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INVESTIGATIVE REPORT

Neisseria gonorrhoeae Antibiotic Resistance in Paris, 2005 to 2007: Implications for Treatment Guidelines

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Quinolone-resistant *Neisseria gonorrhoeae* rates have increased worldwide since 1994. The objective of this study was to appraise: (*i*) the antimicrobial susceptibility of *Neisseria gonorrhoeae* in a venereology clinic in Paris, between 2005 and 2007; and (*ii*) the factors associated with quinolone-resistant *N. gonorrhoeae*. A prospective study of consecutive cases was performed for the period 2005 to 2007. Susceptibility of *N. gonorrhoeae* to five antibiotics (ciprofloxacin, ceftriaxone, spectinomycin, penicillin G and tetracycline) was tested systematically. Clinical and epidemiological data were collected using a standardized form. Male-to-female sex ratio was 22.0. Median age was 30.0 years. Of 115 cases, 84 occurred in men having sex with men (72.6%) and 22 involved the anorectal area (19.1%). The rate of quinolone-resistant *N. gonorrhoeae* was 37.4% (43/115), without significant association with gender, age, sexual behaviour, past history of sexually transmitted diseases and susceptibility to other antibiotics. All *N. gonorrhoeae* were susceptible to ceftriaxone and spectinomycin. The rate of quinolone-resistant *N. gonorrhoeae* in Paris has been increasing since 2004. Ceftriaxone remains the gold standard treatment. *Key words: Neisseria gonorrhoeae; urethritis; HIV; antibiotic resistance; ciprofloxacin; quinolones; men having sex with men.*

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Neisseria gonorrhoeae (NG) is responsible for an acute sexually transmitted infection (STI) that may involve urethral, cervical, anorectal and pharyngeal sites. Complications include epididymoorchitis, pelvic inflammatory disease (endometritis, salpingitis), keratoconjunctivitis, tenosynovitides, septic arthritis and sepsis. Untreated infection can lead to infertility, ectopic pregnancy and chronic pelvic pain.

Moreover, NG infection increases the risk of HIV transmission. In the USA, NG infection is the second most commonly reported notifiable disease, and its prevalence among persons aged 14–39 years is approximately 0.25% (1). The incidence of NG urethritis in France remains between 61 and 105 cases per 100,000 population (2).

Several molecular mechanisms may lead to antimicrobial resistance of NG. Penicillinase-producing NG strains were first reported in the USA in 1976, and penicillin is no longer recommended for the treatment of NG infection since 1986. Quinolone-resistant NG (QRNG) were first reported in 1992 in Australia (3), in 1994 in the UK (4) and in 1995 in the USA (5). A recent review showed that, by 2004, QRNG rates $\geq 15\%$ were reported in the USA, and in Western Europe, Africa, Oceania and Asia (1). Consistent with the World Health Organization (WHO) recommendation that an antimicrobial associated with a resistance of $\geq 5\%$ of strains should be abandoned, fluoroquinolones are no longer recommended for the treatment of NG in the general population in several countries, including France, since 2005 (6) and the USA since 2007 (7).

In a previous report, we showed that the rate of QRNG reached a peak of 30% in Paris in 2004, with higher rates among men having sex with men (MSM), HIV-positive patients and patients with more than 5 partners during the preceding year (8). Following the French guidelines of 2005 (6) and the theoretical subsequent fall in the use of fluoroquinolones for the treatment of NG infections, one could speculate that the decreased pressure for selection should be associated with a parallel decrease in QRNG rates. However, recent studies conducted in regions where exposure to quinolones since the turn of the millennium has been negligible, such as China (9) and Australia (10) showed persistent increases in QRNG rates.

We performed a prospective study to assess the QRNG rate in Paris over the period 2005 to 2007. In addition, we aimed to identify peculiar groups of patients associated with higher rates of QRNG. Finally, we also report here our survey of the susceptibility of NG strains to four other antibiotics (ceftriaxone, spectinomycin, penicillin G and tetracycline).

PATIENTS AND METHODS

Patients and setting

From 1 January 2005 through 31 December 2007, 115 isolates were recovered from 110 consecutive patients diagnosed with go-

norrhoea, in a public venereal clinic. Our study sample represents 18.5% of the 620 NG infections diagnosed in the nine existing Parisian venereology clinics during the period 2005 to 2007.

Patients came mainly from Paris (60%) or its suburbs (40%). They usually referred directly, either for high-risk sexual behaviour or for genital symptoms. These referral criteria were constant throughout the study period. Demographic and clinical data (age, gender, group of sexual transmission, number of partners in the preceding year, site of infection, and previous history of STI) were prospectively collected using standardized medical forms. Over the study period, first-line treatment of gonorrhoea relied on a single intramuscular injection of ceftriaxone (250 mg), according to the French guidelines of 2005 (6).

Case definition

A gonococcal infection was defined by the demonstration of the presence of NG in a swabbing sample, by classical culture. Patients were screened for gonorrhoea if they had genital, rectal and/or pharyngeal discharge and/or pain, or any context of a suspicion of recent STI. Samples were collected from urethral discharge, vaginal discharge, pharyngeal and rectal swabbing. Thus, a patient may present simultaneously with more than one documented infected anatomical site.

The indications and method of swabbing were constant over the period 2000 to 2007, as well as methods for isolation, culture and bacterial identification of NG, which were described previously (11). Hence, the results of the present study can be compared with those of our previous report from 2000 to 2004 (8).

Antibiotic susceptibility assessments

Ciprofloxacin, ceftriaxone, spectinomycin, and tetracycline NG susceptibilities were tested by the agar plate diffusion method using PolyViteX agar medium. The β-lactamase production was detected using the nitrocephin test (Cefinase®, BD BBL, Sparks, MD, USA). The minimum inhibitory concentration (MIC) for penicillin G was measured by the E-test® method. The MIC for ciprofloxacin was measured using the E-test method, in addition to the agar diffusion method. Antibiotic susceptibility results were confirmed by the national reference centre for gonococcus (Centre National de Référence des Gonocoques).

The MIC breakpoints (S ≤ /R >, mg/l) used for assessing antibiotic susceptibilities were identical for the EUCAST (European Committee on Antimicrobial Susceptibility Testing) (12) and the CASFM (Comité de l'Antibiogramme de la Société Française de Microbiologie) 2008 recommendations, for the following antibiotics (13): ciprofloxacin (0.03/0.06), penicillin G (0.06/1.0), ceftriaxone (0.12/0.12) and spectinomycin (64/64). For tetracycline, we used CASFM breakpoints (1.0/4.0), which are different from those of EUCAST (0.5/1.0). The antibiotic susceptibility assessments and MIC breakpoint were unchanged since that of our previous report from 2000 to 2004 (8).

Table I. *Demographic and epidemiological features of 115 consecutive cases of* Neisseria gonorrhoeae *infection*

Features	
Total number of cases, *n* (%)	115 (100)
Median age (interquartile range), years, mean (SD)	30 (25–37)
Cases occurring in men, *n* (%)	110 (95.6)
Cases occurring in MSM, *n* (%)	84 (73.0)
Partners during the preceding 12 months, *n* (%)	
≤4	48 (41.7)
5–10	23 (20.0)
≥11	44 (38.3)
Condom never used, *n* (%)	19 (18.1)[1]
Positive HIV serology, *n* (%)	21 (18.4)[2]

[1]of 105 men; [2]of 114 men
MSM: men having sex with men

Statistical analyses

The main outcome was the rate of QRNG among the cohort of patients with NG infection who referred to our venereal clinic during the study period. The association of antimicrobial resistance with demographic or clinical factors was analysed with R software 2.2.1 (R Development Core Team, Austria, 2005). Qualitative data were analysed using the Fischer exact test. Quantitative data were using the Kruskal-Wallis one-way analysis. The significance threshold was settled at the two-sided $p < 0.05$.

RESULTS

Patients

Over the period 2005 to 2007, a total of 115 NG infections were diagnosed in 110 patients, among a total of 29,594 referrals in our venereal clinic (0.39%). Five of the 110 patients (4.5%) had more than one infection during the study period.

The demographic and epidemiological features of all consecutive cases of NG infections are summarized in Table I. Of 115 cases of NG infections, 110 were diagnosed in men (95.6%) and 5 in women (4.4%). The median age was 30.0 years (range 17–67 years). Almost 20% of the patients were HIV-positive.

Sites of Neisseria gonorrhoeae *isolation*

NG infection was microbiologically documented in all cases. The site of NG isolation was the urethra in 86 cases (74.8%), the anorectal area in 22 cases (19.1%), the pharynx and the anorectal area in 9 cases (7.8%), and the anorectal, urethral and pharyngeal areas in 2 cases (1.7%).

Rates of antibiotic resistant Neisseria gonorrhoeae

Over the period 2005 to 2007, the rate of QRNG was 37.4% (43/115), and the rate of intermediate ciprofloxacin susceptibility was 2.6% (3/115). Compared with our report from 2000 to 2004, the rate of QRNG increased markedly, both overall and according to sexual orientation and the HIV status (Table II).

None of the strains was resistant to ceftriaxone or spectinomycin. The rate of resistance to tetracycline was 17.4% (20/115). The rates of resistance and intermediate susceptibility to penicillin G were 11.3% (13/115) and 60.0% (69/115), respectively. Of the 13 penicillin G resistant strains, 11 produced β-lactamase (9.6% of the 115 cases of NG infections).

Factors associated with Quinolone-resistant Neisseria gonorrhoeae

None of the studied factors was significantly related to the QRNG rate.

Table II. *Rate of quinolone-resistant* Neisseria gonorrhoeae *(QRNG) during 2000 to 2004 and 2005 to 2007 (figures from ref. 8), overall and according to sexual orientation and HIV-serology*

	Number of QRNG (%)	
	2000–2004 (8)	2005 to 2007
Overall, *n* (%)	22/153 (14.4)	43/115 (37.4)
Sexual orientation, *n* (%)		
MSM	20/120 (16.7)	34/84 (40.5)
Heterosexual men	2/28 (7.1)	9/31 (29.0)
HIV serology, *n* (%)		
Positive	8/39 (20.5)	8/24 (33.3)
Negative	13/109 (11.9)	35/91 (38.5)

MSM: men having sex with men

None of the 5 cases occurring in female patients vs. 43 of the 110 cases occurring in male patients (39.1%) were QRNG infection ($p=0.16$). The QRNG Rate was not significantly different between heterosexual and MSM (9/31, 29.0% vs. 34/84, 40.5%; $p=0.27$), and between HIV-negative and HIV-positive patients (35/91, 38.5% vs. 8/24, 33.3%; $p=0.88$).

The rate of QRNG was not significantly associated with the gender, the number of sexual partners during the preceding year or the presence of previous STI (hepatitis B, syphilis, genital herpes and *Chlamydia trachomatis* infection). Similarly, the rate of QRNG was not significantly related to the susceptibility to penicillin G or tetracycline.

DISCUSSION

As shown in Table II, the rate of QRNG in Paris increased from 14% to 37% between the periods 2000 to 2004 and 2005 to 2008, despite a theoretical fall in the use of ciprofloxacine for treating gonorrhoeae. Even more dramatic increases in QRNG rates have been reported worldwide, despite regional recommendations precluding the use of fluoroquinolones for the first-line treatment of gonorrhoeae. Su et al (9). studied the antibiotic susceptibility of NG strains in Nanjing (China) between 1999 and 2006. In Nanjing, a surveillance programme of NG susceptibility to fluoroquinolones was launched in 1994, when the QRNG rate was 2.9%. Yet, Su et al. observed a dramatic rise of QRNG rates from 17.5% in 1995 to 83.9% in 1999 and 99.0% in 2006. Moreover, in 2006, most resistance were at a high level ($MIC_{90} \geq 8$ mg/l). Interestingly, in 2004 to 2006, Tapsall et al. (10) reported rapidly increasing NG resistance to penicillin and fluoroquinolones in areas of Australia where the use of these agents had been discontinued for gonorrhoeae treatment.

Several hypotheses can be raised to explain this continuous and sheer rise in QRNG rates in developed countries in general and, peculiarly, in France: (*i*) the inadequate persisting use of fluoroquinolones for the treatment of NG infections; (*ii*) the spread of QRNG strains from distant reservoirs, such as South-East Asia, where overuse and misuse of antibiotics are widespread; (*iii*) the permanent selective pressure on patients with undiagnosed carriage of NG strains by a pervasive use of fluoroquinolones prescribed for other infectious diseases. Obviously, studies are needed to appraise physicians' adherence to national guidelines and the actual use of antibiotics for NG infections. To our knowledge, such survey has not been performed in France over the past decade.

We found that the rate of QRNG is not significantly related to sexual orientation, HIV-status, number of sexual partners during the preceding years and past history of STI. However, it is of note that the QRNG rate was higher among MSM (40.5%) than among heterosexual men (29.0%), and that the absence of significant difference between these groups could be due to the small sample size.

Interestingly, the rise of QRNG has been proportionally greater (when considering the ratio *increase/initial QRNG rate*) for groups that were previously considered at lower risk of QRNG, namely heterosexual men and HIV-negative men (8). Besides, we also confirm that NG strains remains constantly susceptible to ceftriaxone and spectinomycin. Overall, these results corroborate that the French guidelines of 2005 for the management of NG infections are still relevant in 2008 (6).

Over the past decade, the increase in QRNG rates in France has been dramatic. For instance, these rates were 0.70% in 1998, 3.3% in 2000, 12.8% in 2003 and 31.6% in 2005 (14). The characteristics of our study population are comparable with those of a 2004 to 2006 national survey of NG infections, which reported that 96% of the cases occurred in men, 69% occurred in MSM and 16% occurred in HIV-positive patients (15). These findings suggest that our antibiotic susceptibility data may reflect national trends.

Recent national surveys in the rest of Europe showed similar trends. For instance, in England and Wales, in 2006, 26.5% and 1.7% of NG strains were respectively resistant and intermediately resistant to ciprofloxacin (16). As in our study, the recently observed increase in the QRNG rate was proportionally greater among heterosexual men (16). Other recently reported QRNG rates include 48% in Southern Germany (17) and 59% in Austria (18).

To our knowledge, only one case of spectinomycin resistant and no cases of ceftriaxone resistant NG strains have been reported in France (8, 15). Accordingly, in recent Western surveys, NG strains remain almost constantly susceptible to ceftriaxone and spectinomycin. Through 2006, in England and Wales, no NG strains demonstrated resistance to ceftriaxone and spectinomycin (16). Similarly, a report of 65 NG strains in Southern Germany between July 2004 and June 2005 demonstrated no resistance to ceftriaxone or spectino-

mycin (17). In a report of NG antibiotic susceptibility in Vienna (Austria) in 1999 to 2002, only one of 104 isolates demonstrated resistance to ceftriaxone (18). During the 1986 to 2005 period, only 4 ceftriaxone-resistant NG strains – all of them between 1987 and 1997 (19) – and 5 spectinomycin-resistant NG strains – all of them between 1988 and 1994 (19) – were isolated in the USA through the Gonococcal Isolate Surveillance Project network. However, spectinomycin is scarcely used for NG infections in Western countries, and, since high-level resistance to spectinomycin can result from a single-step mutation, the actual susceptibility of NG strains to spectinomycin should be interpreted with caution (1).

Finally, we showed that only a minority of NG strains with a decreased susceptibility to penicillin produce a β-lactamase (11/82, 13.4%), and thus it can be inferred that the majority of decreased NG susceptibilities to penicillin result from a modification of the penicillin-binding proteins (20).

In summary, our study confirms the relevance of the 2005 French guidelines for the treatment of NG infections (6). The rate of QRNG is still increasing in Paris, and this rise is peculiarly obvious among heterosexual and HIV-negative patients. Practically, an intramuscular single-dose of ceftriaxone remains the gold standard treatment for non-complicated NG infection at any anatomical sites. In patients intolerant to ceftriaxone, spectinomycin is good alternative in non-pharyngeal NG infections. For pharyngeal NG infections in patients intolerant to ceftriaxone, ciprofloxacine may be considered only if susceptibility to this compound is documented.

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The authors declare no conflict of interest.

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