Correspondence


Figure 1. PFGE after Smal digest: the distance between two bands at ~140 kb and at ~160 kb is shorter in the mecA-positive strain (arrow).

after implantation of a total hip prosthesis. *S. epidermidis* resistant to oxacillin, ciprofloxacin, trimethoprim/sulfamethoxazole, gentamicin, clindamycin, erythromycin, fusidic acid and rifampicin, but susceptible to tetracycline, teicoplanin and vancomycin grew in biopsies from periprosthetic tissue. Species identification was made using API ID 32 Staph system (bioMérieux, La Balme les Grottes, Montalieu Vercieu, France); the MIC of vancomycin was 2 mg/L determined by Etest (AB Biodisk, Solna, Sweden) in Mueller–Hinton (MH) agar. A spacer-free, two-stage exchange recovery was made of the prosthesis with an 8 week interval was performed and antimicrobial chemotherapy was administered during the first 6 weeks. The patient was treated with a 5.5 week course of vancomycin (1 g twice daily), followed by teicoplanin (400 mg once daily) for the remaining 4 days, after removal of the central venous catheter. On reimplantation, biopsies from periprosthetic tissue were obtained and vancomycin (1 g twice daily) was given for another 2 weeks, until cultures were reported to be negative.

Unfortunately, relapse occurred 4 months after reimplantation. Again, *S. epidermidis* was isolated, but showed two different phenotypes in susceptibility tests. While one strain was indistinguishable from the pathogen causing the primary infection, the second type was susceptible to oxacillin, but otherwise there was no difference in the resistance pattern. Both strains showed no increase in MIC of vancomycin, as revealed by Etest in MH agar. PCR for the mecA gene was negative in the second type, but positive in the original isolate. Interestingly, pulsed-field gel electrophoresis (PFGE) after Smal digestion revealed only a slight difference between the two strains. The distance between two bands at ~140 kb and at ~160 kb was narrower in the mecA-positive strain (Figure 1), probably representing the location of the mecA gene. Vancomycin (1 g twice daily for 6 weeks) was administered during the implant-free-interval, and a complete recovery was made.

To our knowledge, *in vivo* loss of mecA gene in *S. epidermidis* after treatment has only been published in abstract form, without reporting any further details about antimicrobial agents and duration of therapy. Acquiring methicillin resistance is attributed to intra- and interspecies transfer of SCCmec, but little is known about the loss or deletion of the mecA gene. Long-term storage, high temperatures and UV radiation have been described to be factors influencing the stability of SCCmec in vitro. Moreover, experiments have shown that coagulase-negative staphylococci exposed to glycopeptides may lose high-level resistance to oxacillin, without loss of the mecA gene. Recently published findings indicate that the acquisition and/or loss of SCCmec in *S. epidermidis* may occur in the region of the orfX gene. Our case illustrates that the mecA complex may lose its stability after prolonged antimicrobial treatment.

Acknowledgements

We thank Reno Frei, MD and Professor Brigitte Berger-Bächi, PhD for their discussions regarding this case.

Transparency declarations

None of the authors has a conflict of interest regarding this case report. No funding was available.

References

Sir, 

In the early 1990s, against a background of already worrying rates of erythromycin resistance among isolates of *Streptococcus pneumoniae*, further sharp increases in the prevalence of macrolide resistance were observed 1 to 2 years after the introduction of the macrolides azithromycin and clarithromycin into Europe and the USA.¹ This increase strongly correlated with the consumption of these antibiotics in most countries and overall.¹ A more recent study in Portugal, using molecular epidemiological investigation, demonstrated that the emergence of macrolide resistance had a high correlation with azithromycin usage in that country.²

Telithromycin is the first clinically available ketolide, a new class of antimicrobial within the macrolide–lincosamide–streptogramin B (MLSb) group, which is characterized by potent *in vitro* and clinical activity against Gram-positive cocci including MLSb and multidrug-resistant strains.³ Telithromycin was introduced into clinical practice in Germany in October 2001, followed shortly after by Italy, Spain, Mexico, Brazil and France. The PROTEKT (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin) study is a global, longitudinal, international surveillance programme established in 1999 to study the antimicrobial susceptibility of common bacterial pathogens associated with community-acquired respiratory tract infections, which has now completed its fourth year. One of the primary goals of PROTEKT is to monitor the development of telithromycin resistance post-introduction. In this correspondence, we update our analysis of the first 3 years of this study with year 4 data.⁴

MICs of telithromycin were determined using CLSI (NCCLS) standard methods.⁵ Genotyping and serotyping were performed as described previously.⁶ Statistical analysis was performed using GraphPad Prism software (GraphPad Software, Inc., San Diego, CA, USA). One-way ANOVA was used to examine overall variance of means and Tukey’s multiple comparison test was used to compare the variance of each year with each of the other 3 years.⁷

During the four respiratory seasons (1999–2003), 21 out of 20 750 (0.1%) *S. pneumoniae* isolates demonstrated low-level resistance to telithromycin (MICs of 4–8 mg/L) (Table 1). Among these 21 isolates, 13 different MLST types and seven different serotypes were identified. In addition, clonally-related strains could not be found consistently in the same centres in any of the four years studied. Nineteen of the 21 isolates harboured *erm* (B), and two isolates harboured both *erm* (B) and *mef* (A). The MIC distribution did not change significantly over the 4 years (*P* = 0.75), and the MIC distribution in any one year was not significantly different from any other year (*P* > 0.05 for each year pair). In the 4 years the study has been conducted in the countries described above, more than 5 million courses of telithromycin have been prescribed since its introduction in 2001.

Unlike the rapid increase in resistance that occurred within 2 years of the introduction of azithromycin and clarithromycin, resistance to telithromycin amongst isolates of *S. pneumoniae* has not increased since its introduction in 2001.¹⁴ However, as with any antimicrobial, the development of resistance needs to be carefully monitored.

**Acknowledgements**

We are grateful to our colleagues worldwide for the supply of bacterial isolates as part of the PROTEKT study and the GR Micro PROTEKT team who performed the MIC determinations.

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**Table 1. Distribution of telithromycin MICs in 20,750 isolates of *Streptococcus pneumoniae* isolated from the PROTEKT global antimicrobial surveillance studies, 1999–2003**

<table>
<thead>
<tr>
<th>Time period</th>
<th>n</th>
<th>0.002</th>
<th>0.004</th>
<th>0.008</th>
<th>0.015</th>
<th>0.03</th>
<th>0.06</th>
<th>0.12</th>
<th>0.25</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999–2000</td>
<td>3435</td>
<td>2 (0.06)</td>
<td>14 (0.41)</td>
<td>1009 (31.12)</td>
<td>228 (6.64)</td>
<td>256 (7.45)</td>
<td>166 (4.83)</td>
<td>152 (4.43)</td>
<td>121 (3.52)</td>
<td>21 (0.61)</td>
<td>1 (0.03)</td>
<td>1 (0.03)</td>
<td>1 (0.03)</td>
<td>1 (0.03)</td>
</tr>
<tr>
<td>2000–2001</td>
<td>4256</td>
<td>2 (0.05)</td>
<td>14 (0.33)</td>
<td>327 (7.68)</td>
<td>327 (7.68)</td>
<td>327 (7.68)</td>
<td>327 (7.68)</td>
<td>327 (7.68)</td>
<td>327 (7.68)</td>
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<td>327 (7.68)</td>
<td>327 (7.68)</td>
<td>327 (7.68)</td>
</tr>
<tr>
<td>2001–2002</td>
<td>6739</td>
<td>2 (0.03)</td>
<td>14 (0.21)</td>
<td>136 (1.98)</td>
<td>136 (1.98)</td>
<td>136 (1.98)</td>
<td>136 (1.98)</td>
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<td>136 (1.98)</td>
</tr>
<tr>
<td>2002–2003</td>
<td>3964</td>
<td>2 (0.05)</td>
<td>14 (0.36)</td>
<td>136 (3.43)</td>
<td>136 (3.43)</td>
<td>136 (3.43)</td>
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</table>

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⁴ Correspondence

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Correspondence

Sanofi-Aventis is acknowledged for their financial support of the PROTEKT study.

References


