INTRODUCTION

Solithromycin was designed primarily to overcome macrolide-resistant streptococci, including multidrug-resistant (MDR) Streptococcus pneumoniae (S. pneumoniae), often because of a combination of bacterial ribosome, thereby limiting the emergence of resistant strains (R). In contrast, the older macrolides, such as erythromycin and azithromycin, interact at a single site.

S. pneumoniae is the predominant causative agent of CABP. The introduction of the seven-valent pneumococcal conjugate vaccine (PCV7) into the United States childhood vaccine schedule in 2000, followed by the PCV13 in 2010, in combination with the pneumococcal conjugate vaccine (PCV23) in the high-risk adults, combined with the selective pressure of antimicrobial use, have been associated with the emergence of MDR strains outside of vaccine coverage. These observations highlight the changing landscape of circulating clones of S. pneumoniae and the prevalence of antimicrobial resistance in this species, which support the need for maintained antimicrobial resistance surveillance. Moreover, non-vaccine serotypes are replacing serotypes covered in current vaccines. Indeed, non-encapsulated strains of S. pneumoniae (NEs) such as ST344 and ST448 may be the cause of invasive and non-invasive infections. NEs strains are frequent resistant to a range of currently prescribed antibiotics including penicillin and azithromycin (7). Solithromycin has also demonstrated activity comparable to azithromycin against Haemophilus influenzae, and very potent activity against Moraxella catarrhalis, beta-hemolytic streptococci, and Mycoplasma pneumoniae (macrolide-resistant strains), and other respiratory pathogens.

This study reports the incidence of antibiotic susceptibility among 2014 surveillance isolates of S. pneumoniae from the nine CDC Census divisions. We also show the macrobiotic trend over 6 years in the US.

MATERIALS AND METHODS

A total of 4,567 non-replicative CABP S. pneumoniae United States isolates collected prospectively between the years 2008 to 2014 were investigated in this study. The number of unique isolates per year is as follows: 785 in 2008, 796 in 2009, 502 in 2010, 1389 in 2011, and 715 in 2014. These isolates were collected consecutively from patients with respiratory tract infections (RTI), bloodstream infections (BSI) and other infection types.

Isolates were identified by the submitting laboratories and confirmed by JMI Laboratories (North Liberty, Iowa, US) using standard bacteriological algorithms and methodologies, including the use of Vibrio identification Systems (biolog®), matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS), and DNA sequencing based methods, when required.

Isolates were tested for susceptibility by broth microdilution methods, according to the recommendations of CLSI (8,9). MIC interpretations were based on CLSI breakpoint criteria (8,9). Macrolide resistance rates were based on erythromycin and/or azithromycin and/or clarithromycin MICs as available (in 2014 only azithromycin data was collected).

RESULTS

The antimicrobial susceptibility patterns of US isolates for S. pneumoniae in 2014 are shown in Table 1. These are expressed as MIC50, MIC90, MIC range, and % S, %I or %R based on approved CLSI breakpoints. Solithromycin does not have approved breakpoints, therefore only MICs are presented. Figure 1 shows the distribution of MICs for azithromycin and solithromycin for 2014. The resistance breakpoint for azithromycin is 2 µg/mL, thus 45% of isolates are considered macrolide-resistant. IDSA guidelines for treatment of CABP recommend alternative classes of antibiotic be considered for empirical therapy when the local, high-level resistance rate (≥16 µg/mL) exceeds 25%. Table 2 shows the rates of azithromycin and high-level macrolide resistance by CDC Census Division and also shows the rates of azithromycin and penicillin resistance by CDC Census Division. Figure 3 illustrates the overall and high-level macrolide resistance data by US Census Divisions. Table 3 shows the increasing rate of azithromycin resistance in the US from 2008-2014.

Table 1: Activity of solithromycin and comparators when tested against S. pneumoniae isolated in the US in 2014

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>MIC50 (µg/mL)</th>
<th>MIC90 (µg/mL)</th>
<th>% S</th>
<th>%I</th>
<th>%R</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Solithromycin</strong></td>
<td>0.008</td>
<td>0.25</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Azithromycin</strong></td>
<td>0.25</td>
<td>&gt;32</td>
<td>51.3</td>
<td>42.4</td>
<td>6.3</td>
</tr>
<tr>
<td><strong>Amoxicillin-Clavulanate</strong></td>
<td>0.12-2</td>
<td>&gt;8</td>
<td>92.7</td>
<td>6.0</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Ampicillin</strong></td>
<td>≤0.06</td>
<td>0.06-8</td>
<td>80.8</td>
<td>11.9</td>
<td>7.3</td>
</tr>
<tr>
<td><strong>Ceftriaxone</strong></td>
<td>≤0.25</td>
<td>&gt;25</td>
<td>80.8</td>
<td>1.3</td>
<td>17.9</td>
</tr>
<tr>
<td><strong>Linezolid</strong></td>
<td>1</td>
<td>≤0.12-2</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Moxifloxacin</strong></td>
<td>≥0.12</td>
<td>≤0.12-4</td>
<td>98.3</td>
<td>1.4</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Penicillin</strong></td>
<td>≥0.06</td>
<td>≤0.06-8</td>
<td>57.2</td>
<td>29.5</td>
<td>13.3</td>
</tr>
<tr>
<td><strong>Vancomycin</strong></td>
<td>0.25</td>
<td>≤0.12-1</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- **MICs**: Minimum Inhibitory Concentrations
- **MIC50**: The MIC value at which 50% of the isolates are inhibited
- **MIC90**: The MIC value at which 90% of the isolates are inhibited
- **% S**: Percentage of susceptible isolates
- **%I**: Percentage of intermediate isolates
- **%R**: Percentage of resistant isolates

Figure 1: Distribution of azithromycin and solithromycin activity against S. pneumoniae isolated in the US in 2014

Figure 2: Distribution of macrolide resistance for S. pneumoniae across the US in 2014

Figure 3: Changes in macrolide resistance in S. pneumoniae in 2008-2014

CONCLUSIONS

- S. pneumoniae is the most common bacterial cause of CABP. It is also a frequent pathogen in other respiratory tract infections.
- Antibiotic resistance in S. pneumoniae is a significant clinical challenge as highlighted by the CDC’s list of Threatening pathogens, with S. pneumoniae in the “Urgent” category.
- Almost all community-acquired respiratory tract infections are empirically treated. In the US, the most frequently prescribed antibiotic is a macrolide (such as azithromycin), amoxicillin, amoxicillin/clavulanate or a respiratory fluoroquinolone (usually levofloxacin), are the most frequent agents prescribed. Current agents each have their weaknesses, whether it be inconsistent activity against S. pneumoniae, lack of activity against atypical species, or unpredictable safety and tolerability.
- Macrolide resistance is in steady state in S. pneumoniae is continuing to increase in the US.
- There are regional differences but overall almost half of strains tested were macrolide resistant (azithromycin MIC ≥2 µg/mL) with high-level macrolide resistance (azithromycin MIC ≥16 µg/mL) being reported in 8 of the 9 CDC census divisions, leading to a national average of 33%.
- Both low and high-level macrolide resistance have been reported to cause clinical failures and other negative outcomes including higher hospital stays and higher costs.
- Solithromycin shows activity against all macrolide-resistant strains of Streptococcus pneumoniae isolated, irrespective of the location in the US.

ACKNOWLEDGEMENTS

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