Activities of 16-membered ring macrolides and telithromycin against different genotypes of erythromycin-susceptible and erythromycin-resistant Streptococcus pyogenes and Streptococcus pneumoniae

Annarita Mazzariol¹, Raffaella Koncan¹, Luca Agostino Vitali² and Giuseppe Cornaglia¹*

¹Dipartimento di Patologia, Sezione di Microbiologia, Università degli Studi di Verona, Strada Le Grazie 8, 37134 Verona, Italy; ²Dipartimento di Biologia Molecolare, Cellulare e Animale, Università degli Studi di Camerino, Via F. Camerini 5, 62032 Camerino, Italy

Received 4 August 2006; returned 19 September 2006; revised 24 January 2007; accepted 5 March 2007

Objectives: To test four 16-membered macrolides (josamycin, spiramycin, midecamycin and rokitamycin) along with other compounds in the same class (erythromycin, clarithromycin, roxithromycin and azithromycin) plus clindamycin and telithromycin, against Streptococcus pyogenes and Streptococcus pneumoniae isolates with well-characterized resistance genotypes.

Methods: Four hundred and eighty-six isolates of S. pyogenes and 375 isolates of S. pneumoniae were assayed for their macrolide susceptibilities and investigated by PCR to detect their different erythromycin resistance genes. All strains had been isolated over the period 2002–2003 from specimens of different human origin obtained in 14 different Italian centres.

Results: All 16-membered macrolides showed very low MICs (MIC 50s and MIC 90s, ≤0.06–0.5 mg/L) for the erythromycin-susceptible isolates and for those with the M phenotype, but the telithromycin MICs for the M-type isolates were at least four times higher (MIC 90s, 0.5 mg/L). In S. pyogenes, the MIC 90s of 16-membered macrolides for the cMLS B isolates were ≥256 mg/L, whereas that for telithromycin was 4 mg/L; the MIC 90s of 16-membered macrolides and telithromycin ranged from <0.06 to 0.5 mg/L for the iMLS B isolates with erm(A) and from 0.12 to ≥256 mg/L for those with erm(B). In S. pneumoniae, the MIC 90s of the 16-membered macrolides for the cMLS B isolates ranged from 0.5 to 128 mg/L, whereas for the iMLS B isolates their values ranged from <0.06 to 4 mg/L; the MIC 90s of telithromycin for both the cMLS B and the iMLS B isolates ranged from <0.06 to 0.12 mg/L.

Conclusions: MICs ranged for all the drugs, except telithromycin, from <0.06 to ≥256 mg/L, with 15% to 30% resistant S. pyogenes for all drugs tested except clindamycin (8%) and telithromycin (5.4%) and 10% to 40% resistant S. pneumoniae for all drugs tested except telithromycin (0.3%). In both S. pyogenes and S. pneumoniae, erythromycin resistance related to a mef gene meant that telithromycin MICs were definitely higher than in erythromycin-susceptible isolates, although telithromycin susceptibility was preserved in all cases. In S. pyogenes, the activity of both 16-membered macrolides and telithromycin against the iMLS B strains proved to be dependent on the erm gene involved, being greater against isolates with erm(A).

Keywords: antimicrobial resistance surveillance, macrolides, azalides, group A streptococci, GAS

Introduction

Since the early 1990s, a dramatic increase in the isolation of erythromycin-resistant streptococci has been observed worldwide, some of the highest prevalence values being reported in Italy. The precise implications for clinical outcomes of the different resistance phenotypes need to be fully elucidated, also with a view to the possibility of both testing and using alternative compounds in the same class.

*Corresponding author. Fax: +39-045-58-46-06; E-mail: giuseppe.cornaglia@univr.it

© The Author 2007. Published by Oxford University Press on behalf of the British Society for Antimicrobial Chemotherapy. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org
Data regarding susceptibility to 16-membered macrolides are few and far between, often involving a limited number of compounds and suggesting heterogeneous susceptibility patterns. This prompted us to test four 16-membered macrolides, along with other compounds in the same class and clindamycin and telithromycin, against a substantial number of *Streptococcus pneumoniae* and *Streptococcus pyogenes* isolates representative of different Italian geographical areas and well-characterized with regard to their resistance genotype.

**Materials and methods**

Four hundred and eighty-six isolates of *S. pyogenes* and 375 isolates of *S. pneumoniae* were tested for their susceptibility to four 16-membered macrolides (josamycin, spiramycin, midecamycin and rokitamycin), the 15-membered azalide azithromycin, the lincosamide clindamycin and the ketolide telithromycin.

All strains had been isolated over the period 2002–2003 from specimens of different human origin (92% throat swabs and the others being from either blood or wound exudates) obtained in different geographical areas and from patients of different ages.

MICs were determined by agar dilution on Mueller–Hinton plates supplemented with 5% sheep blood and inoculated with 105–107 cfu/mL using a Steer inoculator. The plates were incubated overnight at 35°C with 5% CO2. *S. pneumoniae* ATCC 49619 was used as a control strain. Interpretation of the results was basically as outlined in the latest CLSI (formerly NCCLS) guidelines. When CLSI breakpoints were not available, the results were interpreted according to either the breakpoints proposed by the French Society for Microbiology (telithromycin, roxithromycin, josamycin, spiramycin and midecamycin) or those published by Ono et al. (6) (rokitamycin).

The resistance phenotype was determined by the double disc test with erythromycin and clindamycin as described previously.

The presence of resistance genes was determined by PCR amplification, as described by Daly et al.8 PCR primers for *mef(E)*, *erm(A)*, *erm(D)*, and the *erm(B)* primers were designed to provide specific PCR products of 363, 553, 590 and 764 bp, respectively. The *mef(E)* primers were as described by Daly et al. (5′-GGG AGA TGA AAA GAA GGA GT-3′ and 5′-TAA AAT GGC ACC GAA AG-3′). The *erm(A)* primers were as described by Daly et al. (5′-TGG TTC GGT GCT TAC TAT TGT-3′ and 5′-CCC CTA TCA AAT TAT AAA CG-3′), and the *erm(B)* primers were 5′-CAC TTC AGT GAT TAC AGA AA-3′ and 5′-CTC ATA GAA TTA TTT CTC GT-3′. Briefly, 1 μL of each lysate was used in a 25 μL reaction mixture at an annealing temperature of 52 °C (*mef*), 48 °C (*erm(A)*) or 56 °C (*erm(B)*). Products were run on a 1.5% agarose gel and visualized with ethidium bromide staining. Data were validated by sequencing selected PCR products.

**Results**

Table 1 lists the MICs and interpretative categories for *S. pyogenes* and *S. pneumoniae*. One hundred and fifty-two *S. pyogenes* isolates (31.3% of the total) were erythromycin-resistant. All of the erythromycin-resistant strains were also resistant to clarithromycin, azithromycin and roxithromycin. Forty-eight isolates (9.9% of the total) proved non-susceptible to clindamycin. The number of isolates non-susceptible to 16-membered macrolides ranged from 78 (rokitamycin, 16% of the total) to 95 (midecamycin, 19.5% of the total). Four hundred and fifty-seven isolates and 375 isolates of *S. pneumoniae*.

<table>
<thead>
<tr>
<th>Strain</th>
<th>Antibiotic</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;</th>
<th>MIC range</th>
<th>% S</th>
<th>% I</th>
<th>% R</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. pyogenes</em></td>
<td>erythromycin</td>
<td>≤0.06</td>
<td>&gt;256</td>
<td>≤0.06→256</td>
<td>68.7</td>
<td>0</td>
<td>31.3</td>
</tr>
<tr>
<td></td>
<td>clarithromycin</td>
<td>≤0.06</td>
<td>&gt;256</td>
<td>≤0.06→256</td>
<td>68.1</td>
<td>0.6</td>
<td>31.3</td>
</tr>
<tr>
<td></td>
<td>roxithromycin</td>
<td>≤0.06</td>
<td>&gt;256</td>
<td>≤0.06→256</td>
<td>69.4</td>
<td>4.5</td>
<td>26.1</td>
</tr>
<tr>
<td></td>
<td>azithromycin</td>
<td>0.25</td>
<td>&gt;256</td>
<td>≤0.06→256</td>
<td>67.7</td>
<td>1.0</td>
<td>31.3</td>
</tr>
<tr>
<td></td>
<td>josamycin</td>
<td>≤0.06</td>
<td>&gt;256</td>
<td>≤0.06→256</td>
<td>81.5</td>
<td>0.8</td>
<td>17.7</td>
</tr>
<tr>
<td></td>
<td>midecamycin</td>
<td>≤0.06</td>
<td>256</td>
<td>≤0.06→256</td>
<td>80.5</td>
<td>3.5</td>
<td>16.0</td>
</tr>
<tr>
<td></td>
<td>rokitamycin</td>
<td>≤0.06</td>
<td>128</td>
<td>≤0.06→256</td>
<td>84.0</td>
<td>1.0</td>
<td>15.0</td>
</tr>
<tr>
<td></td>
<td>spiramycin</td>
<td>0.25</td>
<td>&gt;256</td>
<td>≤0.06→256</td>
<td>80.9</td>
<td>0.6</td>
<td>18.5</td>
</tr>
<tr>
<td></td>
<td>clindamycin</td>
<td>≤0.06</td>
<td>0.25</td>
<td>≤0.06→256</td>
<td>90.1</td>
<td>1.9</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>telithromycin</td>
<td>≤0.06</td>
<td>0.5</td>
<td>≤0.06→32</td>
<td>94.0</td>
<td>0.6</td>
<td>5.4</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>erythromycin</td>
<td>≤0.06</td>
<td>&gt;256</td>
<td>≤0.06→256</td>
<td>61.3</td>
<td>0</td>
<td>38.7</td>
</tr>
<tr>
<td></td>
<td>clarithromycin</td>
<td>≤0.06</td>
<td>&gt;256</td>
<td>≤0.06→256</td>
<td>61.1</td>
<td>0</td>
<td>38.9</td>
</tr>
<tr>
<td></td>
<td>roxithromycin</td>
<td>0.12</td>
<td>&gt;256</td>
<td>≤0.06→256</td>
<td>61.4</td>
<td>1.3</td>
<td>37.3</td>
</tr>
<tr>
<td></td>
<td>azithromycin</td>
<td>0.25</td>
<td>&gt;256</td>
<td>≤0.06→256</td>
<td>53.6</td>
<td>7.5</td>
<td>38.9</td>
</tr>
<tr>
<td></td>
<td>josamycin</td>
<td>≤0.06</td>
<td>128</td>
<td>≤0.06→256</td>
<td>76.0</td>
<td>6.4</td>
<td>17.6</td>
</tr>
<tr>
<td></td>
<td>midecamycin</td>
<td>≤0.06</td>
<td>64</td>
<td>≤0.06→256</td>
<td>81.9</td>
<td>4.2</td>
<td>13.9</td>
</tr>
<tr>
<td></td>
<td>rokitamycin</td>
<td>≤0.06</td>
<td>8</td>
<td>≤0.06→256</td>
<td>87.2</td>
<td>2.1</td>
<td>10.7</td>
</tr>
<tr>
<td></td>
<td>spiramycin</td>
<td>≤0.06</td>
<td>&gt;256</td>
<td>≤0.06→256</td>
<td>74.1</td>
<td>2.2</td>
<td>23.7</td>
</tr>
<tr>
<td></td>
<td>clindamycin</td>
<td>≤0.06</td>
<td>&gt;256</td>
<td>≤0.06→256</td>
<td>69.7</td>
<td>0</td>
<td>30.3</td>
</tr>
<tr>
<td></td>
<td>telithromycin</td>
<td>≤0.06</td>
<td>0.06</td>
<td>≤0.06→8</td>
<td>99.7</td>
<td>0</td>
<td>0.3</td>
</tr>
</tbody>
</table>
Antistreptococcal activities of 16-C macrolides and telithromycin

(94% of the total) were susceptible to telithromycin, with MIC_{50} and MIC_{90} values of ≤0.06 and 0.5 mg/L, respectively.

Table 1 also shows that 145 S. pneumoniae isolates (38.7% of the total) were erythromycin-resistant, virtually all of them also proving resistant to clarithromycin and azithromycin. The results forroxithromycin were very similar, too. The number of isolates non-susceptible to 16-membered macrolides ranged from 48 (rokitamycin, 12.8% of the total) to 97 (spiramycin, 25.8% of the total). Only a single isolate (0.3% of the total) was nonsusceptible to telithromycin (MIC, 8 mg/L).

In terms of genotype distribution, 40 S. pyogenes isolates showed constitutive MLSB resistance (cMLS_{B}, 69 (45.4%) inducible MLSB resistance (iMLS_{B}) and 43 (28.3%) M-type resistance. At PCR analysis, all cMLS_{B} isolates showed the \textit{erm}(B) gene, all \textit{M} isolates showed the \textit{mef}(A) gene and no resistance genes were found in the erythromycin-susceptible isolates. Fifty-one of the iMLS_{B} isolates had the \textit{erm}(A) gene and 18 had the \textit{erm}(B) gene. Concerning \textit{S. pneumoniae}, 87 isolates (60% of all erythromycin-resistant isolates) were cMLS_{B}, 32 (22.1%) iMLS_{B} and 26 (17.9%) M-type. In all the \textit{MLS}_{B} isolates, whether constitutive or inducible, PCR analysis showed an \textit{erm}(B) gene. All the \textit{M}-type isolates had a \textit{mef} gene, no phenotypic difference being observed between strains harbouring \textit{mef}(A) (69.2%) and \textit{mef}(E) (30.8%), respectively (data not shown).

Table 2 breaks down the activities of 16-membered macrolides and telithromycin by different erythromycin resistance phenotypes. In \textit{S. pyogenes}, all 16-membered macrolides showed indistinguishably low MICs both for the erythromycin-susceptible strains and for those with the \textit{M} phenotype, whereas telithromycin MICs for the \textit{M}-type isolates were at least eight times higher than for the erythromycin-susceptible isolates. All the 16-membered macrolides showed MIC_{50}s equal to or above 256 mg/L for all the cMLS_{B} isolates. Among the iMLS_{B} isolates, those with \textit{erm}(B) turned out to be the ones with the higher level of resistance (MIC_{50} = 32 mg/L and MIC_{90} = 256 mg/L in the case of rokitamycin; MIC_{50} and MIC_{90} ≥ 256 mg/L in all other cases), whereas those with \textit{erm}(A) were much more susceptible, ranging in activity from rokitamycin (MIC_{50} and MIC_{90} ≤ 0.06 mg/L) to spiramycin (MIC_{50} = 0.5 mg/L and MIC_{90} = 8 mg/L). Telithromycin proved more active than the 16-membered macrolides against both the cMLS_{B} and the iMLS_{B} isolates, a further distinction being observed between the iMLS_{B} isolates with \textit{erm}(B) (MIC_{50} = 0.12 mg/L and MIC_{90} = 8 mg/L) and those with \textit{erm}(A) (MIC_{50} and MIC_{90} ≤ 0.06 mg/L). All telithromycin-resistant strains carried an \textit{erm}(B) gene; 80.7% of them (21 isolates) had a cMLS_{B} phenotype and 19.3% (5 isolates) had an iMLS_{B} phenotype.

Table 2 also shows that all of the 16-membered macrolides were very active against both the erythromycin-susceptible and the \textit{M}-type isolates of \textit{S. pneumoniae} (MIC_{50}s ≤ 0.06 to 0.12 mg/L). As with \textit{S. pyogenes}, telithromycin MICs were higher (at least 4-fold) for the \textit{M}-type isolates than for the erythromycin-susceptible isolates. All of the 16-membered macrolides showed a wide range of activities against the cMLS_{B} isolates (≤0.06 to >256 mg/L), although the MIC_{90} for these isolates was always >128 mg/L. The iMLS_{B} isolates showed a greater susceptibility, rokitamycin being the most active compound (MIC_{50} ≤ 0.06 mg/L and MIC_{90} = 0.5 mg/L). Telithromycin MICs were consistently low both for the cMLS_{B} and for the iMLS_{B} isolates (MIC_{90} 0.12 and ≤0.06 mg/L, respectively); only one cMLS_{B} (MIC_{90}, 8 mg/L) and no iMLS_{B} strains proved resistant.

Discussion

Resistance to 14- and 15-membered macrolides commonly used in clinical practice could be theoretically overcome by employing ‘diverse’ macrolides, such as 16-membered compounds and telithromycin.

Although telithromycin has been clearly shown to be active against most streptococcal strains, irrespective of their erythromycin susceptibility, data regarding 16-membered compounds are few and far between, often collected on the occasion of specific outbreaks only and limited to the compounds used in those specific countries.

All of the \textit{M} isolates and 65% of the iMLS_{B} isolates (but none of the cMLS_{B} isolates) were susceptible to the 16-membered compound mioakamycin in the Finnish outbreak,7 and all of the \textit{M} isolates and roughly 50% of the iMLS_{B} isolates (but again none of the cMLS_{B} isolates) were susceptible to another 16-membered compound, namely josamycin, in a survey carried out during the Italian outbreak.9 In another Italian survey, only the iMLS_{B} isolates with \textit{erm}(A) presented a definite zone of inhibition around the josamycin or spiramycin discs in the agar diffusion test.10

Consistent with those partial reports, our results showed that all four 16-membered macrolides we tested were generally active against \textit{M}-type isolates of \textit{S. pyogenes} (MIC_{50}s and MIC_{90}s ≤ 0.06 to 0.5 mg/L), but not against the cMLS_{B} isolates (MIC_{50}s, ≥256 mg/L). As regards the iMLS_{B} isolates, the susceptibility values were distinctly lower in the isolates with \textit{erm}(A) (ranging from ≤0.06 to 0.5 mg/L) than in those with \textit{erm}(B) (ranging from 0.12 to ≥256 mg/L). Against pneumococcal isolates too, all 16-membered macrolides tested showed very good activity against the \textit{M}-type erythromycin-resistant isolates, with a wide activity range (≤0.06 to 4 mg/L) against the iMLS_{B} isolates even though only \textit{erm}(B) isolates were represented.

Most \textit{S. pyogenes} and \textit{S. pneumoniae} isolates examined in the present study (94.0% and 99.7%, respectively) were susceptible to telithromycin, but the susceptibility values for the \textit{M}-type erythromycin-resistant isolates (MIC_{90}s, 0.5 mg/L) were at least four times higher than for the erythromycin-susceptible ones (and for most of the erythromycin-resistant MLS_{B} isolates, too), which has been shown to be related to telithromycin acting as a substrate for an efflux pump.11,12

Despite the fair \textit{in vitro} activity of some compounds, most notably rokitamycin, any clinical use against iMLS_{B} streptococci should be regarded with the utmost caution, also on the basis of previous experience with ‘dissociated’ erythromycin resistance in staphylococcal strains, whose \textit{in vitro} susceptibility to noninducing 16-membered macrolides proved to be illusory in the clinical setting because of the ease with which mutants constitutively resistant to all MLS_{B} antibiotics arose as a consequence of nucleotide sequence alterations.13

Moreover, the virtual absence of widely accepted and internationally validated breakpoints for 16-membered macrolides often makes it difficult to translate their \textit{in vitro} activity into precise clinical recommendations and to evaluate the correlation between these susceptibility results and those obtained for
Table 2. MICs for *S. pyogenes* and *S. pneumoniae* strains classified by erythromycin susceptibility

<table>
<thead>
<tr>
<th>Strain</th>
<th>No. of isolates</th>
<th>Antimicrobial</th>
<th>MIC (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>range</td>
</tr>
<tr>
<td><em>S. pyogenes</em> ERY S</td>
<td>334</td>
<td>erythromycin</td>
<td>≤0.06 – 0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clarithromycin</td>
<td>≤0.06 – 0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>roxithromycin</td>
<td>≤0.06 – 0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>azithromycin</td>
<td>≤0.06 – 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>josamycin</td>
<td>≤0.06 – 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>midecamycin</td>
<td>≤0.06 – 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>rokitamycin</td>
<td>≤0.06 – 0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>spiramycin</td>
<td>≤0.06 – 0.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clindamycin</td>
<td>≤0.06 – 0.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>telithromycin</td>
<td>≤0.06</td>
</tr>
<tr>
<td><em>S. pyogenes</em> cMLSB</td>
<td>40</td>
<td>erythromycin</td>
<td>256 – &gt;256</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clarithromycin</td>
<td>256 – &gt;256</td>
</tr>
<tr>
<td></td>
<td></td>
<td>roxithromycin</td>
<td>256 – &gt;256</td>
</tr>
<tr>
<td></td>
<td></td>
<td>azithromycin</td>
<td>256 – &gt;256</td>
</tr>
<tr>
<td></td>
<td></td>
<td>josamycin</td>
<td>32 – &gt;256</td>
</tr>
<tr>
<td></td>
<td></td>
<td>midecamycin</td>
<td>≤0.06 – &gt;256</td>
</tr>
<tr>
<td></td>
<td></td>
<td>rokitamycin</td>
<td>≤0.06 – &gt;256</td>
</tr>
<tr>
<td></td>
<td></td>
<td>spiramycin</td>
<td>≤0.06 – &gt;256</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clindamycin</td>
<td>≤0.06 – 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>telithromycin</td>
<td>≤0.06 – 32</td>
</tr>
<tr>
<td><em>S. pyogenes</em> iMLSB</td>
<td>69</td>
<td>erythromycin</td>
<td>256 – &gt;256</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clarithromycin</td>
<td>2 – &gt;256</td>
</tr>
<tr>
<td></td>
<td></td>
<td>roxithromycin</td>
<td>1 – &gt;256</td>
</tr>
<tr>
<td></td>
<td></td>
<td>azithromycin</td>
<td>16 – &gt;256</td>
</tr>
<tr>
<td></td>
<td></td>
<td>josamycin</td>
<td>≤0.06 – &gt;256</td>
</tr>
<tr>
<td></td>
<td></td>
<td>midecamycin</td>
<td>≤0.06 – &gt;256</td>
</tr>
<tr>
<td></td>
<td></td>
<td>rokitamycin</td>
<td>≤0.06 – &gt;256</td>
</tr>
<tr>
<td></td>
<td></td>
<td>spiramycin</td>
<td>≤0.06 – &gt;256</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clindamycin</td>
<td>≤0.06 – 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>telithromycin</td>
<td>≤0.06 – 32</td>
</tr>
<tr>
<td><em>S. pneumoniae</em> ERY S</td>
<td>230</td>
<td>erythromycin</td>
<td>≤0.06 – 0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clarithromycin</td>
<td>≤0.06 – 0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>roxithromycin</td>
<td>≤0.06 – 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>azithromycin</td>
<td>≤0.06 – 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>josamycin</td>
<td>≤0.06 – 0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>midecamycin</td>
<td>≤0.06 – 0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>rokitamycin</td>
<td>≤0.06 – 0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>spiramycin</td>
<td>≤0.06 – 0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clindamycin</td>
<td>≤0.06 – 0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>telithromycin</td>
<td>≤0.06 – 0.25</td>
</tr>
</tbody>
</table>

continued
erythromycin and the other macrolides commonly used in clinical practice.

Acknowledgements

No specific financial support has been received for this work beyond the research funding from the University of Verona to A. M. and G. C.

Transparency declarations

G. C. has received funds for speaking at symposia organized on behalf of Pfizer and GSK.

References


