Ciprofloxacin resistance emerges in *Neisseria gonorrhoeae* in Victoria, 1998 to 2001

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Abstract

Notifications of gonorrhoea in Victoria increased suddenly in the late 1990s, from an average of 375 cases per year from 1993 to 1997, to over 700 cases in 2000. This paper describes the susceptibility to ciprofloxacin of isolates of *N. gonorrhoeae* in Victoria from 1998 to 2001, and relates these to the reported epidemiologic characteristics of the cases. The proportion of all isolates of *N. gonorrhoeae* that was resistant to ciprofloxacin rose from 3 per cent in 1998 to 11 per cent in 2001. Among homosexual and bisexual men, resistant isolates remained rare (< 1 per cent). Among heterosexual men and women whose infection was acquired overseas, the proportion of resistant isolates increased from 14 per cent to 51 per cent. Among heterosexual men and women whose infection was acquired in Australia, the proportion of resistant isolates increased from 6 per cent to 14 per cent, and disproportionately involved persons born overseas. Patterns of antibiotic resistance are intimately linked to epidemiological characteristics of cases. Clinical treatment and public health and control strategies for resurgent sexually transmitted infections benefit from the insights of collaborative microbiological and epidemiological surveillance. *Commun Dis Intell* 2003;27 Suppl:S75–S79.

Keywords: Neisseria gonorrhoeae, *ciprofloxacin, antibiotic resistance*

Introduction

Notifications of gonorrhoea in Victoria in the late 1990s echoed worldwide trends. Numbers of cases of gonorrhoea in Victoria declined from the mid-1980s and were relatively low (averaging 375 cases per year) from 1993 to 1997, but then surged to 552 cases in 1998, 742 cases in 2000 and 718 cases in 2001.[1,2]

A widely used Australian guideline[3] recommends a single dose of either 500 milligrams of orally administered ciprofloxacin or a 250-milligram intramuscular injection of ceftriaxone to treat suspected or proven uncomplicated urogenital gonorrhoea. Epidemiologically relevant trends in antimicrobial susceptibility should guide this choice.[4] Treatment should also include azithromycin or doxycycline to treat co-existing *Chlamydia* infection.

The proportion of Australian isolates of *Neisseria gonorrhoeae* with reduced susceptibility to ciprofloxacin increased from 5 per cent in 1998 to 17 per cent in 1999 and 18 per cent in 2000.[5] In 2000, the prevalence of reduced susceptibility to ciprofloxacin exceeded 50 per cent in most of the larger countries of the Western Pacific Region.[6]

This review describes the susceptibility to ciprofloxacin of isolates of *N. gonorrhoeae* in Victoria from 1998 to 2001, and relates these to the reported epidemiologic characteristics of the cases.

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Methods

The Communicable Diseases Section of the Victorian Department of Human Services (DHS) and the Microbiological Diagnostic Unit of the University of Melbourne (MDU) collaborate in surveillance of gonorrhoea in Victoria. Legislation requires that cases of gonorrhoea in Victoria be notified to the DHS both by the diagnosing clinician, and by the laboratory that makes the diagnosis. Information in the notification includes an anonymous identifier (first two letters of last and first names), sex, date of birth or age, residential postcode and details of the diagnosing doctor or laboratory. Further details, including sexual orientation, and putative source of infection are routinely sought from the notifying clinician.

Primary diagnostic laboratories send cultures of *N. gonorrhoeae* to the MDU, where antibiotic susceptibility is determined by agar plate dilution methods developed by the Australian National Neisseria Network.[5,7]

We defined the ciprofloxacin susceptibility of isolates of *N. gonorrhoeae* as fully sensitive (minimum inhibitory concentration (MIC) less than or equal to 0.03 mg/L), less sensitive (MIC 0.06 to 0.5 mg/L) or resistant (MIC equal to or greater than 1 mg/L).

This review examined cases of gonorrhoea infections for which the specimens were: collected between 1 January 1998 and 31 December 2001; diagnosed by culture in Victoria; and for which ciprofloxacin susceptibility was established.

Results

N. gonorrhoeae was identified by Victorian diagnostic laboratories in 2,827 cultures from one or more anatomic sites of persons between 1 January 1998 and 31 December 2001 and referred to the MDU for antibiotic susceptibility testing. Twenty-eight cultures were not tested for ciprofloxacin susceptibility. When multiple cultures from the same or different anatomic site of the same person within 28 days were identified, the isolate least susceptible to ciprofloxacin was retained and the others (163 isolates) were excluded, leaving isolates from 2,636 cases for this analysis.

Almost all isolates (97 per cent) from heterosexual men and women were from urogenital anatomic sites. Seventy-five per cent of isolates from homosexual men were urethral, 18 per cent rectal and 7 per cent pharyngeal.

The proportion *N. gonorrhoeae* isolates resistant to ciprofloxacin rose from 3 per cent in 1998 to 11 per cent in 2001 (Table 1).

Table 1. Ciprofloxacin susceptibility of cases of culture-proven gonorrhoea in Victoria, 1998 to 2001

Year	Fully sensitive (%)	Less sensitive (%)	Resistant (%)	Total number of isolates
1998	95	2	3	535
1999	77	18	5	700
2000	79	14	7	756
2001	84	5	11	645

In mid-1999, locally acquired isolates of *N. gonorrhoeae* that were less sensitive (but not fully resistant) to ciprofloxacin emerged suddenly, concentrated in, but not limited to, homosexual and bisexual men. These persisted during 2000 and then declined in 2001.

Over the four years, the prevalence of ciprofloxacin-resistant *N. gonorrhoeae* among heterosexual men and women was 16 per cent (155/942), far greater than among homosexual and bisexual men (0.4 per cent, 6/1,501, Chi-square=240, p<0.001) (Table 2). Only one of 287 male rectal isolates was resistant to ciprofloxacin.

Table 3 describes the ciprofloxacin susceptibility of the 2,358 (89 per cent) isolates with complete data on the sexual orientation of the case and the location where the infection was reportedly acquired.

Table 2. Ciprofloxacin susceptibility of cases of culture-proven gonorrhoea in Victoria, 1998 to 2001, by sex and reported sexual orientation

Sex	Sexual orientation	Fully sensitive (%)	Less sensitive (%)	Resistant (%)	Total number of isolates
Male	Heterosexual	74	10	16	806
	Homosexual or bisexual	89	11	<1	1,501
	Not reported	80	14	6	177
Female	Heterosexual	76	5	18	136
	Homosexual or bisexual	100	0	0	4
	Not reported	67	8	25	12

Table 3. Temporal trends in ciprofloxacin susceptibility of cases of culture-proven gonorrhoea in Victoria, 1998 to 2001, by sex, sexual orientation and location where the infection was reported to have been acquired

Sex and sexual orientation	Location acquired	Year	Fully sensitive (%)	Less sensitive (%)	Resistant (%)	Total number of isolates
Male and female, heterosexual	Australia	1998	93	1	6	114
		1999	79	12	9	178
		2000	76	10	14	184
		2001	83	3	14	206
	Overseas	1998	72	14	14	50
		1999	57	18	24	49
		2000	44	16	40	55
		2001	37	12	51	57
Male, homosexual and bisexual	Australia	1998	>99	0	<1	306
		1999	79	20	<1	418
		2000	86	14	<1	434
		2001	94	6	<1	282
	Overseas	1998	83	17	0	6
		1999	83	0	17	6
		2000	33	67	0	6
		2001	86	0	14	7

Among heterosexual men and women whose infection was acquired overseas, the proportion of ciprofloxacin-resistant isolates increased from 14 per cent in 1998 to 51 per cent in 2001 (Chi-square for trend=18.97, p<0.001). Eighty-three per cent (148/179) of the overseas-acquired infections of heterosexual men and women for which a country or region was specified were acquired in Asia. Of these, 39 per cent were resistant to ciprofloxacin.

Among heterosexual men and women whose infection was acquired in Australia, the proportion of ciprofloxacin-resistant isolates of *N. gonorrhoeae* increased from 6 per cent in 1998 to 14 per cent in 2001 (Chi-square for trend=5.94, p=0.015). Of infections acquired heterosexually by Australian-born persons, 7 per cent (34/518) were ciprofloxacin-resistant. In contrast, 30 per cent (35/118) of infections acquired heterosexually in Australia by overseas-born persons were ciprofloxacin-resistant (Chi-square=53, p<0.001).

From 1998 to 2001, ciprofloxacin-resistant isolates remained rare among homosexual and bisexual men. Four (one each year) were acquired in Australia, and two were acquired overseas.

Three of 2,636 isolates (0.1 per cent) demonstrated clinically insignificant slightly altered susceptibility to ceftriaxone (MIC 0.06 mg/L). Two of these were acquired in Asia.

Discussion

From 1998 to 2001 the annual incidence of ciprofloxacin resistant *N. gonorrhoeae* in Victoria tripled. However, the distribution of ciprofloxacin-resistant isolates of *N. gonorrhoeae* differed markedly in persons of different sexual orientation.

The increase in clinically significant ciprofloxacin resistance was entirely due to infections among heterosexual men and women. The high prevalence of resistance among infections acquired by Victorian travellers to Asia is typical of infections in this region.[6,8]

The high prevalence of ciprofloxacin resistance among infections acquired in Australia by persons who were born outside Australia may be due to misclassification of the source of the infection, or to chains of transmission and sexual networks that were several links from an imported resistant infection.

Regardless of the specific source of the infection, the overall prevalence of ciprofloxacin resistance among heterosexually acquired gonorrhoea diagnosed in Victoria is sufficiently high to render ciprofloxacin inappropriate for presumptive therapy of such infections.[5]

In contrast, less than one per cent of locally acquired infections of homosexual and bisexual men were resistant to ciprofloxacin. Ciprofloxacin therefore remains useful as first-line therapy for uncomplicated urogenital gonorrhoea acquired locally by homosexual and bisexual men.

The wave of ciprofloxacin-'less sensitive' *N. gonorrhoeae* that peaked in 1999 and ebbed in 2000 demonstrates the vulnerability of this population to the emergence of resistant strains. Infections with strains with reduced susceptibility to ciprofloxacin are more likely to fail treatment with the conventional single-dose therapy,[5] and may be precursors to highly resistant strains.[9]

New methods are being used to diagnose gonorrhoea by nucleic acid amplification.[4] These currently provide no information about the antimicrobial susceptibility of the organism causing the infection. Diagnostic strategies that recover isolates for antimicrobial susceptibility testing will be needed to ensure that the shifting patterns of antimicrobial susceptibility of *N. gonorrhoeae* are monitored.

The antimicrobial susceptibilities of isolates of *N. gonorrhoeae* are intimately linked to epidemiological characteristics of cases, and illuminate the transmission dynamics of this resurgent infection. Collaborative microbiological and epidemiological surveillance guide the choice of antibiotics that will efficiently cure uncomplicated gonorrhoea at first presentation, and may help avoid the clinical and public health consequences of selection and dissemination of resistant strains.

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