Molecular Evaluation of Mupirocin Resistances Among Staphylococcus aureus
Collected in United States (USA) Hospitals During 2008-2010

M CASTANHEIRA, LN WOOSLEY, GJ MOET, RE MENDES, RN JIMI
JMI Laboratories, North Liberty, Iowa, USA

ABSTRACT

Mupirocin is approved by the United States (USA) Food and Drug Administration (FDA) for eradication of Staphylococcus aureus nasal carriage in adult patients and healthcare personnel to control the dissemination of methicillin-resistant S. aureus (MRSA). In other countries mupirocin is also used to treat superficial skin and skin-structure infections (SSI) and this use has lead to the emergence of resistance against community-acquired isolates, where mupirocin was made available when a resistance mechanism, but strains showing elevated MIC results contradictory to some recent reports of escalating mupirocin resistance rates were stable and showed no increasing trend during three years monitored, confirming some recent reports of escalating resistance rates against this compound in the USA.

Among HLR strains, mup is still the main resistance mechanism, but strains showing elevated MIC results that did not carry this gene (only in 2010) were detected and will be further characterized.

INTRODUCTION

Background. Recent reports have indicated an escalation in high-level resistance (HLR, MIC, ≥512 µg/mL) to mupirocin among S. aureus (SA) following widespread use of this agent (1) to control the carriage of MRSA on skin and in nasal passages, as well as for treatment of cutaneous infections. Low-level resistance (LLR; MIC, 0.25-512 µg/mL) arises by mutation of the mupirocin target, isoleucyl-tRNA synthetase, whereas HLR is due to presence of the plasmid pMMO that encodes an isoleucyl-tRNA synthetase with reduced affinity for mupirocin (2). In this study analyzing a large collection of SA strains isolated from USA hospitals in a 3 year period, we investigated the mupirocin resistance (LLR) rates among SA isolates causing nosocomial infections. Resistance rates were higher among MRSA isolates compared to MSSA: 7.6, 5.5 and 7.1% resistant (CLSI criteria) for MRSA and 0.7, 0.5 and 0.7% resistant for MSSA, respectively (Table 1). All 281 strains showing HLR (MIC, ≥512 µg/mL) were screened for the presence of mup (PCR and results were confirmed by sequencing). Among S. aureus, HLR (MIC, ≥512 µg/mL) is caused by the acquisition of a plasmid-mediated gene named mupA, which encodes a novel isoleucyl tRNA synthetase, mupA-carrying plasmids show further resistance to other antimicrobial agents including macrolides, pentamidine, tetracyclines, and trimethoprim, suggesting that mupA may select for increased drug resistance. Mupirocin resistance (LLR) usually have acquired base changes in the native isoleucyl tRNA synthetase gene, mupA or a simple copy of mupA in the chromosome.

In this study, we analyzed mupirocin resistance rates among S. aureus collected from USA hospitals in a 3 year period and evaluated the resistance mechanisms against this agent in isolates showing HLR from 2008 to 2010.

METHODS AND MATERIALS

Table 1.

Mupirocin MIC distributions for S. aureus in the USA SENTRY Program determined by the CLSI reference broth microdilution method

<table>
<thead>
<tr>
<th>Organism (no. tested)</th>
<th>≤0.25</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>16</th>
<th>32</th>
<th>64</th>
<th>128</th>
<th>256</th>
<th>≥512</th>
<th>Total resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (5609)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>133 (2.4)</td>
</tr>
<tr>
<td>MSSA (3026)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>43 (1.4)</td>
</tr>
<tr>
<td>MRSA (3135)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>124 (3.9)</td>
</tr>
<tr>
<td>All (4989)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>158 (3.2)</td>
</tr>
</tbody>
</table>

Mupirocin MIC distribution results in the USA SENTRY Program determined by CLSI reference broth microdilution method. Overall, 95.6% of the S. aureus isolates tested were mupinoxin-susceptible according to the CLSI breakpoints (≤4 µg/mL; susceptible).

Materials and methods. Isolates were susceptibility tested by a reference broth microdilution procedure as described by the Clinical and Laboratory Standards Institute (CLSI; M07-A8 document) using validated broth microdilution panels manufactured by TREK Diagnostics (Cleveland, Ohio, USA). Categorical interpretations for all antimicrobials were those found in M100-S21 (2011) and quality control (QC) was performed using, respectively: S. aureus ATCC 29213. All QC results were within specified ranges as published in CLSI documents.

Conclusions. Our results demonstrated a stable rate of mup in a large recent multi-year USA collection of SA strains, mup was detected in the vast majority (98.9%) of the isolates displaying HLR. Elevated mupA MIC rates in prior studies could be due to limited sample sizes or evaluation of isolates from a unique institution. Variations by year were noted, but no clear trend could be detected comparing 2008 and 2010 results (P=0.208; odds ratio [OR], 0.89; confidence interval [CI], 0.67-1.2). Using CLSI breakpoints, 94.9, 96.5, and 93.3% of the strains were susceptible to mup in 2008, 2009, and 2010, respectively. LLI to mupirocin (MIC, ≥256 µg/mL) showed a slight variation among the three years analyzed: 2.7, 1.6, and 0.7% for 2008, 2009 and 2010, respectively (Table 1). However these differences were not statistically meaningful (P=0.041; odds ratio [OR]; 95% confidence interval [CI], 0.70 [0.55-0.90]). Strains showing HLR (MIC, ≥512 µg/mL) were detected in comparable rates of 2.2, 2.7, and 2.5% for 2008, 2009 and 2010, respectively (P=0.041; odds ratio [OR]; 95% confidence interval [CI], 0.70 [0.55-0.90]; Table 1).

Results were higher in 2008, 2009 and 2010 for USA300 isolates compared to MSSA: 7.6, 5.5 and 7.1% resistant (CLSI criteria) for MRSA and 2.7, 1.6 and 2.2% resistant for MSSA from Tulsa, OK and New Orleans, LA, respectively, both collected in 2010.