The rise of fluoroquinolone-resistant *Neisseria gonorrhoeae*

Implications for treatment guidelines

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Neisseria gonorrhoeae (NG) is a gram-negative diplococcus, responsible for an acute sexually transmitted infection. NG infections may involve urethral, cervical, anorectal and pharyngeal sites. Complications include epididymoorchitis, pelvic inflammatory disease (endometritis, salpingitis), keratoconjunctivitis, tenosynovitis, septic arthritis, sepsis, endocarditis and meningitis. Untreated NG infection can lead to infertility, ectopic pregnancy and chronic pelvic pain [1]. In addition, NG infection increases the risk of HIV transmission.

The ideal treatment of NG infection should be safe, effective in 95% of the cases, affordable and available as a single-dose regimen. Ominously, since two decades, the array of antimicrobial agents that match up with these criteria has steadily decreased. Penicillinase producing NG was first reported in the United States in 1976 and since 1986 penicillin is no longer recommended for the treatment of NG. Similarly, high rates of tetracycline resistance have rendered this therapeutic option obsolescent since the early 1990s. Fluoroquinolone-resistant NG (FRNG) was first reported in 1992 in Australia [2], in 1994 in the United Kingdom [3] and in 1995 in the United States [4]. By 2004, rates of FRNG of 15% or higher have been reported in North America, Europe, Africa, Oceania and Asia [1]. In Western Europe, a prevalence of 30% FRNG has been reported in several countries. For instance, recent published rates of FRNG were 30% in France (2004) [5], 48% in Germany (2004) [6] and 59% in Austria (2002) [7].

Several mechanisms of antimicrobial resistance of NG have been described, and the corresponding genetic mutations seem chiefly chromosomally mediated. The key genes for quinolone resistance are GyrA and ParC, respectively encoding for bacterial DNA gyrase and topoisomerase IV. These enzymes, crucial for DNA synthesis and thus for bacterial growth, are blocked by quinolones. Several patterns of mutations of both enzymes have been associated with FRNG worldwide, with high geographical diversity [7].

In this issue of the Journal, Le Lin et al evaluated the rate of FRNG among cases of gonorrhoea infections reported by the network of laboratories in Geneva between 2002 and 2005. Consistent with international guidelines, FRNG were defined by a minimum inhibitory concentration >1 mg/L. Among 91 isolates, the rate of FRNG was 25% over the period 2002–2005, with a steep increase from 7% in 2002 to 47% in 2005. In addition, between 2002 and 2005 3% of the strains were intermediately resistant to ciprofloxacin. In multivariate analysis, the only factor significantly associated with FRNG was a history of sexual contact outside of Switzerland (OR: 7.0; 95% CI: 1.99–24.6, P <0.01).

In accordance with the World Health Organization recommendation that an antimicrobial associated with a resistance of 5% of strains should be abandoned, fluoroquinolones are no longer recommended for the treatment of NG in the United States since 2004 in men who have sex with men (MSM), and in the general population since 2007 [8]. Similarly, since 2005 in France, fluoroquinolones are no longer recommended as the first line treatment of NG in the general population [9]. The study of Le Lin et al brings further evidence that ciprofloxacin should be avoided in the first line treatment of gonorrhoea in Europe. Therefore, the main first line option is now represented by third generation cephalosporins, with ceftriaxone remaining the gold standard. However, in non pharyngeal gonorrhoea, oral cephalosporins such as cefixime are a reasonable option. In patients allergic to cephalosporins, treatment may rely on spectinomycin and azithromycin, since high cure rates – of 98% and 99%, respectively – have been reported in several studies [1].

Key words: Neisseria gonorrhoeae; antimicrobial resistance; ciprofloxacin; quinolones; men having sex with men; HIV

The author declares neither financial disclosure nor conflicts of interest.

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