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A new sexually transmitted infection (STI) in Geneva? Ciprofloxacin-resistant *Neisseria gonorrhoeae*, 2002–2005

Brigitte Le Lin[a], *Roberta Pastore*[a,b], *Nadia Liassine*[c], *Carmen Aramburu*[a,b], *Philippe Sudre*[a]

[a] General Directorate of Health, Geneva, Switzerland
[b] European Programme for Intervention Epidemiology Training (EPIET), Geneva, Switzerland
[c] Unilabs Genève, Geneva, Switzerland

Summary

Principles: Neisseria gonorrhoeae (NG) resistant to ciprofloxacin (CR) was documented for the first time in Geneva in 2002 and increased from 7% that year to 47% in 2005. We describe *NG* cases during this period and compare characteristics of CR and ciprofloxacin susceptible (CS) cases.

Method: Geneva microbiological laboratories identified *NG* cases. Antimicrobial susceptibility testing (AST) was performed on a sample of reported cases. The attending physicians completed questionnaires on demographic and epidemiological characteristics. Risk exposures were assessed by comparing CR and CS cases using logistic regression.

Results: 238 *NG* cases were reported. Of 91 on which AST was performed, 23 (25%) were CR; 91% of these were male *vs* 87% of CS patients. Men having sex with men (MSM) represented 38% of CR cases compared with 31% of CS cases (p >0.05). Among CR cases 65% were Swiss compared with 56% of CS cases. Median age was 35 years for both. Casual sexual contacts were reported for 88% of CR cases and 72% of CS cases (p >0.05). The difference between CR and CS cases in terms of sexual activity outside Switzerland (50% and 19% respectively) remained significant after adjusting for sexual preference and nationality (OR: 7.0, CI 95: 1.99–24.6).

Conclusion: Although CR infection was more common among Swiss MSM, only sexual activity outside Switzerland was independently associated with CR. Physicians should request AST before treatment and reconsider first-line use of ciprofloxacin. Surveillance of gonococcal antimicrobial resistance is essential in monitoring epidemiologic trends and updating recommendations on first-line treatment.

Key words: Neisseria gonorrhoeae infection; ciprofloxacin resistance; population surveillance; Switzerland

Introduction

An increase in the number of *Neisseria gonorrhoeae* infections and the development of resistance to fluoroquinolones have been described in many countries of Europe, Africa and Asia and in the United States [1–9]. In some of them replacement of ciprofloxacin as first-line treatment for gonorrhoea has been recommended [10–14].

Reporting *Neisseria gonorrhoeae* to public health authorities has been mandatory for laboratories in Switzerland since 1987. Notifications of gonococcal infections increased by 97% between 1997 (269) and 2003 (531), growing by 119% in males and 48% in females [15].

In Geneva, notifications of gonococcal infections increased nearly twofold between 2001 and 2002 [16, 17] and rose again slightly in 2004.

Neisseria gonorrhoeae resistant to ciprofloxacin (CR) was documented for the first time in Geneva in 2002 by Unilabs Genève [18]. Quinolone resistance in Geneva increased from 7% in 2002 to 47% in 2005 (Figure 1).

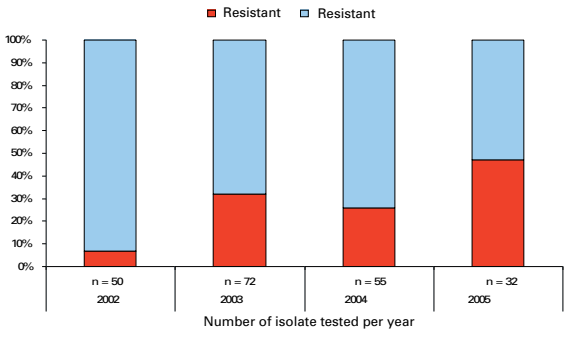

Figure 1

Percentage of isolates susceptible and resistant to ciprofloxacin among *Neisseria gonorrhoeae* cases. Geneva, January 2002 – October 2005.

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As a consequence of the detection of an increasing number of *Neisseria gonorrhoeae* cases in 2002 in Geneva, and of increasing resistance to quinolone in 2004 by Unilabs Genève laboratory, Geneva cantonal health authorities supplemented laboratory-based notification with a voluntary physician-based surveillance system to improve the description and monitoring of cases' epidemiological features.

We report the results obtained by the Geneva surveillance system in describing all gonorrhoea cases comparing patients with quinolone-resistant and quinolone-susceptible strains.

Methods

A *Neisseria gonorrhoeae* case is diagnosed by phenotypic identification and/or by molecular amplification (COBAS AMPLICOR NG test). For each laboratory case, a questionnaire on demographics, clinical and epidemiological characteristics, including possible risk exposures, is completed by the attending physician (questionnaire in French available on request).

In addition, all laboratories were encouraged to notify the General Directorate of Health (DGS) of the results of antimicrobial susceptibility testing when diagnosis was obtained through culture. Microbiological methods used to test antimicrobial susceptibility were based on the CLSI recommendations [19], using the disk diffusion technique in combination with a beta-lactamase test. The minimum inhibitory concentration (MICs) was determined by the E-test method (AB Biodisk, Solna, Sweden) to define a ciprofloxacin-resistant strain. A strain was classified as susceptible to ciprofloxacin if the MIC was <0.06 mg/L or the diameter ≥47 mm; it was classified as intermediate if MIC was 0.06–1 mg/L and resistant if CMI was >1.

Associations between quinolone-resistant gonococcal infection and specific exposures were examined by univariate analysis, calculating odds ratios (OR) and 95% confidence intervals (95 CI). The χ^2 test was used to compare proportions between groups. Multivariate analysis was performed using logistic regression models; variables of clinical and statistical importance (having a p value <0.2 in univariate analysis) were used to build the model. Multivariate models were built by the backward method and the model with the best log-likelihood value was chosen. Analysis was performed with SPSS v. 14.

Results

A total of 238 cases were reported between 2002 and October 2005. Median age was 35 years and 75% of cases were aged under 41 years. The male/female sex ratio was 9:1. 79% of cases named Switzerland as the country where infection was acquired. 67% reported acquiring the infection during a single sexual encounter. 40% of male cases reported homosexual contacts, and of the 68 individuals with known HIV status 24 (35%) were HIV positive.

Seven (3%) of all reported cases had at least two separate episodes of gonococcal infection during a maximum period of 5 months. Four of them were males reporting a homosexual contact. One was HIV positive. Three of these cases had a second infection within one month and this was considered a recurrence of the same infection. Of these three recurrences, two were ciprofloxacin-resistant.

The isolates from 91 patients of the overall 238 cases were tested for ciprofloxacin susceptibility. The distribution of most of the variables among tested and non-tested patients was similar except for the presumptive place of infection (Table 1). Twenty-three of the 91 isolates (25%) were CR and 3 (3%) were intermediately resistant to ciprofloxacin. The following analysis was performed in only CR and CS cases. The mean age for CR patients was 34.4 years compared to 36.2 years for ciprofloxacin-susceptible cases (CS) (p = 0.4). 91% of CR patients and 87% of CS were male; 67% of CR patients were Swiss nationals compared to 52% of CS (OR for nationality: 1.6, CI 95: 0.5–4.6). Among CR patients 84% were unmarried compared to 67% among CS patients (OR: 2.6, CI 95: 0.7–11). Fifteen of 17 CR patients (88%) reported an "occasional" sexual contact as the presumed source of infection compared with 34/47 (72%) among CS patients (OR: 2.8, CI 95: 0.5–14). Among CR patients, 10/20 (50%) reported sexual contact outside Switzerland (6 in South-East Asia, 3 in Europe and 1 in Africa) compared to 11/58 (19%) among CS patients (OR: 4.2, CI 95:1.4–13). Among CR patients 8/21 (38%) were men having sex with men (MSM), compared to 17/54 (31%) among CS patients (OR: 1.3; CI 95:0.4–3.8).

Four variables were kept in the final logistic regression model (log-likelihood 73.2, p value 0.008): sexual contact outside Switzerland, type of sexual contact (homosexual/heterosexual), nationality and age (Table 2). Adjusting for those factors only sexual contact outside Switzerland was found to be associated with CR infection (adjusted OR 7.0, CI 95: 1.99–24.6).

Table 1

Distribution of demographic characteristics and some risk exposure among patients with *N. gonorrhoeae* infection tested or non-tested for ciprofloxacin resistance, Geneva 2002–2005.

Variables	Tested N/tot	%	Non-tested N/tot	%
Sex (M)	80/91	87.9	134/147	91.1
Nationality (Swiss)	46/84	54.8	64/125	51.2
Sex relation (homosexual)	25/87	28.7	46/128	35.9
Place of infection				
Outside Switzerland	21/91	23.1	18/147	12.2
Unknown	13/91	14.3	37/147	25.2
Mean age	35.7	34.3		

Table 2

Risk factors for ciprofloxacin-resistance among *N. gonorrhoeae* isolates, Geneva 2002–2005.

Variable		Univariate analysis Crude OR (95% CI)	p-value	Multivariate analysis (N = 68) Adjusted OR (95% CI)	p-value
Sexual contact outside Switzerld (N = 78)	. yes	4.2 (1.4–12.7)	0.007	7.0 (1.99–24.6)	0.002
	. no	ref	–	–	–
Sex relation (N = 75)	. homo/bisexual	1.3 (0.4–3.8)	0.6	1.0 (0.3-3.4)	0.96
	. hetero	ref	–	–	–
Nationality (N = 79)	. Swiss	1.6 (0.5–4.6)	0.3	0.9 (0.7–1.1)	0.29
	. non-Swiss	ref	–	–	–
Age in years* (N = 91)	<= 40	1.6 (0.4–5.3)	0.5	0.94 (0.88–1.01)	0.10
	> 40				

*in the multivariate analysis age was included as continuous numerical variable

Discussion

Neisseria gonorrhoeae ciprofloxacin resistance is emerging in Geneva: 7% of strains tested in 2002 were CR compared to 47% at the end of October 2005, nearly a sevenfold increase. Similar trends have been observed in other European countries [6].

Descriptive analysis suggests that quinolone-resistant infection emerging in Geneva is more common than quinolone-sensitive infection among Swiss men aged below 40 who had sexual contacts with other men. When adjusting for potential confounders, sexual contact outside Switzerland, as the presumptive way of acquiring *N. gonorrhoeae* infection, is the only significant risk factor for a ciprofloxacin-resistant gonococcal infection.

These results are subject to several limitations. Antimicrobial susceptibility testing was only available for one third of all cases; however, considering the distribution of the main variables among tested and non-tested patients, those with a known susceptibility profile may be considered representative of all the patients. Information was obtained on a voluntary basis through physicians and CR patients were, perhaps, more likely to be tested in the event of recurrence, a potential source of selection bias. This may cause the prevalence of antibiotic resistance among patients with *N. gonorrhoeae* infection to be overestimated. The sample size available for the analysis of risk factors associated with CR was small. Notwithstanding the validity of the statistical results, caution should be exercised in referring them to the general population.

Physicians should be encouraged to request culture and sensitivity tests prior to treatment and to reconsider ciprofloxacin treatment for all patients with *Neisseria gonorrhoeae* infection, particularly in regard to persons at increased risk.

In many countries the replacement of ciprofloxacin as a first-line treatment for gonorrhoea with third-generation cephalosporins (e.g. ceftriaxone, cefixime or cefotaxime) has been recommended [10–14].

Antibiotic resistance is increasingly compromising the effective treatment of gonorrhoea and has become a major public health concern. Clinical treatment and public health strategies for control of emergent STI will benefit from the combined availability of microbiological and epidemiological data. Our findings demonstrate the importance of gonococcal antimicrobial resistance surveillance at the national level if we are to remain responsive to the changes in epidemiological trends and regularly update recommendations on first-line treatment of STI.

Correspondance:
PD Dr Philippe Sudre
Direction générale de la santé
Avenue de Beau-Séjour 22–24
Case postale 76
CH-1211 Genève 4, Plainpalais
E-Mail: philippe.sudre@etat.ge.ch

References

1 Hsueh PR, Tseng SP, Teng LJ, Ho SW. High prevalence of ciprofloxacin-resistant Neisseria gonorrhoeae in Northern Taiwan. Clin Infect Dis. 2005;40(1):188–92.

2 Borgen K, van Loo I, Koedijk F, van de Laar M. Increase of gonococcal quinolone resistance in the Netherlands from 2002–2004. Euro Surveill Wkly. 2005;10(11).

3 Iverson CJ, Wang SA, Ohye RG, Trees DL, Knapp JS, Effler PV, O'Connor NP, Levine WC. Fluoroquinolone resistance among Neisseria gonorrhoeae isolates in Hawaii, 1990–2000: role of foreign importation and increasing endemic spread. Sex Transm Dis. 2004;31(12):702–8

4 Tanaka M, Nakayama H, Notomi T, Irie S, Tsunoda Y, Okadome A, et al. Antimicrobial resistance of Neisseria gonorrhoeae in Japan, 1993–2002: continuous increasing of ciprofloxacin-resistant isolates. Int J Antimicrob Agents. 2004; 24(Suppl 1):S15–22.

5 Herida M, Sednaoui P, Goulet V. Gonorrhoea surveillance system in France: 1986-2000. Sex Transm Infect. 2004;31(4):209–14.

6 Fenton KA, Lowndes CM. Recent trends in the epidemiology of sexually transmitted infections in the European Union. Sex Transm Infect. 2004;80(4):255–63.

7 Fenton KA, Ison C, Johnson AP, Rudd E, Soltani M, Martin I, et al. GRASP collaboration. Ciprofloxacin resistance in Neisseria gonorrhoeae in England and Wales in 2002. Lancet. 2003;361(9372):1867–9.

8 Bala M, Ray K, Kumari S. Alarming increase in ciprofloxacin and penicillin-resistant Neisseria gonorrhoeae isolates in New Delhi, India. Sex Transm Dis. 2003;30(6):523–5.

9 Dan M, Poch F, Shpitz D, Sheinberg B. High-Level Ciprofloxacin Resistance in Neisseria gonorrhoeae: First Report from Israel. Emerg Infect Dis. 2001;7(1).

10 Prashini M, Willen S. Ciprofloxacin-resistant gonorrhoeae in South Africa. Lancet. 2005;336(9492):1159.

11 Berglund T, Colucci B, Lund B, Qvarnstrom I, Sandstrom E. Increasing incidence of ciprofloxacin resistant gonorrhea in Sweden. Choose a correct antibiotic and follow up the treatment! Lakartidningen. 2004;101(28-19):2332–5.

12 Increases in fluoroquinolone-resistant Neisseria gonorrhoeae among men who have sex with men.United States, 2003, and revised recommendations for gonorrhea treatment, 2004. MMWR. 2004;53(816):335–8.

13 Roy K, Wang SA, Meltzer MI. Optimizing treatment of antimicrobial-resistant Neisseria gonorrhoeae. Emerg Infect Dis. 2005;11(8):1265–73.

14 Kolader M, Peerbooms PG, Vader PC, van Bergen JE, Fennema JS, de Vriers HJ. The rise in fluoroquinolone-resistant Neisseria gonorrhoeae among people attending the Municipal Health Service's clinic for sexually transmitted diseases in Amsterdam, the Netherlands; cefotaxime now first-choice treatment for uncomplicated gonorrhoeae. Ned Tijdschr Geneeskd. 2004;148(43):2129–32.

15 Bulletin OFSP. Infections sexuellement transmissibles: evolution en Suisse de 1997 à 2003. Bulletin. 2005;46:844–9.

16 Bulletin OFSP. Surveillance épidémiologique des infections à Neisseria gonorrhoeae, canton de Genève, 2000–2002. Bulletin. 2003;48:860–3.

17 Abraham S, Toutous-Trellu L, Pechere M, Hugonnet S, Liassine N, Yerly S, et al. Increased incidence of sexually transmitted infections in Geneva, Switzerland. Dermatology. 2006; 212(1):41–6.

18 Liassine N, Luescher D, Descombes MC. Infections à Neisseria gonorrhoeae et suivi de la sensibilité aux antibiotiques. Présentation à la 23ème Reunion Interdisciplinaire de Chimiothérapie Anti-infectueuse (RICAI), Paris, 4–5 décember 2003

19 Clinical and Laboratory Standards Institute. 2006. Performance standards for antimicrobial disk susceptibility tests, 9th ed. Approved standard M2-A9. CLSI, Wayne, PA.

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