Comparative activity of telithromycin against typical community-acquired respiratory pathogens

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Objectives: Respiratory tract infections (RTIs) remain a significant cause of morbidity and mortality. Major bacterial pathogens in RTIs, such as Streptococcus pneumoniae, have exhibited increasing resistance to a variety of antibiotics during the past decades. Telithromycin, the first ketolide, was designed especially to overcome this resistance. The present study was conducted to assess the comparative activity of telithromycin against typical RTI pathogens in Austria.

Methods: A total of 1015 bacterial isolates was tested, including S. pneumoniae, Streptococcus pyogenes, Staphylococcus aureus and Haemophilus influenzae. MICs of the following antimicrobials: penicillin G, ampicillin (for H. influenzae), azithromycin, clarithromycin, erythromycin A and telithromycin were determined using the NCCLS broth microdilution method.

Results: Telithromycin showed excellent activity against S. pneumoniae, with 99.8% of all isolates being susceptible. Penicillin remained active with an MIC 50 and MIC 90 of 0.007 mg/L. Nevertheless, a notable increase in penicillin intermediate-resistant and resistant isolates, from 4.9% in 1996 to the present rate of 10%, was observed. There was also a distinct rise in the resistance levels of S. pneumoniae against the macrolides. All tested isolates of S. pyogenes were susceptible to penicillin and telithromycin, and only low levels of resistance against telithromycin were found in S. aureus (2.2%, MIC90 of 0.5 mg/L). No telithromycin-resistant isolate of H. influenzae could be detected.

Conclusions: This study demonstrates the rising prevalence of resistance among S. pneumoniae not only to penicillin but also to other antimicrobials. It also shows the value of telithromycin as an attractive option for the empirical treatment of community-acquired RTIs in an era of widespread antibacterial resistance.

Keywords: ketolides, susceptibilities, streptococci

Introduction

Respiratory tract infections (RTIs), such as community-acquired pneumonia (CAP), acute exacerbations of chronic bronchitis (AECB) and acute sinusitis and tonsillitis/pharyngitis, are among the most common infectious diseases. The burden of illness with community-acquired RTIs is a global problem with widespread public health and socioeconomic implications. In particular, one of the greatest public health challenges is the treatment of community-acquired RTIs in an age of increasing antibacterial resistance.¹² In recent years, the increase in the incidence of respiratory tract pathogens that are resistant to current antibacterials continues to threaten the utility of existing agents, and highlights the need for newer broad-spectrum antibacterials for the empirical treatment of community-acquired RTIs.³⁻⁵

Whereas oral penicillins remain an effective, inexpensive treatment for RTIs caused by penicillin G-susceptible streptococci, these agents are not active against β-lactamase-producing pathogens (e.g. Haemophilus influenzae and Moraxella catarrhalis). The β-lactams also lack appreciable activity against the atypical/intracellular microorganisms, Mycoplasma pneumoniae, Chlamydia pneumoniae and Legionella pneumophila, which are notable respiratory pathogens in CAP. Furthermore, β-lactam resistance in Streptococcus pneumoniae has reached alarming levels in many regions.⁶⁻⁸ The macrolides provide a useful alternative in cases of penicillin G resistance, and for patients known to be allergic to β-lactams. However, macrolide resistance among common respiratory pathogens is increasing, especially since the introduction of the newer agents of this class.⁹,¹⁰ Also, resistance to the fluoroquinolones has begun to emerge.¹¹

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Table 1. Interpretative MIC categories (mg/L) for tested isolates

<table>
<thead>
<tr>
<th></th>
<th>S. pneumoniae</th>
<th>S. pyogenes</th>
<th>S. aureus</th>
<th>H. influenzae</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
<td>I</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>≤0.06</td>
<td>0.12–1</td>
<td>≥2</td>
<td>≤0.12</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>≤1</td>
<td>2</td>
<td>≥4</td>
<td>≤1</td>
</tr>
<tr>
<td>Erythromycin A</td>
<td>≤0.25</td>
<td>0.5</td>
<td>≥1</td>
<td>≤0.25</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>≤0.25</td>
<td>0.5</td>
<td>≥1</td>
<td>≤0.25</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>≤0.5</td>
<td>1</td>
<td>≥2</td>
<td>≤0.5</td>
</tr>
</tbody>
</table>

NT, not tested.

The ketolides are the latest family of antibacterials to be developed for the treatment of community-acquired RTIs. Telithromycin is the first agent of this new class of macrolide–lincosamide–streptogramin group B antibacterials (M+L+S) to become available for clinical use. Telithromycin has a mechanism of action very similar to erythromycin A, from which it has been derived. It inhibits protein synthesis potently by interacting close to the peptidyl transferase site of the bacterial 50S ribosomal subunit. The novel structure of the ketolides confers excellent intrinsic activity against strains that have become resistant to other M+L+S antibacterials, with only a very low potential to select for resistance or cross-resistance to M+L+S agents in vitro and in vivo.3 Telithromycin has demonstrated clinical efficacy across a range of community-acquired RTIs, and potent in vitro activity against the pathogens commonly indicated in these infections, including drug-resistant S. pneumoniae.9,10,12 This paper describes the prevalence in Austria of resistance and the comparative activity of telithromycin and other currently available antimicrobial agents against the most common community-acquired, non-atypical respiratory tract pathogens.

Materials and methods

Bacterial isolates

A total of 1015 bacteria were tested, including S. pneumoniae (n = 542), Streptococcus pyogenes (n = 223), Streptococcus aureus (n = 183) and Haemophilus influenzae (n = 67). Isolates were collected in the years 2001–2002 by the 25 participating centres of the Austrian Bacterial Surveillance Network in Vienna, Innsbruck, Graz, Salzburg, Klagenfurt, Villach, Leoben, Oberwart, Wels, Steyr, Vöcklabruck, Ried, Krems, Mistelbach, Wiener Neustadt, Linz and St. Pölten. Isolates were obtained from patients with community-acquired RTIs, namely sinusitis, otitis media, pharyngitis, pneumonia and AECB. Only one isolate per patient was collected. Sources for isolation of RTI pathogens were cultures from blood, sputum, bronchoalveolar lavage, middle ear fluid, nasopharyngeal swab or aspirate and sinus aspirate. Strains were identified and stored using standard laboratory methods. Additional information on the age and sex of the patient, the infection, culture source, in/outpatient status and date of sample collection was listed on standard report forms.

Antimicrobial susceptibility testing

MICs were determined using the NCCLS broth microdilution method.13,14 For S. pneumoniae and S. pyogenes, Mueller–Hinton broth was supplemented with 5% lysed horse blood, for H. influenzae the supplement contained Iso-Vitalex 1%, NAD 15 mg/L, haemin 30 mg/L, horse serum 50 mg/L, potassium chloride 20 mg/L and magnesium sulphate 7 mg/L. A final inoculum of 7 × 10⁴ to 1 × 10⁵ cfu was used, and microtitre plates were incubated at 36.5°C in ambient air for 16–20 h. MIC endpoints were read as the lowest concentration of antimicrobial that totally inhibited macroscopically visible growth of the inoculum. Standard quality control strains (ATCC) were included in each run.

Isolates were tested against the following antimicrobials: penicillin G, ampicillin (for H. influenzae), azithromycin, clarithromycin, erythromycin A and telithromycin. Percentage susceptibilities were calculated based on NCCLS breakpoints, and the NCCLS tentative breakpoints for telithromycin (Table 1).

Results

Streptococcus pneumoniae (n = 542)

Telithromycin demonstrated excellent activity against S. pneumoniae, with 99.8% of all isolates being susceptible. MIC₉₀ and MIC₅₀ values were 0.015 and 0.03 mg/L, respectively. Penicillin remained active with both MIC₉₀ and MIC₅₀ values of 0.007 mg/L. Nevertheless, a notable increase in intermediate-resistant and resistant isolates from 4.9% in 1994–1996 to the present rate of 10% was observed. On average, 90% of S. pneumoniae isolates were susceptible to all three macrolides tested (Table 2).

Streptococcus pyogenes (n = 223)

The susceptibility of S. pyogenes to erythromycin, clarithromycin and azithromycin was 90.6%, 92.8% and 90.6%, respectively. All isolates tested were susceptible to penicillin and telithromycin (Table 2).

Staphylococcus aureus (n = 183)

The prevalence of resistance among S. aureus against penicillin was 73.2%, with an MIC₉₀ of 16 mg/L. Only low levels of resistance were found against telithromycin (2.2%, MIC₉₀ of 0.5 mg/L). Levels of susceptibility to the macrolides tested ranged from 55.7% (erythromycin) to 83.6% (clarithromycin) (Table 2).

Haemophilus influenzae (n = 67)

All isolates of H. influenzae were susceptible to telithromycin. Ampicillin also showed good activity with MIC₉₀ and MIC₅₀ of 0.5 and 1 mg/L. For the macrolides tested, the MIC₉₀ was 4 mg/L for azithromycin and 8 mg/L for erythromycin and clarithromycin (Table 2).
Discussion

RTIs remain a significant cause of morbidity and mortality, despite the wide range of antimicrobial agents available. Lower RTIs—CAP and AECB—are estimated to be responsible for more than 4.3 million deaths globally per annum, while upper RTIs—sinusitis, tonsillitis/pharyngitis and acute otitis media—whereas not life-threatening, have a significant socioeconomic impact and represent a major cause of antibiotic prescribing in the community.16,17

Major bacterial pathogens in RTIs, such as S. pneumoniae, S. pyogenes or H. influenzae have exhibited decreasing susceptibility to a variety of antibiotics during the past decades as a result of increasing drug use.2 Whereas wide variations in bacterial resistance rates are noted from country to country, rising resistance rates are observed worldwide. Of particular concern is the development of multi-resistance. For example, penicillin resistance in S. pneumoniae is often associated with resistance to macrolides, co-trimoxazole, tetracycline and fluoroquinolones.18 β-Lactamase production, the most common resistance mechanism seen in H. influenzae, is also increasing with levels currently at 20%–30% in most countries, but up to 60% in South Korea.2,19

The best way to prevent the spread of resistant clones is through the rapid eradication of bacterial pathogens. Bacterial eradication, however, can only be achieved by the correct use of a suitable agent, at an adequate dose, for a sufficient duration. For the optimal empirical therapy of RTIs, there is thus an urgent need for new agents that will cover all major respiratory tract pathogens, including those resistant to existing agents. These new agents must also have a low potential to select for resistance, have a favourable safety and tolerability profile and a convenient dosing regime to optimize patient compliance.

Telithromycin, the first ketolide antibacterial, was designed especially for the therapy of RTIs. Clinical trial data suggest that the ketolides have similar safety profiles to the newer macrolides, are well tolerated and can be used safely.9 Telithromycin has potent in vitro activity against common and atypical respiratory pathogens, including β-lactam- and macrolide-resistant strains and does not induce MLSB resistance.20 Large global studies, such as the PROTEKT (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin) have also shown favourable results for telithromycin.5,8,12

The present study was conducted to assess the activity of telithromycin against typical RTI pathogens, in comparison with commonly prescribed antibiotics in Austria. Austria is a participating member in global studies such as the Alexander Project or the PROTEKT study, but because of the low number of strains included per species, the goal of setting up treatment guidelines based on local resistance patterns cannot be met adequately. Another interesting aspect was telithromycin activity in the face of distinctly rising resistance rates: whereas in 1994–1996 only 2.9% of S. pneumoniae were intermediate-resistant and 2.0% fully resistant to penicillin, these numbers rose to 7.8% and 2.2% in 2000.21,22 Whereas these figures are the results of studies by the Austrian Bacterial Surveillance Network, where over 500 S. pneumoniae strains were tested in 1999–2000, the resistance rates of S. pneumoniae in Austria, according to the PROTEKT study (1.8% intermediate-resistant and 5.3% resistant strains), were based on only 57 isolates in the same years.

In addition, because of the increasing importance of S. aureus in RTIs in the at-risk population, this pathogen was also tested.

The present study shows the potent activity of telithromycin against major respiratory pathogens. The results confirm findings published

Table 2. In vitro activity of telithromycin and other agents against S. pneumoniae (n = 542), S. pyogenes (n = 223), S. aureus (n = 183) and H. influenzae (n = 67).

<table>
<thead>
<tr>
<th></th>
<th>S. pneumoniae</th>
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<th>H. influenzae</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC (mg/L)</td>
<td>Susceptibility (%)</td>
<td>MIC (mg/L)</td>
<td>Susceptibility (%)</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>0.007 0.007 0.007</td>
<td>90 78 78</td>
<td>0.01 0.01 0.01</td>
<td>100 100 100</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>NT NT NT</td>
<td>NT NT NT</td>
<td>0.5 0.5 0.5</td>
<td>0 0 0</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>0.015 0.03 0.06</td>
<td>99.8 91.3 91.3</td>
<td>0.003 0.015 0.003</td>
<td>100 100 100</td>
</tr>
<tr>
<td>Erythromycin A</td>
<td>0.06 0.125 0.4</td>
<td>88.3 82.3 82.3</td>
<td>0.006 0.015 0.006</td>
<td>100 100 100</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>0.01 0.01 0.01</td>
<td>90.2 90.2 90.2</td>
<td>0.01 0.01 0.01</td>
<td>90.2 90.2 90.2</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>0.01 0.01 0.01</td>
<td>90.2 90.2 90.2</td>
<td>0.01 0.01 0.01</td>
<td>90.2 90.2 90.2</td>
</tr>
<tr>
<td>NT, not tested.</td>
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previously, that telithromycin maintains its anti-pneumococcal activity against strains that are resistant to β-lactam and macrolide antibiotics. The single isolate of *S. pneumoniae* with intermediate resistance to telithromycin was also resistant to penicillin and macrolides. This type of resistance is often mediated by a *mef*-encoded efflux. Whereas MIC values increase for these strains, the increase is less effective against ketolides, either because of ketolides’ high intrinsic activity and tight ribosomal binding, or because ketolides are poor substrates for efflux pumps. Nevertheless, continuous monitoring of this potential for development of resistance is clearly needed, especially since additional, previously unidentified mutations or mechanisms may be involved in this process. 

Telithromycin also showed good activity against *S. pyogenes* and *H. influenzae*, where no resistance was found, and 97.8% of *S. aureus* strains tested proved susceptible to telithromycin.

For the first time in Austria, rates of macrolide resistance in *S. pneumoniae* have reached the 10% mark, probably reflecting the steady increase in macrolide consumption, especially of those macrolides dosed only once or twice daily. This trend has been recorded earlier in other European countries, for example Spain and Italy. However, there was no clear difference in the activity of erythromycin and the newer macrolide agents, azithromycin and clarithromycin.

This distinct rise in the prevalence of resistance among *S. pneumoniae*, not only to penicillin, but also to other antimicrobials, highlights the need for continuing surveillance of resistance rates at both the international and national level, so that changes in susceptibility patterns can be detected quickly and appropriate measures put into place.

In conclusion, telithromycin demonstrated excellent activity against major pathogens of RTIs and is therefore an attractive option for the empirical treatment of community-acquired RTIs in an era of widespread antibacterial resistance.

### References


