Multidrug-resistant *Neisseria gonorrhoeae*

John Tapsall MD

∞∞ See related research paper by Ota and colleagues, page 287

In this issue of *CMAJ*, Ota and colleagues[1] report a substantial increase in infections of quinolone-resistant *Neisseria gonorrhoeae* in the province of Ontario. The increase, from 4% in 2002 to 28% in 2006, has been occurring in a time of rising rates of gonorrhea. The epidemiologic investigations of Ota and colleagues show that high rates of resistance to quinolones are significantly associated with male sex and age over 30 years. Quinolone-resistant *N. gonorrhoeae* was detected with similar frequency in men who have sex with men and in heterosexual men. At one clinic attended by men who have sex with men, resistant strains represented 55% of isolates.

Making sense of these trends starts with understanding the microbiology of the organism. Much of the genetic material of *N. gonorrhoeae* is subject to high rates of change by way of both spontaneous mutation and acquisition of external genetic material through horizontal gene transfer. The notorious propensity of the gonococcus to develop resistance to antibiotics originates at the molecular level by means of these processes. It is driven in some circumstances by selection pressure exerted by antibiotics.

Similar changes, driven in turn by selection pressure exerted by the host, occur in the genes that mediate the transmissibility and pathogenicity of gonococci. As a result, gonococcal populations are made up of multiple, constantly evolving subtypes. Molecular-based studies[2–4] have shown that only small numbers of "successful" subtypes (usually specific to particular sexual networks) predominate and persist. A spread of multidrug-resistant gonococci occurs when these successful subtypes also acquire resistance genes.

In developed countries, the spread of quinolone-resistant *N. gonorrhoeae* infection has followed a pattern in which different resistant subtypes are imported, sometimes over many years. The subtypes are eventually introduced into a country's sexual networks and then achieve sustained endemic transmission. Studies in California from 2001 to 2003[5] reported separate instances of rapidly increasing rates of *N. gonorrhoeae* infection among heterosexual men, women and men who have sex with men. Subsequent phenotyping of gonococci from men who have sex with men showed that 2 strains accounted for most of the cases.[6] In Hawaii, imported strains of quinolone-resistant *N. gonorrhoeae* were first detected in 1991 and became endemic there in 2001.[7]

Long-term data from Sydney, Australia, were recently reanalyzed and showed the same pattern.[8] Quinolone-resistant *N. gonorrhoeae* infection was introduced sporadically into the country from 1984 onward. A failure of treatment in 1991 was followed by the spread, in distinct patient groups, of resistant subtypes that were phenotypically different. By 2006, more than 50% of all *N. gonorrhoeae* isolates were resistant to quinolones. Significant increases in quinolone-resistant infection were observed after 1995 in Sydney despite the cessation of ciprofloxacin use as the standard treatment and despite a lack of widespread use of quinolones.

A marked disparity exists, however, between the rates of drug-resistant infections in urban and rural areas. Rates in urban areas continue to rise in the absence of antibiotic selection pressure. In stark contrast, gonococci from isolated and remote communities with exceptionally high rates of disease remained fully susceptible to all antibiotics.

These trends can be explained by the continuing importation and spread of drug-resistant gonococci. Sydney is the main entry point into Australia for business and tourist travel from nearby countries with high rates of multidrug-resistant gonococci. Ontario's role as a transit hub has a similarly wide influence on disease patterns in Canada. Canadian reports have documented the introduction of quinolone-resistant *N. gonorrhoeae* into Canada in the 1990s and the failure of

Key points

- Resistance of *Neisseria gonorrhoeae* to antibiotics, including quinolones, has increased rapidly in recent years and has reduced the options for treatment.
- Studies have shown the wide and global spread of gonorrhea following the recurring emergence of multidrug resistance in settings with high rates of gonorrhea and uncontrolled use of antibiotics.
- Many developed countries, including Canada, now recommend the use of third-generation cephalosporins instead of quinolones for the treatment of gonorrhea.
- Gonococcal resistance to third-generation cephalosporins given orally has emerged in Japan and elsewhere, with even wider spread of gonococci that have determinants for cephalosporin resistance.
- A sustained and integrated international effort to reduce rates of gonorrhea and the misuse of antibiotics is required to stem further emergence and spread of multidrug-resistant strains of *N. gonorrhoeae*.

John Tapsall is with the World Health Organization Collaborating Centre for Sexually Transmitted Diseases, Department of Microbiology, Prince of Wales Hospital, Sydney, Australia.

DOI:10.1503/cmaj.081721

treatment in 1995.[9,10] Together with the conclusions of Ota and colleagues,[1] these data suggest that the long-term epidemiologic pattern in Canada is similar to that in other countries with significant exposure to the Pacific rim.

Ota and colleagues note that Ontario's role as a transit hub is one reason to reinforce the existing guidelines for the treatment of *N. gonorrhoeae* that exclude quinolones. Canada, like the United States, the United Kingdom and Australia, currently recommends the use of third-generation cephalosporins (cefixime or injectable ceftriaxone, or both) for gonorrhea treatment. However, concerns have been expressed recently about the long-term effectiveness of the oral components of this regimen.[11,12] In Japan, cefixime was removed from national treatment guidelines because of concerns over increased treatment failure with this agent.[12] Treatment failure with ceftibuten, another oral cephem, was described in a recent study from Hong Kong.[13] Smaller recent studies show an even wider distribution of the Hong Kong genotype, which has genetic markers for decreased susceptibility to oral cephalosporins.[4,14]

So far, no treatment failures with the injectable ceftriaxone have been reported. The Japanese recommendation for ceftriaxone use is a 1-g dose given intravenously.[12] Most other Asian jurisdictions recommend a 250-mg dose given intramuscularly, in contrast to the 125-mg dose recommended in Canada and the United States.[11]

These recent data showing the emergence and spread of cephalosporin-resistant gonococci are strikingly similar to the data showing the emergence of quinolone-resistant strains in Asia and their subsequent widespread dissemination to the Pacific rim and beyond. A recognition of these parallels has led to renewed calls for better control of gonococcal disease, including enhanced global surveillance of resistance and improved treatment.[11,12] The World Health Organization has already expanded its regional surveillance programs and consolidated the reporting and analysis of the data generated. However, these initiatives require functioning national programs, which are difficult to establish.[10]

The World Health Organization recommends the substitution of a drug in treatment regimens when the rate of resistance is 5% or higher in a general community.[15] This cutoff point defines the requirements for an effective treatment in individuals and for the purposes of public health. By monitoring drug resistance in *N. gonorrhoeae,* standard treatment regimens can be optimized and wider measures adopted for control of gonococcal disease.

To make a sustained difference in the continuing problem of multidrug-resistant *N. gonorrhoeae* infection, 2 overlapping goals must be met: broadly based control of drug resistance[16] and control of gonorrhea.[15] Both objectives should be approached in the wider contexts of global control of antimicrobial resistance[17] and sexually transmitted infection.[15]

Individual practitioners can make an important contribution to solving the problem. Appropriate use of antibiotics in general is fundamental to the control of drug resistance in all community-acquired pathogens. Familiarity with and adherence to recommended treatment regimens for gonorrhea is also crucial. If failure of a current treatment regimen is seen or suspected, patients should be referred to specialists for advice and treatment, and practitioners should contact the appropriate public health authorities.

High rates of gonorrhea exist in many settings. In addition, the gonococcus exists in an "antibiotic soup" resulting from general misuse of antibiotics, which subjects the organism to substantial evolutionary pressures. Until these crucial areas are addressed more effectively, all countries will be at risk from the emergence and spread of even more resistant variants of this highly adaptable pathogen.

Competing interests: None declared.

REFERENCES

1. Ota KV, Jamieson F, Fisman DN, et al. Prevalence of and risk factors for quinolone-resistant *Neisseria gonorrhoeae* infection in Ontario. *CMAJ* 2008;180:287-90.
2. Choudhury B, Risley CL, Ghani AC, et al. Identification of individuals within sexual networks: a population-based study. *Lancet* 2006;368:139-46.
3. Sarafian SK, Knapp JS. Molecular epidemiology of gonorrhea. *Clin Microbiol Rev* 1989;2(Suppl):S49-55.
4. Wong WW, Huang CT, Li LH, et al. Molecular epidemiological identification of *Neisseria gonorrhoeae* clonal clusters with distinct susceptibility profiles associated with specific groups at high risk of contracting human immunodeficiency virus and syphilis. *J Clin Microbiol* 2008; 46:3931-4. Epub 2008 Oct. 8.
5. Bauer HM, Mark KE, Samuel M, et al. Prevalence of and associated risk factors for fluoroquinolone-resistant *Neisseria gonorrhoeae* in California, 2000–2003. *Clin Infect Dis* 2005;41:795-803.
6. Morris SR, Knapp JS, Moore DF, et al. Using strain typing to characterise a fluoroquinolone-resistant *Neisseria gonorrhoeae* transmission network in southern California. *Sex Transm Infect* 2008;84:290-1.
7. Newman LM, Wang SA, Ohye RG, et al. The epidemiology of fluoroquinolone-resistant *Neisseria gonorrhoeae* in Hawaii, 2001. *Clin Infect Dis* 2004;38:649-54.
8. Tapsall JW, Limnios EA, Murphy D. Analysis of trends in antimicrobial resistance in *Neisseria gonorrhoeae* isolated in Australia, 1997–2006. *J Antimicrob Chemother* 2008;61:150-5.
9. *Neisseria gonorrhoeae* with decreased susceptibility to ciprofloxacin in British Columbia: an imported phenomenon. *Can Commun Dis Rep* 1995;21:137-9.
10. Emergence of *Neisseria gonorrhoeae* strains with decreased susceptibility to ciprofloxacin — Quebec, 1994–1995. *Can Commun Dis Rep* 1996;22:121-5.
11. Workowski KA, Berman SM, Douglas JM Jr. Emerging antimicrobial resistance in *Neisseria gonorrhoeae*: urgent need to strengthen prevention strategies. *Ann Intern Med* 2008;148:606-13.
12. Deguchi T, Yasuda M. Lack of nationwide surveillance of antimicrobial resistance in *Neisseria gonorrhoeae* in Japan. *Ann Intern Med* 2008;149:363-4.
13. Lo JYC, Ho KM, Leung AOC, et al. Ceftibuten resistance and treatment failure in gonococcal infection. *Antimicrob Agents Chemother* 2008;52:3564-7.
14. Tapsall JW, Ray S, Lo JYC, et al. Distribution of a cephalosporin-resistant sequence type of *Neisseria gonorrhoeae* with a mosiac PBP2 associated with treatment failure in the Asia-Pacific region [poster presentation, abstract P052]. *Programme and abstracts of the 16th International Pathogenic Neisseria Conference*; 2008 Sept. 7–12; Rotterdam, Netherlands. Available: www.ipnc2008.org/Abstracts%20poster%20presentations%20IPNC%202008.pdf (accessed 2008 Dec 24).
15. Tapsall JW. Antibiotic resistance in *Neisseria gonorrhoeae*. Geneva (Switzerland): World Health Organization; 2001. WHO/CDS/DRS/2001.3:16.
16. *Global strategy for the containment of antimicrobial resistance*. Geneva (Switzerland): World Health Organization; 2001. WHO/CDS/DRS/2001.2.
17. Simonsen GS, Tapsall JW, Allegranzi B, et al. The antibiotic resistance containment and surveillance approach — a public health approach. *Bull World Health Organ* 2004;82:928-34.

Correspondence to: *Dr. John Tapsall, Department of Microbiology, Prince of Wales Hospital, Barker St., Randwick, Sydney NSW 2031, Australia; j.tapsall@unsw.edu.au*