect information regarding the patients' sexual practices and to take also extragenital samples.

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