

Letter to the Editor

Emergence of high-level fluoroquinolone-resistant *Streptococcus pneumoniae* in Turkey

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Int J Infect Dis 2003; 7: 288–289

Streptococcus pneumoniae resistant to penicillin and macrolides has become increasingly prevalent in all parts of the world, and newer fluoroquinolones (FQs) with improved Gram-positive activity have been introduced as alternative first-line therapy in community-acquired lower respiratory tract infections.¹

So far, in Turkey, the incidence of high-level penicillin resistance in pneumococci is still low (3.9%), as confirmed in a national multicenter study;² however, here we report the first strain of *S. pneumoniae*, isolated from a bacteremic cancer patient, exhibiting a high level of resistance to all FQs.

A 63-year-old male with small-cell lung cancer was hospitalized because of a febrile neutropenia episode after 7 days of his third course of chemotherapy. On the third day of hospitalization, *S. pneumoniae* grew in two consecutive bottles of blood culture taken before empirical antimicrobial therapy was started. Oral ciprofloxacin 500 mg b.i.d. for 10 days had been empirically prescribed for a non-neutropenic febrile episode occurring after his second course of chemotherapy, 20 days previously.

The isolate was susceptible to all antibiotics tested, except for FQs. MICs for penicillin G (0.016 mg/L), ampicillin (0.064 mg/L), co-amoxiclav (0.032/0.015 mg/L), cefuroxime (0.12 mg/L), cotrimoxazole (0.25/4.75 mg/L), tetracycline (0.5 mg/L), erythromycin (0.047 mg/L), clarithromycin (0.015 mg/L), azithromycin (0.125 mg/L), moxifloxacin (6 mg/L), gatifloxacin (12 mg/L), trovafloxacin (12 mg/L), grepafloxacin (16 mg/L), levofloxacin (16 mg/L), ofloxacin (32 mg/L) and ciprofloxacin (>32 mg/L) were determined by E test (AB Biodisk, Solna, Sweden) in Mueller–Hinton agar plus 5% sheep blood, following the manufacturer's recommendations.

Because of the withdrawal of both trovafloxacin and grepafloxacin from the market in August 1999, following only 2 months of clinical use, at the time when the strain had been isolated, levofloxacin was the single 'respiratory' FQ used clinically in Turkey for 1.5 years, together with earlier FQs such as ciprofloxacin and ofloxacin. We found that the isolate was resistant not only to available and withdrawn FQs, but also to newer 'respiratory' FQs (i.e. moxifloxacin and gatifloxacin) never marketed before in Turkey. This finding emphasizes the concern that *S. pneumoniae* may display cross-resistance between the older and the more recently introduced FQs. Chen et al³ found that isolates of *S. pneumoniae* with reduced susceptibility to ciprofloxacin (MIC ≥ 4 mg/L), which had become resistant before the introduction of the Gram-positive respiratory FQs in Canada, were often non-susceptible to these newer agents as well.

Taking into consideration the presence of high-level FQ resistance in our isolate, high-level FQ resistance is hereafter likely to be encountered in clinical isolates with sequential mutations in FQ targets,⁴ rendering them resistant even to newer FQs. Prior exposure to FQs, such as the recent use of ciprofloxacin in our patient, can contribute to the selection of FQ-resistant strains, as was likely in recent observations on respiratory tract infections caused by *S. pneumoniae* resistant to levofloxacin, irrespective of penicillin resistance.^{5,6} Likewise, emergence of FQ-resistant viridans group streptococci in connection with the use of levofloxacin prophylaxis during neutropenia has been reported recently.⁷

Although recent reports suggest that decreased susceptibility to FQs among pneumococci is associated with increasing numbers of FQ prescriptions,^{3,8} no such systematic evaluation of FQ activity and the factors associated with reduced susceptibility has yet been done in Turkey.

Also, in these reports, decreased susceptibility was most pronounced among those in the group above 65 years of age, to which our patient belonged, suggesting a possible source of and reservoir for FQ-resistant pneumococci.

Furthermore, there are areas of the world where resistant isolates have emerged, albeit in relatively low frequencies at the present time.^{8,9} Although it might be

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inappropriate to extrapolate from one nation's experience to other nations, similar increases in both the prevalence and the degree of decreased susceptibility to FQs could be expected in Turkey, where liberal use of antimicrobials, including FQs, is common. More worrisome would be the potential for increased resistance of *S. pneumoniae* to even the latest FQs, as in the isolate reported here.

All FQs should now be used with greater care than in the past, because of the clonal dissemination potential of antibiotic-resistant *S. pneumoniae*, both across geographic borders¹⁰ and in institutional settings.¹¹ It may also be appropriate to consider routine testing of the susceptibility of respiratory *S. pneumoniae* isolates to FQs.

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