Increasing incidence of ciprofloxacin-resistant *Neisseria gonorrhoeae* infection in Canada

Background and epidemiology: After declining for 2 decades, the reported rate of gonorrhea in Canada has risen by more than 40% over the past 5 years.[1] In 2001, over 6000 cases were reported, the highest burden of disease occurring among individuals less than 30 years old and among males.[2,3] Globally, the World Health Organization estimated that 62 million new cases of gonorrhea occurred in 1999.[4]

Gonorrhea is caused by the organism *Neisseria gonorrhoeae*. Transmission occurs through contact with secretions from infected mucosal surfaces. Common clinical manifestations include urethritis and cervicitis. The incubation period varies from 1 to 10 days.

Uncomplicated cases of gonorrhea can be treated with single-dose antimicrobial therapy.[5] However, the choice of therapy is limited to the more expensive third-generation cephalosporins and fluoroquinolones (FQs), such as ciprofloxacin, owing to emerging and prevalent resistance of *N. gonorrhoeae* strains to antibiotics, including penicillins and tetracyclines. More recently, FQ resistance has emerged and become endemic in many parts of the world, which further limits therapeutic choices.

FQ resistance was first identified in 1992.[6] Although most prevalent in the Far East, FQ-resistant strains of *N. gonorrhoeae* have now been documented in many parts of the world, including Canada.[6–9] Currently, Canadian provincial laboratories submit all gonococcal isolates with decreased susceptibility to at least 1 antibiotic to the National Laboratory for Sexually Transmitted Diseases for further testing. In the last 5 years, the national laboratory received 3000–5000 isolates per year. In the last decade, the incidence of ciprofloxacin resistance in *N. gonorrhoeae* (minimal inhibitory concentration of drug ≥ 1.0 mg/L) has increased more than 200-fold, from 0.01% to 2.1% (Fig. 1). In 2001, such resistance was identified in 4.4% (95% confidence interval [CI] 0.5%–9.3%) of isolates tested in Atlantic Canada, 2.1% (95% CI 1.6%–2.5%) in central Canada (Ontario, Quebec, Northwest Territories and Nunavut) and 2.4% (95% CI 1.4%–3.5%) in western Canada.

Diagnosis: Diagnosis is made by means of Gram's staining and culture of specimens obtained from the urethra, cervix, rectum or other suspected sites of infection. Gram's staining of pharyngeal samples is neither sensitive nor specific and is therefore not recommended. An amplified nucleic acid test, such as the polymerase chain reaction or the ligase chain reaction, can be performed on urine specimens; however, current technology allows susceptibility testing to be performed only on cultures of *N. gonorrhoeae*. Therefore, if antimicrobial resistance is suspected, specimens should be taken for culture rather than for a nucleic acid test.

Clinical management: The clinical manifestations of a gonococcal infection are the same regardless of the resistance profile of the organism. The most common manifestation in men is acute urethritis, which may be complicated by acute epididymitis. The majority of infections in woman are asymptomatic; if symptoms do occur, the most common is cervicitis. Complications include salpingitis, pelvic inflammatory disease and perihepatitis. Rectal and pharyngeal infections can occur and are usually asymptomatic. Hematogenous dissemination can cause meningitis, endocarditis, rash, tenosynovitis and arthritis.

It is critical that a travel history be taken when interviewing a patient with suspected gonorrhea. Travel to an area where FQ resistance in *N. gonorrhoeae* is

Table 1: Recommended regimens* for the treatment of uncomplicated gonorrheal infections† in nonpregnant patients[5]

Drug	Dosage
Cefixime	400 mg orally in single dose
Ceftriaxone	125 mg intramuscularly in single dose
Ciprofloxacin‡	500 mg orally in single dose
Ofloxacin‡	400 mg orally in single dose

*All regimens should be followed by empirical treatment for chlamydial and nongonococcal infections with either azithromycin (1 g orally in a single dose) or doxycycline (100 mg orally twice daily for 7 days).
†Urethral, endocervical, rectal and pharyngeal infections.
‡Not to be used if the patient has recently travelled to an area where fluoroquinalone resistance is endemic or if the local rate of ciprofloxacin resistance is greater than 3%.

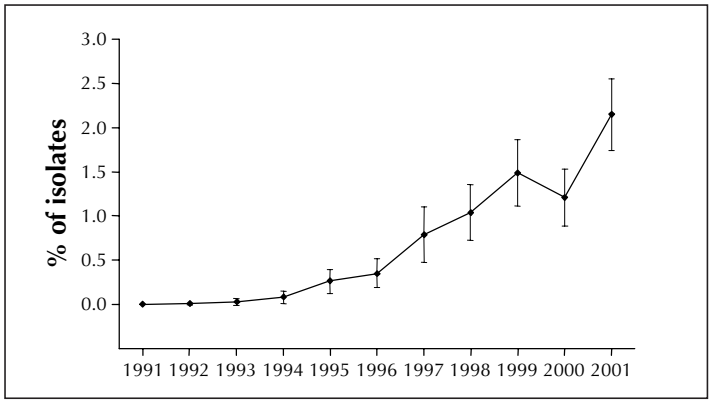

Fig 1: Proportion of *Neisseria gonorrhoeae* isolates resistant to ciprofloxacin in Canada, from 1991 to 2001. [Source: National Laboratory for Sexually Transmitted Diseasess, National Laboratory for Microbiology, Health Canada.]

endemic (e.g., Asia, Australia, Hawaii and California[10–12]) should alter the therapy chosen.

The increasing rate of FQ-resistant *N. gonorrhoeae* in Canada, the United States and other parts of the world makes it necessary to exercise caution when treating gonorrhea. Failure to cure a case of gonorrhea has public health implications beyond that of the infected patient. Because of continued transmission of the organism and the potential for emergence of antimicrobial resistance, it has been recommended that the efficacy of the treatment regimen should approach 100% and that a regimen with an efficacy of less than 97% not be used. In most cases, any of the regimens listed in Table 1 would be appropriate.[5] However, an FQ should not be used if a patient has recently travelled to an area where FQ resistance is endemic or if the local rate of ciprofloxacin resistance is greater than 3%. If an FQ is used in either of these 2 situations, a test of cure is recommended.

Prevention: The risk of transmission of gonorrhea can be reduced through consistent use of condoms and limiting the number of sexual partners. All individuals with gonorrhea should be counselled and tested for other STDs, including HIV infection. All cases of gonorrhea must be reported to the public health department for investigation of contacts.

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References

1. Hansen L, Wong T, Mathias M. Gonorrhea resurgence in Canada. *Int J STD AIDS*. In press.
2. Reported gonorrhea cases and rates in Canada by age group and sex, 1980–2000 [table]. Ottawa: Division of Sexual Health Promotion and STD Prevention and Control, Bureau of HIV/AIDS, STD and TB, Health Canada; 2001. Available: www.hc-sc.gc.ca/pphb-dgspsp/std-mts/stddata1201/tab2-1_e.html (accessed 2003 Mar 6).
3. Reported cases and rates of notifiable STD from January 1 to September 30, 2002 and January 1 to September 30, 2001 [table]. Ottawa: Division of Sexual Health Promotion and STD Prevention and Control, Centre for Infectious Disease Prevention and Control, Health Canada. Available: www.hc-sc.gc.ca/pphb-dgspsp/std-mts/stdcases-casmts/index.html (accessed 2003 Mar 6).
4. World Health Organization. *Global prevalence and incidence of selected curable sexually transmitted infections: overview and estimates*. Geneva: The Organization; 2001.
5. *Canadian STD guidelines: 1998 edition*. Ottawa: Division of STD Prevention and Control, Bureau of HIV/AIDS, STD and TB, Laboratory Centre for Disease Control, Health Canada; 1998. Cat no H49-119/1998E. Available: www.hc-sc.gc.ca/pphb-dgspsp/publicat/std-mts98 (accessed 2003 Mar 6).
6. Ison C, Dillon J, Tapsall J. The epidemiology of global antibiotic resistance among *Neisseria gonorrhoeae* and *Haemophilus ducreyi*. *Lancet* 1998; 351(Suppl 3):8-11.
7. Decreased susceptibility of *Neisseria gonorrhoeae* to fluoroquinolones — Ontario, 1992–1994. *Can Commun Dis Rep* 1995;21(3):1-3.
8. *Neisseria gonorrhoeae* with decreased susceptibility to ciprofloxacin in British Columbia: an imported phenomenon. *Can Commun Dis Rep* 1995; 21(15):1-2.
9. Emergence of *Neisseria gonorrhoeae* strains with decreased susceptibility to ciprofloxacin — Quebec, 1994–1995. *Can Commun Dis Rep* 1996;22(15):1-5.
10. Fluoroquinolone-resistance in *Neisseria gonorrhoeae*, Hawaii, 1999, and decreased susceptibility to azithromycin in *N. gonorrhoeae*, Missouri, 1999. *MMWR Morbid Mortal Wkly Rep* 2000; 49(37):833-7.
11. Fluoroquinolone-resistant *Neisseria gonorrhoeae* — San Diego, California, 1997. *MMWR Morbid Mortal Wkly Rep* 1998;47(20):405-8.
12. Increases in fluoroquinolone-resistant *Neisseria gonorrhoeae* — Hawaii and California, 2001. *MMWR Morbid Mortal Wkly Rep* 2002;51(46):1041-4.