Methicillin-Resistant Staphylococcus aureus Recovered from Healthcare- and Community-Associated Infections in Egypt

Mohamed Abdel-Maksoud,1 Mona El-Shokry,1,2,3 Ghada Ismail,3 Soad Hafez,4 Amani El-Kholy,5 Ehab Attia,6 and Maha Talaat1,2

1US Naval Medical Research Unit No. 3, Cairo 11517, Egypt
2Global Disease Detection Center, US Centers for Disease Control and Prevention, Cairo, Egypt
3Ain Shams University, Cairo 11566, Egypt
4Alexandria University, Alexandria 21599, Egypt
5Cairo University, Cairo 12316, Egypt
6Ministry of Health and Population, Cairo 11516, Egypt

Correspondence should be addressed to Mona El-Shokry; mona.elshokry@gmail.com

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1. Introduction

Methicillin-resistant Staphylococcus aureus (MRSA) infection is a significant contributor to morbidity and mortality in hospitalized patients worldwide and has been associated with several hospital outbreaks since the late 1970s [1]. Compounding the problem of healthcare-associated MRSA (HA-MRSA) is the growing prevalence of community-associated MRSA (CA-MRSA) raising the challenge of selecting the optimum therapy for both HA and CA MRSA infections [2].

MRSA rates among S. aureus clinical isolates scored the highest in Egypt compared to other African countries and to southern and eastern Mediterranean countries [3, 4].

Vancomycin has been the cornerstone for treating patients with HA-MRSA infection over the last 20 years [5]. Conceivably, treatment failure in cases of MRSA infections was mainly attributed to phenotypes with reduced susceptibility to vancomycin (RSV) which have brought vancomycin’s utility into question [6]. Clindamycin, a member of macrolide-lincosamide-streptogramin B (MLSB) antibiotics, has surfaced as an efficient alternative for MRSA infections due to its special pharmacokinetic properties especially for penicillin allergic patients [7]. Consequently, inducible resistance to MLSB antibiotics has emerged worldwide necessitating the need to detect such resistance by a simple D-test on a routine basis [8].
The objective of this study was to analyze the pattern of resistance of healthcare- and community-associated MRSA in Egypt and to determine the trend of resistance of HA-MRSA over time (2005 through 2013).

Data Analysis. Statistical analysis was performed using Z-score test for two population proportions. A p value < 0.05 was considered statistically significant.

2. Materials and Methods
This is an active prospective cohort study which took place in 12 hospitals in Egypt from 2005 to 2013. Healthcare-associated S. aureus (HA-S. aureus) isolates were recovered from patients acquiring infections after ≥3 calendar days of an admission to a health facility [9].

S. aureus strains were isolated from pus (12), wound swabs (23), urine (19), blood (135), bronchoalveolar lavage (123), endotracheal tube (6), sputum (56), and unknown sources (74).

Community-associated S. aureus (CA-S. aureus) isolates were collected through a sentinel surveillance program for acute febrile illnesses implemented in 12 infectious disease hospitals in Egypt from 2005 to 2013. These isolates were recovered from patients presenting with clinical symptoms <3 calendar days of an admission to a health facility indicating community-associated transmission [9]. They were isolated from blood (144) and CSF (39).

All isolates were shipped to the US Naval Medical Research Unit No. 3 (NAMRU-3) laboratories for identification and susceptibility testing to ensure the standardization of the techniques used and unifying the antimicrobial discs for susceptibility testing in concordance with Clinical Laboratory Standards Institute (CLSI) guidelines. S. aureus ATCC 25923 was used to verify the quality and accuracy of testing procedures [10, 11].

MRSA strains were tested against 11 antimicrobial discs (Becton Dickinson and Company, Sparks, MD, USA). The antibiotics used and their disk potencies are shown in Table 1. Strains showing reduced susceptibility to vancomycin (RSV) are strains with MIC levels ≥2 mg/mL, while strains were confirmed to be VISA (vancomycin intermediate S. aureus) or VRSA (vancomycin resistant S. aureus) when vancomycin MIC levels were 4–8 μg/mL and >8 μg/mL, respectively [11].

2.1. The Double Disc Susceptibility Test (D-Test). The presence of inducible clindamycin resistance (iMLSB) was sought in MRSA isolates that were erythromycin resistant and clindamycin sensitive (ER-R and CL-S) using the D-test [10].

3. Results
A total of 631 S. aureus isolates were collected between 2005 and 2013. Of these, 448 (71%) were HA-S. aureus and 183 (29%) were CA-S. aureus. MRSA constituted 76.6% (343/448) of HA-MRSA and 11.5% (21/183) of CA-MRSA.

<table>
<thead>
<tr>
<th>Table 1: Resistance of MRSA strains to antimicrobial discs.</th>
</tr>
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<tbody>
<tr>
<td><strong>HA-MRSA (n = 343)</strong></td>
</tr>
<tr>
<td>Amoxicillin (10 μg)</td>
</tr>
<tr>
<td>Penicillin (10 μg)</td>
</tr>
<tr>
<td>Tetracycline (30 μg)</td>
</tr>
<tr>
<td>Gentamicin (10 μg)</td>
</tr>
<tr>
<td>Ciprofloxacin (5 μg)</td>
</tr>
<tr>
<td>Erythromycin (15 μg)</td>
</tr>
<tr>
<td>Clindamycin (2 μg)</td>
</tr>
<tr>
<td>Rifampicin (5 μg)</td>
</tr>
<tr>
<td>SXT* (1.25 μg/23.75 μg)</td>
</tr>
<tr>
<td>Vancomycin E-test</td>
</tr>
</tbody>
</table>

* SXT: trimethoprim-sulfamethoxazole.

Resistance of HA-MRSA isolates to 11 antimicrobial discs was considerably high for most antibiotics used in the panel ranging from 55.6% to 100%, while resistance to rifampicin and trimethoprim-sulfamethoxazole was relatively lower (20.4% and 17.2%, resp.) (Table 1). On the other hand, CA-MRSA isolates showed a wider range of susceptibility to most antibiotics with resistance rates ranging from 9% to 20%, except for tetracycline (85%) and penicillin and ampicillin (100% each). MDR of HA-MRSA was significantly higher compared to CA-MRSA (85.7% and 47.6%, resp.).

The rate of HA-MRSA has significantly increased from 48.6% in 2005 to 86.8% in 2013. During the same time period, the proportion of HA-S. aureus with RSV (MIC levels ≥2 mg/mL) has significantly increased from 4.2% (3/72) in 2005 to 25.8% (51/197) in 2013 (p < 0.001).

Susceptibility to vancomycin was detected in 80.2% (275/343) of HA-MRSA and 95.2% (20/21) of CA-MRSA. VISA was detected in 1.2% (4/343) of HA-MRSA while none of CA-MRSA strains showed VISA pattern. VRSA was not detected in either HA-MRSA or CA-MRSA (Table 2).

A total of 29 HA-MRSA and three CA-MRSA isolates displaying CL-S and ER-R phenotype were tested using D-test. iMLSB (D-test positive) was identified in 5.3% (18/343) of HA-MRSA strains and in 9.5% (2/21) of CA-MRSA strains (Table 3).

4. Discussion
In the present study, prevalence of MRSA was higher among HA-S. aureus strains compared to CA-S. aureus strains. In support of this, other prospective surveillance studies conducted in Egypt reported similar findings [12, 13]. Meanwhile, reports emanating from Middle East countries also revealed increasing rates in the incidence of MRSA: in Saudi Arabia (77.5%) [14] and in Libya (54–68%) [15]. The compelling finding in this study was the substantial increase in MRSA prevalence over time. The prevalence rate of HA-MRSA has almost doubled from 48.6% to 86.8% between 2005 and 2013. Similar trends were also reported from a similar study conducted in Lebanon [16]. In contrast, successful attempts to reduce MRSA rates were also reported from USA.
The emergence and spread of resistance to vancomycin are a threat to the already challenging therapy of MRSA and raise an alarming situation to the clinicians in hospital as well as in community. Alternative therapies should be considered where vancomycin MIC is >1 μg/mL to avoid treatment failure [27]. Clindamycin is one of the options that could be used for treating patients with either HA-MRSA or CA-MRSA. Different rates of inducible clindamycin resistance were reported from other countries, in USA and in India [29, 30].

In light of the previous data, reporting MRSA as susceptible to clindamycin without checking for inducible resistance using D-test may result in institution of inappropriate clindamycin therapy. On the other hand, negative result for inducible clindamycin resistance confirms clindamycin susceptibility and provides a very good therapeutic option [29].

The results of the study indicate the importance of developing policies and regulations for antibiotic use at the country level, implementing antibiotic stewardship programs to promote appropriate use of antibiotics, and increasing the awareness of clinicians and the public on rational use of antibiotics. In light of the restricted range of antibiotics available for the treatment of MRSA and the known limitations of vancomycin, clindamycin should be considered as an alternative for the management of serious MRSA infections sensitive to clindamycin. Laboratories should start considering using a D-test for diagnosis of inducible clindamycin resistance to avoid treatment failure. Enhancing infection prevention and control programs to contain HA-MRSA is crucial for Egypt.

**Disclosure**

The views expressed in this paper are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the US Government. This work was supported/funded by USAID, work unit no. 263-P-00-10-00005-00. The study protocol was approved by the Naval Medical Research Central Institutional.

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**Table 2: Minimum inhibitory concentration (MIC) levels of vancomycin amongst MRSA strains.**

<table>
<thead>
<tr>
<th>MIC (μg/mL)</th>
<th>HA-MRSA (n = 343)</th>
<th>CA-MRSA (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>&lt;2*</td>
<td>275</td>
<td>80.2</td>
</tr>
<tr>
<td>3</td>
<td>64</td>
<td>18.6</td>
</tr>
<tr>
<td>4**</td>
<td>4</td>
<td>1.2</td>
</tr>
</tbody>
</table>

HA: healthcare-associated; CA: community-associated; MRSA: methicillin-resistant *Staphylococcus aureus*; *<2 μg/mL: susceptible to vancomycin; **4 μg/mL: VISA.

**Table 3: D-test for inducible clindamycin resistance.**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>HA-MRSA (n = 343)</th>
<th>CA-MRSA (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>ER-R, CL-S (D--ve)</td>
<td>11</td>
<td>3.2</td>
</tr>
<tr>
<td>ER-R, CL-S (D+ve)</td>
<td>18</td>
<td>5.3</td>
</tr>
</tbody>
</table>

HA: healthcare-associated; CA: community-associated; MRSA: methicillin-resistant *Staphylococcus aureus*; ER: erythromycin; CL: clindamycin; R: resistant; S: sensitive.
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Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

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