Emerging international strain of multidrug-resistant *Neisseria gonorrhoeae*

Infection in a man with urethral discharge

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Gonorrhea is the second most common notifiable sexually transmitted infection (STI) in Canada. The incidence of gonorrhea in Canada has been increasing steadily in the past decade, rising from 33.5 cases per 100 000 population in 2010 to 55.4 cases per 100 000 population in 2015.[1] Gonorrhea is a frequent cause of urethritis in men and cervicitis in women. Common complications include epididymitis, pelvic inflammatory disease, and infertility.

Treatment options are increasingly limited owing to the evolution of antimicrobial resistance (AMR). The mainstay of treatment worldwide includes ceftriaxone or cefixime, but strains resistant to both these antibiotics threaten their usefulness.[2]

Case

A 36-year-old heterosexual man presented to a walk-in clinic in Calgary, Alta, in early May 2018 with purulent urethral discharge and dysuria. He reported that, in the preceding 6 months, he had had vaginal sex in December 2017 with a woman visiting from China and he had had vaginal and oral sex with a woman from Taiwan in February 2018. Condoms were used for vaginal sex but not for oral sex. He could not recall any identifying information for his contacts; partner notification was therefore impossible. Past medical history was unremarkable, and he had no previous history of STIs.

Nucleic acid amplification testing (NAAT) for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* was performed from a urethral swab collected during

Editor's key points

- Gonorrhea is the second most common notifiable sexually transmitted infection in Canada, and incidence has been on the rise. Owing to the evolution of antimicrobial resistance (AMR), treatment options are increasingly limited.
- Combination therapy with an extended-spectrum cephalosporin (a single 800-mg dose of oral cefixime or a single 250-mg dose of intramuscular ceftriaxone) plus a single 1-g dose of oral azithromycin is recommended for the treatment of uncomplicated anogenital gonococcal infection, but strains resistant to these antibiotics have been reported in many countries.
- Nucleic acid amplification testing has become the preferred method for detecting *Neisseria gonorrhoeae*, but culture is still required for antibiotic susceptibility testing.
- This case highlights the importance of AMR surveillance and the need for culture in cases of treatment failure or for patients with sexual contact from countries with a high prevalence of AMR. Cases of presumed treatment failure should be reported to the local public health authority for assistance with management and partner notification.

Points de repère du rédacteur

- La gonorrhée est la deuxième infection transmise sexuellement à déclaration obligatoire la plus courante au Canada, et son incidence est à la hausse. En raison de l'évolution de la résistance aux antimicrobiens (RAM), les options thérapeutiques sont de plus en plus limitées.
- Une thérapie combinée, composée de céphalosporine à large spectre (une dose unique de 800 mg par voie orale de céfixime ou une dose unique de 250 mg de ceftriaxone par voie intramusculaire) et d'une seule dose de 1 g par voie orale d'azithromycine, est recommandée pour traiter une infection anogénitale à gonocoques sans complication, mais des souches résistantes à ces antibiotiques ont été signalées dans de nombreux pays.
- Le test d'amplification des acides nucléiques est devenu la méthode privilégiée pour la détection des *Neisseria gonorrhoeae*, mais il faut aussi effectuer une culture pour analyser la sensibilité aux antibiotiques.
- Ce cas met en évidence l'importance de la surveillance de la RAM et la nécessité de procéder à une culture dans les cas où le traitement échoue ou pour les patients ayant eu des partenaires sexuels de pays où la prévalence de la RAM est élevée. Les cas d'échec présumé du traitement devraient être signalés aux autorités locales de la santé publique pour obtenir de l'aide dans la prise en charge et prévenir les partenaires.

the visit to the medical clinic. Results were positive for *N gonorrhoeae* and negative for *C trachomatis*. He received the preferred treatment according to Canadian STI treatment guidelines, consisting of a single 250-mg dose of intramuscular (IM) ceftriaxone plus a single 1-g dose of oral azithromycin.[3] His symptoms initially resolved but returned 4 weeks after treatment, and results of repeat NAAT were again positive for *N gonorrhoeae*.

He was referred to the STI clinic in Calgary for further management, where he presented with purulent urethral discharge. Findings on examination of the external genitalia were otherwise normal. He denied any sexual contacts since February 2018. The patient was re-treated with 250 mg of IM ceftriaxone plus a single 1-g dose of oral azithromycin, pending further test results.

Subsequent culture from the urethral swab was positive for *N gonorrhoeae;* culture from the pharyngeal swab was negative for *N gonorrhoeae*. Syphilis and HIV serologic test results were negative. The isolate was found by gradient diffusion testing to be resistant to ceftriaxone and cefixime at the Alberta Provincial Laboratory for Public Health. Antibiotic susceptibility testing was confirmed at the National Microbiology Laboratory by agar dilution and showed resistance to multiple antibiotics: ceftriaxone, resistant (minimum inhibitory concentration [MIC] of 0.5 µg/mL); cefixime, resistant (MIC of 2 µg/mL); penicillin, resistant (MIC of 2 µg/mL); ciprofloxacin, resistant (MIC of 32 µg/mL); azithromycin, susceptible (MIC of 0.25 µg/mL); tetracycline, resistant (MIC of 2 µg/mL). The interpretations of susceptibility met the criteria of the Clinical Laboratory Standards Institute and the European Committee on Antimicrobial Susceptibility Testing. For cefixime and ceftriaxone, the World Health Organization criteria for decreased susceptibility were also met (≥0.25 µg/mL and ≥0.125 µg/mL, respectively).[4-6]

Because the patient was persistently symptomatic, he was treated with 240 mg of IM gentamicin and a single 2-g oral dose of azithromycin, as per national STI treatment guidelines.[7] A test of cure 4 weeks after treatment showed negative urethral culture and negative urine NAAT results. At this time, the patient's symptoms had completely resolved.

Discussion

Nucleic acid amplification testing has become the preferred method for detecting *N gonorrhoeae,* thus resulting in a decline in the number of cultures available for antimicrobial susceptibility testing.[8] In contrast to culture, NAAT is highly sensitive and does not require a viable bacterium, which allows testing in remote areas where time-to-culture from collection is lengthy. Owing to the ability to detect very small amounts of bacteria, noninvasive specimens such as first-void urine can be used for NAAT. Despite the advantages of NAAT, culture is still required for antibiotic susceptibility testing. Current Canadian guidelines recommend culture in cases of suspected treatment failure or AMR (eg, sexual contact with an individual from a country with high prevalence of AMR or use of an alternative treatment regimen).[3]

Neisseria gonorrhoeae with reduced susceptibility to extended-spectrum cephalosporins (ESCs) and clinical treatment failures with oral ESCs have necessitated revisions to treatment guidelines globally.[9] A first-line regimen is expected to cure a minimum of 95% of cases, therefore if resistance has developed to a level of 3% to 5%, treatment recommendations are often changed.[10] Since 2011, the Canadian STI guidelines have recommended dual therapy with ESCs and azithromycin regardless of whether there is simultaneous *C trachomatis* infection.[3] The rationale is to enhance treatment effectiveness with 2 antimicrobials that have unrelated mechanisms of action, thereby delaying the development of drug resistance. Currently, 800 mg of oral cefixime or 250 mg of IM ceftriaxone in combination with a single 1-g dose of oral azithromycin is the preferred treatment for uncomplicated anogenital gonorrhea infections according to the Canadian STI guidelines.[3]

Gonorrhea AMR is a worldwide public health concern. Globalization and international travel contribute to the spread of AMR, but it is difficult to ascertain the true global burden, as AMR surveillance does not exist in many settings worldwide.[2] Decreased susceptibility or resistance to ceftriaxone is reported in many countries and particularly in the Western Pacific Region and in Southeast Asia.[2,11] Additional challenges to controlling the emergence of AMR are the lack of appropriate diagnostic tests and antimicrobial stewardship programs in resource-limited settings. The Alberta case is the second ceftriaxone-resistant *N gonorrhoeae* isolate in Canada. Sequence typing and whole-genome sequencing of this isolate at the National Microbiology Laboratory revealed that this isolate is closely related to previous strains from Japan (2015), Australia (2017), and Quebec (2017), supporting the theory of ongoing transmission of a ceftriaxone-resistant *N gonorrhoeae* strain worldwide.[12] Our patient failed empiric therapy with 250 mg of IM ceftriaxone plus a single 1-g dose of oral azithromycin, which highlights the concern that dual therapy cannot reliably overcome ceftriaxone-resistant strains. According to a modeling study, treatment failures with 250 mg of ceftriaxone can occur if the MIC is above 0.125 to 0.25 mg/L,[13] and it is well known that 1 g of azithromycin as a single effective agent is inadequate for the treatment of gonorrhea.[14]

With the emergence of ceftriaxone-resistant *N gonorrhoeae* strains, alternative treatment regimens are urgently needed. A randomized, open-label trial in 2014 compared 240 mg of IM gentamicin plus 2 g of oral azithromycin with 320 mg of oral gemifloxacin plus 2 g of oral azithromycin for treatment of uncomplicated gonorrhea and found that 100% of patients treated with gentamicin and 99.5%

treated with gemifloxacin were cured.[15] Gastrointestinal side effects most likely related to high-dose azithromycin were common in both groups. The Canadian STI guidelines recommend 240 mg of IM gentamicin plus a single 2-g dose of oral azithromycin for ceftriaxone-resistant cases or for patients with anaphylactic reactions to penicillin or allergy to cephalosporins.[7] Gemifloxacin is currently not available in Canada. Monotherapy with 2 g of oral azithromycin is no longer recommended as an alternative owing to increasing rates of resistance; the proportion of azithromycin-resistant isolates in Canada increased from 1.3% in 2010 to 4.7% in 2015.[16]

A test of cure is recommended for all patients with suspected drug resistance, or for those treated with alternative regimens, and should be performed 3 to 7 days after completion of treatment using culture and after 2 to 3 weeks using NAAT. Cases with clinical treatment failure should be discussed with an STI specialist and reported to the local public health authority for assistance with management and partner notification.

Conclusion

Our case highlights the importance of AMR surveillance and the need for culture in cases of treatment failure or for patients with sexual contact from countries with a high prevalence of AMR (eg, Southeast Asia or the Western Pacific Region). Adherence to treatment guidelines with the use of dual therapy is fundamental to limiting the further development of AMR.

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Competing interests
None declared

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References

1. Choudhri Y, Miller J, Sandhu J, Leon A, Aho J. Gonorrhea in Canada, 2010-2015. *Can Commun Dis Rep* 2018;44(2):37-42.
2. Wi T, Lahra MM, Ndowa F, Bala M, Dillon JR, Ramon-Pardo P, et al. Antimicrobial resistance in *Neisseria gonorrhoeae:* global surveillance and a call for international collaborative action. *PLoS Med* 2017;14(7):e1002344.
3. Public Health Agency of Canada. *Canadian guidelines on sexually transmitted infections.* Ottawa, ON: Public Health Agency of Canada; 2018. Available from: **www.canada.ca/en/public-health/services/infectious-diseases/sexual-health-sexually-transmitted-infections/canadian-guidelines.html**. Accessed 2018 Oct 18.
4. Clinical and Laboratory Standards Institute. *Performance standards for antimicrobial susceptibility testing*. 29th ed. CLSI supplement M100. Wayne, PA: Clinical and Laboratory Standards Institute; 2018.
5. European Committee on Antimicrobial Susceptibility Testing. *Breakpoint tables for interpretation of MICs and zone diameters*. Version 9.0. Basel, Switz: European Committee on Antimicrobial Susceptibility Testing; 2019. Accessed 2019 Jan 15.
6. World Health Organization. *Global action plan to control the spread and impact of antimicrobial resistance in* Neisseria gonorrhoeae. Geneva, Switz: World Health Organization; 2012. Available from: **www.who.int/reproductivehealth/publications/rtis/9789241503501/en**. Accessed 2019 Jan 14.
7. Public Health Agency of Canada. *Canadian guidelines on sexually transmitted infections. Treatment of* N. gonorrhoeae *in response to the discontinuation of spectinomycin. Alternative treatment guidance statement.* Ottawa, ON: Public Health Agency of Canada; 2017. Available from: **www.canada.ca/content/dam/phac-aspc/documents/services/publications/healthy-living/gonorrhea-alternate-treatment/alternate-treatmemt-gonorrhea-07-2017.pdf**. Accessed 2018 Sep 11.
8. Moncada J, Schachter J, Hook EW 3rd, Ferrero D, Gaydos C, Quinn TC, et al. The effect of urine testing in evaluations of the sensitivity of the Gen-Probe Aptima Combo 2 assay on endocervical swabs for *Chlamydia trachomatis* and *Neisseria gonorrhoeae:* the infected patient standard reduces sensitivity of single site evaluation. *Sex Transm Dis* 2004;31(5):273-7.
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. Epub 2011 Dec 12.
10. Tapsall JW. Antibiotic resistance in *Neisseria gonorrhoeae. Clin Infect Dis* 2005;41(Suppl 4):S263-8.
11. Yin YP, Han Y, Dai XQ, Zheng HP, Chen SC, Zhu BY, et al. Susceptibility of *Neisseria gonorrhoeae* to azithromycin and ceftriaxone in China: a retrospective study of national surveillance data from 2013 to 2016. *PLoS Med* 2018;15(2):e1002499.
12. Lahra MM, Martin I, Demczuk W, Jennison AV, Lee KI, Nakayama SI, et al. Cooperative recognition of internationally disseminated ceftriaxone-resistant *Neisseria gonorrhoeae* strain. *Emerg Infect Dis* 2018;24(4):735-43.
13. Chisholm SA, Mouton JW, Lewis DA, Nichols T, Ison CA, Livermore DM. Cephalosporin MIC creep among gonococci: time for a pharmacodynamic rethink? *J Antimicrob Chemother* 2010;65(10):2141-8. Epub 2010 Aug 6.
14. Bignell C, Garley J. Azithromycin in the treatment of infection with *Neisseria gonorrhoeae. Sex Transm Infect* 2010;86(6):422-6.
15. Kirkcaldy RD, Weinstock HS, Moore PC, Philip SS, Wiesenfeld HC, Papp JR, et al. The efficacy and safety of gentamicin plus azithromycin and gemifloxacin plus azithromycin as treatment of uncomplicated gonorrhea. *Clin Infect Dis* 2014;59(8):1083-91. Epub 2014 Jul 16.
16. Public Health Agency of Canada. *Canadian antimicrobial resistance surveillance system 2017 report*. Ottawa, ON: Public Health Agency of Canada; 2017. Available from: **www.canada.ca/content/dam/phac-aspc/documents/services/publications/drugs-health-products/canadian-antimicrobial-resistance-surveillance-system-2017-report-executive-summary/CARSS-Report-2017-En.pdf**. Accessed 2018 Oct 15.

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