

# Treatment failure of pharyngeal gonorrhoea with internationally recommended first-line ceftriaxone verified in Slovenia, September 2011

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We describe the second case in Europe of verified treatment failure of pharyngeal gonorrhoea, caused by an internationally occurring multidrug-resistant gonococcal clone, with recommended first-line ceftriaxone 250 mg in Slovenia. This is of grave concern since ceftriaxone is last remaining option for empirical treatment. Increased awareness of ceftriaxone failures, more frequent test-of-cure, strict adherence to regularly updated treatment guidelines, and thorough verification/falsification of suspected treatment failures are essential globally. New effective treatment options are imperative.

## Background

*Neisseria gonorrhoeae* has developed resistance to all antimicrobial drugs previously used as first-line treatment for gonorrhoea [1]. Resistance to currently recommended first-line third-generation cephalosporins – cefixime and ceftriaxone – is emerging [1-3], and treatment failures with cefixime have been verified in Japan [4] and several European countries, namely Norway [5], the United Kingdom [6], Austria [7] and France [8]. One failure to treat pharyngeal gonorrhoea with ceftriaxone, the last remaining option for empirical treatment, has also been verified in Europe (Sweden) [9]. It is likely that treatment failures with ceftriaxone will initially accumulate for pharyngeal gonorrhoea because these infections are harder to treat than urogenital infections [1,10,11]. It is of grave concern that during the past year, the first three extensively drug-resistant (XDR) [1] *N. gonorrhoeae* strains that also had high-level ceftriaxone resistance were reported from Japan, France and Spain [8,12,13].

In this emergent situation of fear that gonorrhoea may become untreatable [1,8,12], the European Centre for Disease Prevention and Control (ECDC) has prepared a response plan for the European Union [14]. The World Health Organization (WHO) has published the

'Global Action Plan to Control the Spread and Impact of Antimicrobial Resistance in *Neisseria gonorrhoeae*' [15].

This report describes a ceftriaxone treatment failure of pharyngeal gonorrhoea in Slovenia in 2011, which is the second one strictly verified in Europe (and possibly globally).

## Case description

In early September 2011, a Slovenian bisexual woman in her early 30s visited a dermatovenereologist in Ljubljana, Slovenia (Day 1). She had no symptoms of gonorrhoea, however, she was sampled and administered the internationally recommended first-line treatment of 1×250 mg ceftriaxone intramuscularly (Table), based on the fact that she had had unprotected oral and vaginal sex with gonorrhoea-positive casual male partner in late August 2011 in Belgrade, Serbia. The partner could later not be traced in Serbia.

Microscopy of Gram-stained smear of a cervical specimen was negative for *N. gonorrhoeae*. However, two days later (Day 3), a pharyngeal culture was shown to be positive for *N. gonorrhoeae*, while the cervical culture was negative. *Chlamydia trachomatis* DNA was identified in an additional cervical sample, using the COBAS TaqMan CT Test v2.0 (Roche Diagnostics). During a follow-up visit seven days after the initial visit (Day 8), a test-of-cure (TOC) pharyngeal culture was taken and examination showed no signs or symptoms of pharyngeal gonorrhoea, and she was given doxycycline at a dosage of 100 mg twice a day, for seven days, for a concomitant chlamydial infection. However, two days later (Day 10) the TOC culture confirmed gonococci in a pharyngeal sample. About three weeks later (Day 30), the patient returned with symptoms of acute pharyngitis (pain, inflammation and fever) and was given one dose of 250 mg ceftriaxone intramuscularly and

one oral dose of 1 g azithromycin. Finally, a follow-up examination after about four months (Day 173) showed no signs of infection, and a pharyngeal TOC culture was negative for *N. gonorrhoeae* (Table). The patient repeatedly reassured that she had not had any sexual contacts between the ceftriaxone therapy and the TOC.

### Characterisation of *N. gonorrhoeae* isolates

The pre- and post-treatment *N. gonorrhoeae* isolates were species-confirmed by sugar utilisation test and Phadebact Monoclonal GC Test (Pharmacia Diagnostics). The isolates were indistinguishable using serovar determination (Bpyut), full-length *porB* gene sequencing, multilocus sequence typing (MLST; ST1901 [12]), and *N. gonorrhoeae* multi-antigen sequence typing (NG-MAST; ST1407 [16]). Using Etest (AB bioMérieux), both isolates showed a ceftriaxone minimum inhibitory concentration (MIC) of 0.125 mg/L (Table), and overall indistinguishable antibiograms (cefixime 0.25 mg/L, spectinomycin 16 mg/L, azithromycin 0.5 mg/L, and ciprofloxacin 32 mg/L) and were beta-lactamase-negative. According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [17], the MIC of ceftriaxone for these isolates were equal to the resistance breakpoint ( $>0.125$  mg/L). Sequencing of resistance determinants for third-generation cephalosporins [1,8,12,18,19] showed that both isolates contained an identical *penA* mosaic allele XXXIV [12], which has been correlated with decreased susceptibility or resistance to third-generation cephalosporins and treatment failure with cefixime [5,20,21]. In addition, they contained *mtrR* and *penB* alterations that further increase the MICs of third-generation cephalosporins [1,8,12,19].

### Discussion

This study describes the second verified case in Europe (possibly globally) of treatment failure of pharyngeal gonorrhoea with the internationally recommended first-line treatment of 250 mg ceftriaxone, the last remaining treatment option. The failure was strictly verified in accordance with WHO recommendations [1,15], i.e. detailed clinical records were obtained, reinfection was excluded as much as possible, pre- and post-treatment isolates were indistinguishable using highly discriminatory typing, ceftriaxone MICs were elevated, and the isolates contained well-known cephalosporin resistance determinants. The reporting of the case was unfortunately delayed because it took several months before the patient returned for follow-up examination and TOC after the third antimicrobial treatment (to prove successful eradication of infections).

This case shows that ceftriaxone at a dosage of  $1 \times 250$  mg may in rare cases not be enough for treatment of pharyngeal gonorrhoea caused by gonococcal strains with ceftriaxone MICs of 0.125 mg/L. A 250 mg ceftriaxone dose also results in median times of free ceftriaxone above the MIC of only 24.1 h (range: 10.5–52.2 h) for the detected MIC of 0.125 mg/L [22], and rare treatment failures may happen in the lower range. Nevertheless, these cases are likely to be treatable with enhanced ceftriaxone doses or dual antimicrobial treatment that has already been introduced as first-line empiric treatment in the United States [10] and the United Kingdom [23]. It may be crucial to promptly revise also other national and regional treatment guidelines, and a revision of the European guidelines from the International Union against Sexually Transmitted Infections (IUSTI) and WHO [2] are currently in progress.

**TABLE**

Details of verified ceftriaxone treatment failure of one case of *Neisseria gonorrhoeae* pharyngeal infection, Slovenia, September 2011

Age (years)/ Sex	Place of exposure	Healthcare clinic (day of presentation)	Symptoms (signs)	Positive diagnostics	Negative diagnostics	MIC (mg/L) <sup>a</sup> Ceftriaxone	MLST (NG-MAST) <sup>a</sup>	Treatment
32/ female	Serbia (Belgrade)	STD (1)	- (-)	GC culture (pharynx) and CT PCR (cervix)	GC culture (cervix) and microscopy (cervix)	0.125	ST1901 (ST1407)	Ceftriaxone 250 mg $\times$ 1 IM
		STD (8)	- (-)	GC culture (pharynx)	NA	0.125	ST1901 (ST1407)	Doxycycline 100 mg b.i.d., 7 days PO <sup>b</sup>
		STD (30)	Pharyngitis (inflammation in pharynx)	NA	NA	NA	NA	Ceftriaxone 250 mg $\times$ 1 IM and azithromycin 1 g $\times$ 1 PO
		STD (173)	- (-)	NA	GC culture (pharynx), CT PCR (cervix)	NA	NA	NA

b.i.d.: twice a day; CT: *Chlamydia trachomatis*; GC: *Neisseria gonorrhoeae*; IM: intramuscular administration; MIC: minimum inhibitory concentration; MLST: multilocus sequence typing; NA: not applicable; NG-MAST: *Neisseria gonorrhoeae* multi-antigen sequence typing; PCR: polymerase chain reaction; PO: per oral administration; STD: sexually transmitted diseases.

<sup>a</sup> MIC (mg/L) as determined by Etest, MLST [12] and NG-MAST [16] of *N. gonorrhoeae* pre- and post-treatment isolates.

<sup>b</sup> Treatment of concomitant *C. trachomatis* infection.

It is worrying that the gonococcus causing this treatment failure was assigned to MLST ST1901 and NG-MAST ST1407, which is a multidrug-resistant gonococcal clone that also shows decreased susceptibility and resistance to cefixime and is spreading worldwide [5,7,8,13,20,21,24-28]. The previously reported treatment failures with cefixime in Norway [5], Austria [7], France [8] and likely in the United Kingdom [6], were caused by this gonococcal clone or its evolving subtypes. This clone has also shown its capacity to develop high-level resistance to ceftriaxone [8,13].

In conclusion, the second case in Europe (possibly worldwide) of clinical failure using standard ceftriaxone treatment for pharyngeal gonorrhoea, caused by an internationally occurring multidrug-resistant gonococcal clone, has been strictly verified in Slovenia. An increased awareness of treatment failures with ceftriaxone, more frequent TOC (all cases of pharyngeal cases may be crucial), strict adherence to appropriate treatment guidelines, which need to be regularly updated based on antimicrobial resistance surveillance data, and thorough verification/falsification of suspected treatment failures (including subsequent tracing of sexual contacts of the index case with the treatment failure) are essential globally. A stronger focus on pharyngeal gonorrhoea, including increased sampling of pharyngeal specimens and promotion of condom use also when practising oral sex, is also crucial because pharyngeal infection is harder to treat than urogenital infection, relatively common, and is frequently an asymptomatic reservoir for infection and emergence of resistances [1,5]. Ultimately, new options for effective treatment of gonorrhoea are imperative.

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