Abstract

Introduction: In 2013, the Center for Disease Control (CDC) designated methicillin-resistant *Staphylococcus aureus* (MRSA) as a serious threat. In addition to its intrinsic virulence, MRSA has become resistant to numerous antibacterial agents. In many instances, mupirocin is used empirically to decolonize patients harboring MRSA to decrease the possibility of progression to disease. *In vitro* susceptibility information is critical to identify patients who would benefit from use of mupirocin for decolonization and treatment of infections caused by MRSA. Methods: One-hundred and sixty-three recent MRSA single patient clinical isolates were collected from the Clinical Microbiology Laboratory. *In-vitro* susceptibility testing was performed using E-test methodology for tigecycline, ceftaroline, daptomycin, vancomycin, linezolid, and mupirocin. Results: Of the 163 MRSA isolates tested, >99% demonstrated susceptibility to tigecycline, ceftaroline, daptomycin, vancomycin, linezolid, and mupirocin. Results: Of the 163 MRSA isolates tested, >99% demonstrated susceptibility to tigecycline, ceftaroline, daptomycin, vancomycin, linezolid, and mupirocin. Seventy (43%) had vancomycin MICs ≥ 1.5 µg/ml, twenty-four isolates (15%) were resistant to mupirocin, and three appeared to express mupirocin hetero-resistance. Conclusion: While antibiotic susceptibility to mupirocin is not routinely performed in clinical microbiology laboratories, the level of resistance to mupirocin identified in this surveillance study suggests that susceptibility testing should be added to routine MRSA panels.

Keywords

Methicillin-Resistant Staphylococcus aureus, Mupirocin Resistance, Antibiotic Susceptibility, MIC Creep

1. Introduction

Methicillin-resistant Staphylococcus aureus (MRSA) is a ubiquitous, virulent pathogen found in a variety of hospital, long-term care facility and community settings [1][2]. It has been recognized as a serious threat by the Center for Disease Control and Prevention (CDC) in 2013 [3]. A recent survey from the CDC on antimicrobial-resistant pathogens associated with healthcare-associated infections (HAIs) found MRSA to be associated with 54.6% of central line-associated bloodstream infections (CLABSI), 58.7% of catheter-associated urinary tract infections (CAUTI), 48.4% of ventilator-associated pneumonia (VAP), and 43.7% of surgical site infections (SSI) [4]. Active intravenous agents include vancomycin, tigecycline, ceftaroline, linezolid, and daptomycin. Mupirocin is a topical agent used to eradicate nasal carriage with MRSA as well as topical treatment for MRSA associated wound infections and impetigo in adult patients and health care personnel. As mupirocin susceptibility is not routinely performed in most clinical microbiology laboratories, it is assumed to be an active agent when used. This in vitro susceptibility surveillance study using E-test methodology was undertaken to determine mupirocin susceptibility along with comparator antibiotics against recent MRSA isolated from a variety of clinical patient specimens.

2. Materials and Methods

The Clinical Microbiology Laboratory at New York Hospital Queens identifies MRSA using Vitek-2 panels. Single-patient clinical MRSA isolates from April 2013 to July 2014 were included. Isolates were stored on columbia naladixic acid agar (CNA) plates at 4°C until ready for use. Isolates were re-streaked onto new CNA plates to ensure purity before conducting susceptibility studies.

Minimal inhibitory concentrations (MICs) were determined for mupirocin, vancomycin, tigecycline, ceftaroline, linezolid, and daptomycin by E-test according to manufacturer’s specifications (bioMérieux, France). The Clinical Laboratory Standards Institute (CLSI) guidelines were used for susceptibility interpretation for vancomycin, daptomycin, ceftaroline, and linezolid [5]. Tigecycline susceptibility was determined using FDA breakpoints. ATCC 43300 was used as a methicillin resistant Staphylococcus aureus quality control strain. Definition of mupirocin susceptibility based on MICs was as follows: mupirocin susceptible ≤ 4 µg/ml; low-level resistance 8 - 256 µg/ml and high-level ≥ 512 µg/ml [6]. The study was reviewed and approved by The New York Hospital Queens Institutional Review Board.

3. Results

3.1. Patient and Isolate Characteristics

Of the 163 patients, 88 (54%) were female, with mean age of 66 years (range 2 - 102 years). Anatomic locations of the isolates were as follows: 42 (26%) blood, 78 (48%) wounds, 15 (9%) urine, 3 (2%) nose, 3 (2%) nares, and 22 (13%) sputum (Table 1).

3.2. Susceptibility Results

For vancomycin, 92 (56%) of isolates had MICs of ≤1.0 µg/ml, 70 (43%) had MICs ≥ 1.5 µg/ml. Of the 42 blood isolates, 22 (52%) had MICs ≥ 1.5 µg/ml. For ceftaroline, 162 (99%) of isolates had MICs of ≤1.0 µg/ml and one isolate had MIC of 1.5 µg/ml. For daptomycin, 162 (99%) of the isolates had MICs of ≤1.0 µg/ml and one isolate had MIC of 1.5 µg/ml. For linezolid, all isolates (100%) had MICs of ≤4 µg/ml. For tigecycline, 162 (99%) of the isolates had MICs of ≤0.5 µg/ml and one isolate had MIC of 0.75 µg/ml. For mupirocin, 139 (85%) of the isolates were susceptible with 24 (15%) demonstrating high level resistance MIC ≥ 512 µg/ml (Table 2). Three of the isolates displayed mupirocin heteroresistance (colony growth within the ellipse). Colonies taken
Table 1. Source of isolates and mupirocin resistant strains.

<table>
<thead>
<tr>
<th>Source of Isolate</th>
<th>Number of Isolates</th>
<th>Number and Mupirocin Resistance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>42</td>
<td>10 (26)</td>
</tr>
<tr>
<td>Wounds</td>
<td>78</td>
<td>12 (15)</td>
</tr>
<tr>
<td>Urine</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Sputum</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Nares</td>
<td>3</td>
<td>1 (33)</td>
</tr>
<tr>
<td>Nose</td>
<td>3</td>
<td>1 (33)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>163</td>
<td>24</td>
</tr>
</tbody>
</table>

Table 2. Antibiotic susceptibility of 163 methicillin-resistant Staphylococcus aureus by E-test.

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>MIC\textsubscript{50} µg/ml</th>
<th>MIC\textsubscript{90} µg/ml</th>
<th>MIC Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mupirocin</td>
<td>0.094</td>
<td>&gt;1024</td>
<td>0.064 - &gt;1024</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1.0</td>
<td>1.5</td>
<td>0.19 - 3.0</td>
</tr>
<tr>
<td>Linezolid</td>
<td>0.5</td>
<td>1.5</td>
<td>0.047 - 4.0</td>
</tr>
<tr>
<td>Ceftaroline</td>
<td>0.5</td>
<td>1.0</td>
<td>0.023 - 1.5</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>0.25</td>
<td>0.75</td>
<td>0.032 - 1.5</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>0.125</td>
<td>0.38</td>
<td>0.047 - 0.75</td>
</tr>
</tbody>
</table>

from within this area demonstrated the same phenomenon when repeated. All other results with the remaining 160 isolates demonstrated clear and sharp margins with all of the other antibiotics tested by E-test.

4. Discussion

A recent meta-analysis of health-care-associated infections evaluated financial impact on the US health-care system. The total annual costs for CLABSI, VAP, SSI, Clostridium difficile associated infection and CAUTI was estimated at 9.8 billion US dollars [7]. MRSA was the major contributor of CLABSI and SSI in their investigation and led to the highest attributable length of stay [7]. In another study, the direct cost of HAIs in the United States was more than triple this amount [8]. As a result of the serious morbidity and mortality associated with MRSA, the CDC targeted this multi-drug resistant organism in 2013 as a serious threat [3].

In this investigation, we found that over 99% of our isolates were susceptible to tigecycline, daptomycin, ceftaroline and all were susceptible to linezolid. Results from vancomycin susceptibility data should be of concern since 43% of isolates from all sources had MICs ≥ 1.5 µg/ml and of these, one-half were from bloodstream isolates. A prior investigation from our facility documented the majority of MRSA clinical isolates to have vancomycin MICs ≤ 1 µg/ml [9]. The increase in MIC (now documented with E-test methodology) is in accordance to other reports of increasing vancomycin MICs among MRSA isolates and suggests consideration of alternate therapeutic modalities for these patients due to increased risk of treatment failure and/or mortality when vancomycin MICs are ≥ 1.0 µg/ml [10]-[13].

Former investigations showed varying susceptibility levels to mupirocin ranging from 0% to 38% while our study documented 15% high level resistance [14]-[17]. However, in our investigation, we had the unexpected finding of mupirocin hetero-resistance. Etiology of this finding may be due to simultaneous expression of single amino acid changes in the inherent isoleucyl-tRNA synthetase (IleRS) gene and acquisition of a new IleRS gene, or other possibilities yet to be determined [18]. Hetero-resistance has been demonstrated with vancomycin among Staphylococcus aureus isolates [1].
Limitations of this study include lack of correlation with patient clinical data and small number of isolates. Further studies of interest would be the clinical impact of mupirocin hetero-resistance as well as further investigation into the nature of this mechanism.

Administration of intranasal mupirocin to intensive care unit patients and to those undergoing surgery can reduce SSIs, be cost effective, and improve patient outcomes [19]-[24]. Prevention of even 20% of HAIs can save 5.7 - 6.8 billion US dollars [8]. As MRSA is associated with such a large proportion of these, screening and decolonization of MRSA using mupirocin can make a significant impact. In conclusion, while antibiotic susceptibility testing is not routinely performed in clinical microbiology laboratories, the level of resistance to mupirocin identified in this surveillance study suggests that susceptibility testing should be added to routine MRSA panels [25].

References


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