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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.

N. gonorrhoeae was detected in a urine specimen and pharyngeal swab on nucleic acid amplification testing (Abbott RealTime CT/NG assay) and in a culture of a urethral specimen. All *N. gonorrhoeae*–positive specimens on nucleic acid amplification testing were also confirmed as positive with the use of a duplex polymerase-chain-reaction (PCR) assay targeting the *porA* pseudogene and *opa* genes. According to the local laboratory, testing with the disk-diffusion method showed that the *N. gonorrhoeae* strain was resistant to cefuroxime, ciprofloxacin, and tetracycline. The patient declined to undergo testing for syphilis and human immunodeficiency virus infection.

The patient received one dose of ceftriaxone intramuscularly at a dose of 500 mg plus 1 g of azithromycin orally.[3] At the test of cure on day 15, a urine specimen was negative, but a pharyngeal swab remained positive for *N. gonorrhoeae* on the identical nucleic acid amplification test. The patient reported that he did not have sexual contact after treatment, and he did not return until day 79, when a pharyngeal swab was positive for *N. gonorrhoeae* on the nucleic acid amplification test.

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 showed that the strain was resistant to ceftriaxone, azithromycin, cefixime, cefotaxime, penicillin, tetracycline, and ciprofloxacin, but it was susceptible to spectinomycin. Whole-genome sequencing of one isolate with the use of Illumina MiSeq (BioProject accession number PRJNA305360) and conventional sequencing identified *N. gonorrhoeae* multilocus sequence type ST1901 and a new *N. gonorrhoeae* multiantigen sequence type ST12133 in all specimens (the isolate and PCR specimens). Resistance determinants,[1] mosaic penicillin-binding protein 2 X (which decreases ceftriaxone target affinity), deletion of one adenine in the *mtrR* promoter (which increases MtrCDE efflux of ceftriaxone and azithromycin), and *penB* (which decreases PorB influx of ceftriaxone and azithromycin) were detected in all specimens.

The patient was considered to have treatment failure because the post-treatment isolate was resistant to ceftriaxone and azithromycin, all specimens contained resistance determinants and identical sequence types, and reinfection was deemed to be unlikely. The *N. gonorrhoeae* strain that caused the failure belonged to the identical *N. gonorrhoeae* multiantigen sequence

Table 1. Failure of Dual Antimicrobial Therapy in a Patient with Gonorrhea.*

Day, Symptoms, and Test Results	Ceftriaxone	Azithromycin	Multilocus Sequence Type	Multiantigen Sequence Type	PBP2	*mtrR*⁂	*penB*§	23S rRNA¶	Treatment
	MIC (mg/liter)†								
Day 1, urethral discharge and dysuria									
Positive: *N. gonorrhoeae* culture (urethra) and *N. gonorrhoeae* PCR (urine and pharynx)	NA	NA	NA	NA	NA	NA	NA	NA	One dose of ceftriaxone 500 mg intramuscularly plus azithromycin 1 g orally
Negative: *Chlamydia trachomatis* PCR (urine and pharynx)	NA	NA	NA	NA	NA	NA	NA	NA	
Day 15, no symptoms									
Positive: *N. gonorrhoeae* PCR (pharynx)	NA	NA	ST1901	ST12133	PBP2 X	Adenine deletion	KD	WT	None
Negative: *N. gonorrhoeae* PCR (urine)	NA	NA	NA	NA	NA	NA	NA	NA	
Day 79, no symptoms									
Positive: *N. gonorrhoeae* PCR (pharynx)	NA	NA	ST1901	ST12133	PBP2 X	Adenine deletion	KD	WT	None
Negative: *N. gonorrhoeae* PCR (urine)	NA	NA	NA	NA	NA	NA	NA	NA	
Day 98, no symptoms									
Positive: *N. gonorrhoeae* culture (pharynx) and *N. gonorrhoeae* PCR (pharynx)	0.25, resistant	1, resistant	ST1901	ST12133	PBP2 X	Adenine deletion	KD	WT	One dose ceftriaxone 1 g intramuscularly plus azithromycin 2 g orally
Negative: *N. gonorrhoeae* PCR (urine)	NA	NA	NA	NA	NA	NA	NA	NA	
Day 112, no symptoms									
Negative: *N. gonorrhoeae* PCR (pharynx)	NA	NA	NA	NA	NA	NA	NA	NA	None

* KD denotes lysine and aspartic acid, MIC minimum inhibitory concentration, NA not applicable, PBP2 penicillin-binding protein 2, PCR polymerase chain reaction, rRNA ribosomal RNA, and WT wild type.

† Resistance breakpoints according to the European Committee on Antimicrobial Susceptibility Testing (www.eucast.org) were used (i.e., MIC, >0.125 mg per liter for ceftriaxone, and MIC, >0.5 mg per liter for azithromycin). The Clinical and Laboratory Standards Institute (http://clsi.org) does not state any breakpoints for azithromycin; however, isolates with a MIC of 0.25 mg per liter or less of ceftriaxone are considered to be susceptible. The gonococcal isolate was also resistant to cefixime (MIC, 0.5 mg per liter), cefotaxime (MIC, 1 mg per liter), penicillin G (MIC, 4 mg per liter), tetracycline (MIC, 4 mg per liter), and ciprofloxacin (MIC, >32 mg per liter); however, it was susceptible to spectinomycin (MIC, 12 mg per liter).

⁂ Deletion of one adenine in the inverted repeat sequence of the *mtrR* promoter results in an overexpression of the MtrCDE efflux pump.

§ The *penB* mutations in *porB1b* decrease the influx of many antimicrobial agents through an outer membrane protein channel (PorB1b).

¶ Mutations in the macrolide target 23S rRNA result in azithromycin resistance (in positions C2611 and A2059).

type genogroup as multilocus sequence type ST1901, *N. gonorrhoeae* multiantigen sequence type ST6800, which is spreading in Japan and is associated with decreased susceptibility to cephalosporins and azithromycin.[4,5]

In addition, the treatment failure reflected difficulties in treating pharyngeal gonorrhea as compared with urogenital gonorrhea.[1,3] Pharyngeal gonorrhea is rare in heterosexual men. However, this patient reported no homosexual exposure; this highlights the need to test all potential sites of infection. A test of cure, partner notification and treatment, and effective antimicrobial stewardship and robust surveillance need to be considered so that gonorrhea may continue to be a treatable infection.

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