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Sir,

Resistance to the fluoroquinolone class of antimicrobials is considered extremely rare in Haemophilus species. In addition, according to the British Society for Antimicrobial Chemotherapy surveillance of respiratory tract infections of 958 clinical isolates of Haemophilus influenzae examined in 2000/01, only for three isolates were the MICs of ciprofloxacin ≥0.12 mg/L, and no MICs were >0.5 mg/L.

In November 2001, two fluoroquinolone-resistant Haemophilus species were isolated at the clinical microbiology laboratory of the Pretoria Academic Hospital. One isolate was an H. parainfluenzae (N16) and the other an H. influenzae type B (N15). Upon testing by the Kirby Bauer disc diffusion method with a 5 µg gatifloxacin disc, neither isolate had a zone of inhibition. MIC testing confirmed that both isolates were resistant to gatifloxacin and the MIC of this agent was 8 mg/L. Both isolates were also resistant to the other fluoroquinolones tested (Table 1). DNA sequencing of gyrA and gyrB revealed that N15 contained two mutations within gyrA, resulting in substitution of serine-84 with leucine and aspartate-88 with tyrosine. Beidenbach & Jones1 and Georgiou et al.2 have described similar strains. Despite having similar susceptibility to fluoroquinolones, N16 only possessed a single mutation in gyrA, resulting in substitution of serine-84 with leucine. Neither isolate had a mutation in the quinolone resistance determining region of gyrB, parC or parE. These data suggest that N16 may possess additional mechanisms contributing to resistance.

The clinical impact of the resistance of these two isolates is difficult to determine. N15 came from patient 1, a 51-year-old male admitted for secondary bacterial pneumonia superimposed on a pre-

Table 1. MICs (mg/L) of five fluoroquinolones

<table>
<thead>
<tr>
<th></th>
<th>Ciprofloxacin</th>
<th>Norfloxacin</th>
<th>Levofloxacin</th>
<th>Moxifloxacin</th>
<th>Gatifloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCTC 8466a</td>
<td>0.03</td>
<td>0.06</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>N15</td>
<td>4</td>
<td>8</td>
<td>4</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>N16</td>
<td>4</td>
<td>8</td>
<td>4</td>
<td>16</td>
<td>8</td>
</tr>
</tbody>
</table>

*aControl strain used for susceptibility testing.
sumed recurrent TB infection. He was treated with co-amoxiclav, and an intercostal drain was inserted to reduce the concomitant pleural effusion. He responded well to therapy, and an acid-fast smear of his sputum confirmed TB; TB therapy (rifampicin, isoniazid, ethambutol and pyrazinamide), as recommended by the South African Department of Health, was commenced. The patient was unable to recall prior fluoroquinolone use. N16 was isolated from a 55-year-old female, with previous renal impairment, admitted with pneumonia. She was treated with cefuroxime and responded well. She had received ciprofloxacin for a urinary tract infection within the previous 10 months of admission.

Emergence of these highly resistant Haemophilus species may be the result of several factors. Firstly, in the South African community, there is considered to be a relatively high use of fluoroquinolone antibiotics for the treatment—among other infections—of sexually transmitted diseases and urinary tract infections. Secondly, during the winter of 2001, two new fluoroquinolones (moxifloxacin and gatifloxacin) were licensed for use, widely advertised and recommended in the treatment of community-acquired pneumonia. It should be noted that both of the isolates described in this report were resistant to these new agents. Previous use of a fluoroquinolone has been associated with fluoroquinolone resistance in Haemophilus influenzae, and it is suggested that prior exposure to a quinolone selected the bacteria described. However, the high-level resistance of both these isolates has been considered previously to be extremely rare, and such strains have not been isolated easily in the laboratory after exposure to the older fluoroquinolones, such as ciprofloxacin and ofloxacin. Therefore, we caution the use of these newer fluoroquinolones, and emphasize the importance of vigilance and surveillance of bacterial species considered previously to be exquisitely susceptible to these agents, so that any changes in the population can be identified quickly and policies put in place to prevent transmission.

References


Clinical and bacteriological implications of macrolide resistance in group A streptococcal pharyngitis

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Keywords: macrolides, resistance, clarithromycin, penicillin, Streptococcus pyogenes

Sir,

Portier et al.1 reported a multicentre, open-label, comparative study of 5 day clarithromycin modified release (MR) versus 10 day penicillin V in the treatment of pharyngitis due to group A β-haemolytic streptococci (GABHS), showing equivalence between both treatments.

In this study, Portier et al. provide the clinical and bacteriological results for the patients infected with clarithromycin-resistant strains, but there is no comparison with results of patients infected with susceptible strains. In fact, patients infected with a clarithromycin-resistant strain were excluded from the per protocol (PP) analysis.

We have performed further analysis, using a Fisher two-sided test, to evaluate whether patients infected with a clarithromycin-resistant strain had different bacteriological and clinical results from patients infected with a clarithromycin-susceptible strain when treated with clarithromycin or penicillin V.

In the intention-to-treat analysis (ITT), in the group of patients treated with clarithromycin, clinical cure at visit three was obtained in 89.6% (146 of 163) of patients with susceptible strains, and in 71.4% (10 of 14) of patients with resistant strains [P = 0.066; odds ratio (OR) 3.4; 95% confidence interval (CI) 0.7–13.5], thus showing a better response in the former group. With respect to the bacteriological eradication at visit three (the principal criterion for efficacy analysis), the success rate was much higher in the group with susceptible strains than in the group with resistant ones [88.3% (121 of 137) versus 28.6% (4 of 14); P < 0.001; OR 18.9; 95% CI 4.6–89.4].

When the comparison between patients infected with a clarithromycin-resistant strain and those infected with a clarithromycin-susceptible strain was performed in the group of patients treated with penicillin V, a statistically significant difference was found for bacteriological efficacy (86.1% versus 60%; P = 0.019; OR 4.14; 95% CI 1.07–14.66) but not for clinical efficacy (P = 0.31). Nevertheless, it should be taken into account that, in the bacteriological evaluation of the patients infected with a clarithromycin-resistant strain, five of 15 patients (five of six of those considered ‘not cured’) were classified as indeterminate (a much higher proportion than in the group of patients infected with a clarithromycin-susceptible strain). If the patients with indeterminate results are excluded from the analysis, then in the group treated with clarithromycin, differences between patients with a clarithromycin-susceptible and those with a clarithromycin-