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Emergence of Increased Azithromycin Resistance During Unsuccessful Treatment of *Neisseria gonorrhoeae* Infection With Azithromycin (Portland, OR, 2011)

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Abstract

We describe the emergence of an azithromycin-resistant *Neisseria gonorrhoeae* variant in a man from Portland, Oregon, during sole treatment with 2 g azithromycin. This report highlights the ease with which gonococcal macrolide resistance can emerge, the threat of multidrug resistant *N. gonorrhoeae*, and the need for adherence to Centers for Disease Control and Prevention treatment guidelines.

CASE REPORT

Gonorrhea remains the second most common bacterial sexually transmitted infection worldwide. Sadly, the treatment of gonorrhea has been complicated by the notorious ability of the etiological agent, *Neisseria gonorrhoeae*, to rapidly develop resistance to all therapeutic antimicrobials previously used as first-line treatments.[1] Although azithromycin 2 g orally has proven effective for the treatment of gonorrhea[2] and is considered an attractive option for treatment of patients with cephalosporin allergy, azithromycin monotherapy is not recommended by the Centers for Disease Control and Prevention (CDC) because of concerns about rapid emergence of macrolide resistance.[3] Azithromycin-resistant *N. gonorrhoeae* strains defined by a minimum inhibitory concentration (MIC) of 2.0 μg/mL or greater,[4] including high-level azithromycin-resistant (AzHLR) strains with MIC of 256 μg/mL or greater, have been identified in many countries.[4–9] Surprisingly, there are few reports of treatment failures with 2 g of azithromycin,[10] compared with the documented

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cases of treatment failures with 1-g dose of azithromycin.[11–13] We report a case of verified treatment failure with 2 g of azithromycin for urogenital gonorrhea and the emergence of a variant of azithromycin-resistant *N. gonorrhoeae* during treatment.

In August 2011, a 26-year-old man (index patient) presented to a sexually transmitted disease clinic in Multnomah County, OR, with dysuria and urethral discharge of 7 days duration. He reported sex with 2 male partners in the past 60 days and denied recent travel. Examination revealed urethral discharge; Gram-negative intracellular diplococci were identified. He reported penicillin allergy and was treated with azithromycin 2 g orally. A urethral discharge specimen was *N. gonorrhoeae* culture positive. A urine specimen was positive for N. gonorrhoeae and negative for *Chlamydia trachomatis* by nucleic acid amplification test (NAAT). On the twelfth day after treatment, he returned to the clinic with persistent urethritis. He reported no sex since his initial clinic visit. He again had urethral discharge, which contained Gram-negative intracellular diplococci, and was *N. gonorrhoeae* culture positive. His urine NAAT was also *N. gonorrhoeae* positive and *C. trachomatis* negative. He declined ceftriaxone and was treated with the available oral cephalosporin (cefpodoxime, 400 mg) and azithromycin 1 g orally with no subsequent signs or symptoms of medication allergy, despite his reported penicillin allergy. His symptoms resolved after treatment with cefpodoxime and azithromycin. A third urethral specimen was *N. gonorrhoeae* culture negative, and his urine NAAT was also *N. gonorrhoeae* and *C. trachomatis* negative.

One of the index patient's partners (SP-A) presented 6 days after the patient's initial visit. He named the index patient as his only recent partner and was treated with azithromycin 2 g orally because of self-reported penicillin allergy. A rectal specimen from SP-A was *N. gonorrhoeae* culture positive. His test-of-cure rectal, urethral, and pharyngeal specimens were all *N. gonorrhoeae* culture negative; his urine NAAT was also *N. gonorrhoeae* and *C. trachomatis* negative. A second partner (SP-B) was notified of exposure to gonorrhea and referred to the Multnomah County clinic. He initially declined evaluation and treatment but presented in December 2011. His urine NAAT was *N. gonorrhoeae* and *C. trachomatis* negative, and his rectal and pharyngeal specimens were all *N. gonorrhoeae* culture negative.

The pre-treatment and post-treatment urethral isolates from the index patient, designated P1101 and P1102, respectively, were sent to the University of Washington Neisseria Reference Laboratory for antimicrobial susceptibility testing (AST) as part of the Gonococcal Isolate Surveillance Project (GISP). The Gonococcal Isolate Surveillance Project is a CDC-supported sentinel surveillance system that monitors *N. gonorrhoeae* antimicrobial susceptibility trends in the United States. The rectal isolate from SP-A was also transported to the University of Washington Neisseria Reference Laboratory for AST. Agar dilution ASTwas performed according to the GISP protocol using previously described quality control *N. gonorrhoeae* strains.[14] Genotypic characterization was done by pulsed field gel electrophoresis (PFGE) with 3 restriction endonucleases, *Nhe*I, *Spe*I, and *Bgl*II, used separately and *N. gonorrhoeae* multiantigen sequence typing (NGYMAST), screening for azithromycin resistance–associated mutations in the peptidyltransferase region of domain Vof the 23S rRNA gene and mutations in the *mtrR* promoter region and/or within the *mtrR*-

coding region, using previously described polymerase chain reaction assays and sequencing.[15–18]

P1101 had an azithromycin MIC of 1.0 μg/mL, whereas P1102 exhibited an increased azithromycin MIC of 8.0 μg/mL, but the other AST results were identical (penicillin, tetracycline, 2.0 μg/mL; ciprofloxacin, 8.0 μg/mL; cefpodoxime, 0.5 μg/mL; cefixime, 0.125 μg/mL; and ceftriaxone, 0.06 μg/mL). Antimicrobial susceptibility testing results for the SP-A rectal isolate (penicillin, ≤0.25 μg/mL; tetracycline, 1.0 μg/mL; ciprofloxacin, ≤0.015 μg/mL; cefpodoxime, 0.03 μg/mL; cefixime, ≤0.015 μg/mL; and ceftriaxone, ≤0.008) differed from those of P1101 and P1102. The pre-treatment and post-treatment isolates both were NGYMAST ST3709 (*por*, 2237; *tbpB*, 110), and were indistinguishable by PFGE using separate digests with 3 restriction endonucleases (data not shown). The SP-A rectal isolate had PFGE patterns that were distinctly different from those of P1101 and P1102 (data not shown); and its novel ST6683 (*por*, 1900; *tbpB*, 29) was also different from ST3709 for the index patient's P1101 and P1102 by both hypervariable alleles (www.ng-mast.net).

P1101 and P1102 both had a deletion of adenine (A) within the 13-base-pair inverted repeat of the *mtrR* promoter (Table 1), which causes overexpression of the *mtrCDE*-encoded efflux pump.[19] It is interesting to note that the post-treatment isolate had the C2599T (*N. gonorrhoeae* numbering) mutations in all 4 alleles of the 23S rRNA concurrently with an H105Y amino acid alteration within the *mtrR* coding sequence, whereas the pre-treatment isolate had C2599T mutations in only 2 alleles of the 23S rRNA but had no mutation in the *mtrR* coding region (Table 1). Unlike the A2143G (*N. gonorrhoeae* numbering)/A2059G (*Escherichia coli* numbering) mutations previously shown to be associated with AzHLR (MIC ≥ 256 μg/mL) isolates from Argentina, the United Kingdom, and the United States,[9,20,21] the C2599T mutations have only been reported in isolates with azithromycin MIC of 4 to 8 μg/mL.[17,20] The H105Y mutation and other *mtrR* mutations (A39T, G45D, and E202G) have been shown to elevate resistance of *N. gonorrhoeae* to various macrolides and hydrophobic antimicrobial agents.[22]

This index case fulfills the criteria for a verified treatment failure[23]; a variant of *N. gonorrhoeae* with azithromycin resistance–associated mutations conferring increased resistance was selected during unsuccessful sole treatment with azithromycin. This is supported by previously published in vitro selection of spontaneous mutants of *N. gonorrhoeae*, which resulted in increased azithromycin MIC[17,21], and 2 previous reports of gonococcal de novo increased azithromycin resistance which did not document the possible resistance mechanisms.[10,13] It is also noteworthy that the azithromycin MIC of the pre-treatment isolate was elevated but less than the defined azithromycin resistance of MIC of 2.0 μg/mL or greater.[4] This finding concurs with previous cases of treatment failures with 1 g azithromycin in which the azithromycin MICs (0.125–0.5 μg/mL) of the pre-treatment isolates were consistently well within the susceptible MIC range.[11,12] A prospective comparison of erythromycin base and estolate (initial 1.5-g dose then 500 mg 4 times daily for a total of 9.0 g) for treating gonococcal urethritis demonstrated an incremental increase in treatment failure rates as the erythromycin MIC for pre-treatment isolates increased from 0.06 to 2.0 μg/mL.[24] To our knowledge, the relationship of azithromycin MIC to treatment failure with 2-g dose of azithromycin has not yet been established in recent prospective

published studies. Azithromycin-resistant *N. gonorrhoeae* isolates have been reported from Europe, Latin America and the Caribbean, East Asia, and other parts of the world.[4,6–8] Although GISP has not observed clear azithromycin susceptibility trends during the past several years,[25] a cluster of gonococcal isolates with azithromycin resistance was identified in San Diego in 2009 among men who have sex with men,[5] and an isolate with high-level azithromycin resistance was recently identified in Hawaii.[9] However, the ST3709 associated with azithromycin treatment failure in the index case is different from those reported previously for the azithromycin-resistant *N. gonorrhoeae* isolates from Hawaii (ST649) and San Diego (ST2992 and ST4198). Disturbingly, both isolates from the index patient had elevated cefixime MIC (0.125 μg/mL) and were ST3709, which is highly related to ST1407, a globally disseminated gonococcal clone previously associated with cefixime treatment failure in Norway and Austria.[26,27] ST3709 and ST1407 share the *tbpB* allele (allele 110), and the *por* alleles (*por*-2237 and *por*-908) differ at only one nucleotide (www.ng-mast.net). The emergence and spread of gonococci with both cephalosporin and macrolide resistance would gravely complicate treatment of gonorrhea.

One puzzling aspect of this case is that neither of the patient's sex partners seemed to be infected with the strain which infected the patient. The isolate from SP-A had a novel ST6683; the PFGE patterns and AST results also differed from those of the isolates from the index patient. It is possible that the patient had at least 1 other sex partner, although he denied this repeatedly. An alternative explanation may be that SP-A was infected with both ST3709 and ST6683 strains, but only the ST6683 gonococcal strain was isolated from his rectal specimen.

Multidrug resistant *N. gonorrhoeae* is a growing public health threat. The effectiveness of the cephalosporins, the cornerstone of treatment of gonorrhea, is threatened by declining gonococcal susceptibility to cefixime in the United States and worldwide.[28] The Centers for Disease Control and Prevention recommend the use of combination therapy with ceftriaxone 250 mg as a single intramuscular injection together with 1 dose of oral azithromycin 1 g or doxycycline 100 mg twice daily for 7 days as the most effective treatment regimen for urogenital, anorectal, and pharyngeal gonorrhea.[29] The gonorrhea treatment guidelines further recommend restricting use of azithromycin monotherapy to limited circumstances. As in this case, clinicians occasionally prescribe azithromycin as 2-g oral monotherapy to patients with reported penicillin allergy. Clinicians should be mindful that adverse events, such as gastrointestinal intolerance, are sometimes inaccurately reported as allergy by patients who self-report penicillin allergy. Prevalence of actual IgE–mediated penicillin hypersensitivity is low among persons with reported penicillin allergy.[30] Furthermore, penicillin allergy may not equate to cephalosporin allergy. If azithromycin monotherapy is prescribed, clinicians should ask the patient to return within 1 week for a test of cure, using either culture or NAAT. If the follow-up NAAT is positive for *N. gonorrhoeae*, a culture for confirmation and AST should be performed.[29] This report highlights the emerging threat of multidrug-resistant *N. gonorrhoeae*. New antimicrobial options are urgently needed to prevent the emergence of untreatable gonococcal infections.

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TABLE 1.

Characterization of Pre-treatment and Post-treatment *N. gonorrhoeae* Isolates From the Index Patient

Isolate	mtrR Promoter Region Mutations	Amino Acid Changes in Coding Region of MtrR	23S rRNA*			
			Allele 1	Allele 2	Allele 3	Allele 4
Pre-treatment P1101	Deletion of A	No mutation	C2599T mutation	No mutation	No mutation	C2599T mutation
Post-treatment P1102	Deletion of A	H105Y mutation	C2599T mutation	C2599T mutation	C2599T mutation	C2599T mutation
Susceptible control strain SC113	No mutation	No mutation	No mutation	No mutation	No mutation	No mutation

*23S rRNA *N. gonorrhoeae* numbering.

A indicates adenine; C, cytosine; T, thymine; H, histidine; Y, tyrosine.

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