Methicillin-resistant *Staphylococcus aureus* bacteraemia diagnosed at hospital admission: distinguishing between community-acquired versus healthcare-associated strains

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Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) infections diagnosed at hospital admission are often referred to as community-acquired. This designation may include MRSA strains previously acquired in a healthcare setting (healthcare-associated) as well as those that have emerged from community-based *S. aureus* strains.

Methods: To understand further the epidemiology of MRSA from the community, a case-control study was performed. During 1997–2002, 254 patients with and without MRSA bacteraemia at hospital admission were studied.

Results: All patients with MRSA bacteraemia in the first 24 h of hospital admission had a recent exposure to a healthcare setting: true community-acquired MRSA was not detected. Independent risk factors for healthcare-associated MRSA bacteraemia, defined as MRSA bacteraemia in the first 24 h of hospital admission among patients with a recent exposure to a healthcare setting or intervention, included previous MRSA infection or colonization (OR = 17, \( P < 0.001 \)), cellulitis (OR = 4, \( P = 0.006 \)), presence of a central venous catheter (OR = 3, \( P < 0.001 \)) and skin ulcers (OR = 3, \( P = 0.007 \)).

Conclusions: In this study, MRSA bacteraemia diagnosed in the first 24 h of hospital admission represented healthcare-associated MRSA strains and not true community-acquired strains. The clinical characteristics associated with healthcare-associated MRSA bacteraemia can assist clinicians in targeting measures to prevent cross-transmission and may help to streamline empirical vancomycin therapy.

Keywords: *S. aureus*, methicillin resistance, risk factors

Introduction

The epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) is changing.1 Although previously considered a purely nosocomial pathogen, recovered solely from hospitalized patients, MRSA is now being recovered with increasing frequency at hospital admission.2–4 These ‘community-acquired’ MRSA strains arise from two different patient populations: those with true community-acquired MRSA strains, which have emerged *de novo* from community-based *S. aureus* strains,3,5,6 and healthcare-associated strains, which have been acquired in hospital during a recent exposure to a healthcare setting or intervention.2,7 The latter patient population is twice as likely to harbour MRSA as persons without exposure to a healthcare setting.8–11 This changing epidemiology has probably led to an increase in the number of patients with MRSA infections or colonization diagnosed at hospital admission, although trends have not been examined extensively. Once admitted to hospital, this patient population can serve as an important reservoir of MRSA, contributing substantially to patient-to-patient transmission and to MRSA dissemination in the hospital setting.12,13

To explore further the changes in the epidemiology of MRSA from the community setting, over a 5.5 year period, patients with MRSA bacteraemia diagnosed at hospital admission were investigated. The rate of MRSA bacteraemia diagnosed at hospital admission, the frequency of community-acquired and healthcare-associated infections and the clinical characteristics of patients at high-risk of harbouring MRSA at admission among patients with a recent exposure to a healthcare setting, were investigated.
Material and methods

Study population
The Beth Israel Deaconess Medical Center (BIDMC) is a 430 bed tertiary care teaching hospital in Boston, MA, USA, with an average of 27 000 patient discharges per year.

During January 1997–June 2002, medical records of patients with MRSA recovered from at least one blood culture within 24 h of hospital admission were extracted from the computerized microbiology record database. An episode of MRSA bacteraemia was considered healthcare-associated if MRSA was recovered from blood cultures obtained within 24 h of hospital admission, and the patient was recently exposed to a healthcare setting or intervention defined by one or more of the following criteria: (1) requirement for intravenous therapy, chemotherapy, specialized nursing or wound care at home, or an ambulatory visit 30 days prior to the bacteraemia; (2) requirement for chronic haemodialysis; (3) hospitalization for more than 2 days in the previous 6 months and (4) residence in a long-term care facility or nursing home.

Study design
To identify risk factors for healthcare-associated MRSA bacteraemia, a case-control study was performed. A case was defined as a patient of age ≥18 years with a healthcare-associated MRSA bacteraemia. For each case, one control was selected among patients with the same admission date. Controls were required to meet the criteria for exposure to a healthcare setting or intervention, as defined for cases, without recovery of MRSA from blood cultures obtained at hospital admission. Thus, controls were selected from the same source population as case patients. If more than one control was available for each case, then controls with the admission time closest to the case were chosen.

Data were extracted from computerized patient medical records, and included all inpatient and outpatient visits, nursing home visits, and inpatient and outpatient pharmacy, laboratory and microbiology records. Data obtained for cases and controls at hospital admission included age, gender, number and length of hospitalizations within the previous 6 months, residence in long-term facilities or nursing homes, non-ambulatory status (defined as wheel chair- or bed-bound), intravenous drug abuse, comorbid status, as defined by the Charlson score,15 number and length of hospitalizations in the previous 90 days, presence of a central venous catheter (CVC) and admission to an intensive care unit (ICU) within 30 days of study inclusion. Antibiotics administered within 30 days before study inclusion were recorded. This information was obtained by reviewing the pharmacy databases and nursing home visit records. Antibiotic exposure was analysed by individual antibiotics and by classes. MRSA isolated from other culture sites within 24 h of hospital admission, and documentation of MRSA and Clostridium difficile in the previous 90 days, were recorded.

Identification and susceptibility testing of MRSA isolates
S. aureus isolates were identified by standard methods.16 Antimicrobial susceptibility testing was assessed by the automated Vitek I system (bioMerieux Vitek, Durham, NC, USA) using NCCLS guidelines and the manufacturer’s instructions.17

Statistical analysis
Statistical analysis was performed using the software program Intercooled Stata (version 7.0; Stata Corporation, TX, USA). Differences in group proportions were assessed using χ2 test or Fisher’s exact test. Potential risk factors for healthcare-associated MRSA bacteraemia were analysed by logistic regression analysis. Only those variables with an alpha value <0.1 on univariate analysis were included in the multiple logistic regression models. To express the predictive power of the model, the area under the receiver operating characteristic (ROC) curve was calculated for two different models. A two-tailed P < 0.05 was considered statistically significant.

Results

Recovery of MRSA within 24 h of hospital admission at the BIDMC
The number of MRSA isolates recovered from the blood within 24 h of hospital admission increased significantly over the study period; from 0.3/1000 patient admissions in 1998 to 1.3/1000 patient admissions in 2002 (P < 0.001) (Figure 1).

Patient characteristics
During January 1997–June 2002, 230 blood cultures from 158 patients obtained within 24 h of hospital admission yielded MRSA. Only the first episode of MRSA recovered from blood per patient during the 5.5 year study period was included in the analysis. A total of 28 episodes of MRSA bacteraemia were excluded since they represented recurrent MRSA bacteraemia in the same patient (26 patients), or clinical data pertaining to the episode was not available (two patients). Thus, a total of 130 patients with MRSA bacteraemia detected within 24 h of hospitalization were analysed.

MRSA was isolated from blood only in 52 (40%) patients. In the remaining 78 patients, MRSA was also recovered from the following culture sites, within the first 24 h of hospital admission (number of patients): skin/wound culture (21), urine (nine), sputum (eight), catheter tip (eight), intra-abdominal fluid collection (eight), bone (five), culture site not documented (23).

Of the 130 patients, 127 (98%) met the criteria for healthcare-associated MRSA bacteraemia. Thus, the case-control study included 127 cases of healthcare-associated MRSA bacteraemia and 127 controls, who met the criteria for recent exposure to a healthcare setting or intervention in whom blood cultures obtained within 24 h of admission did not yield MRSA. Table 1 summarizes the criteria met by cases and controls for recent exposure to a healthcare setting or intervention.
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Table 1. Criteria for recent exposure to a healthcare setting or intervention stratified among patients with and without methicillin-resistant Staphylococcus aureus bacteremia at hospital admission

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (%) (n = 127)</th>
<th>Controls (%) (n = 127)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous 30 days</td>
<td></td>
<td></td>
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<tr>
<td>outpatient intravenous therapy or chemotherapy</td>
<td>57 (45)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25 (20)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>wound care/specialized nursing care at home</td>
<td>15 (12)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>ambulatory care visits</td>
<td>72 (57)</td>
<td>63 (50)</td>
</tr>
<tr>
<td>requirement for chronic haemodialysis</td>
<td>31 (24)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8 (6)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hospitalization &gt; 2 days in the previous 6 months</td>
<td>113 (89)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>95 (75)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Residence in nursing home/long-term care facility</td>
<td>52 (41)</td>
<td>49 (38)</td>
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<sup>a</sup>P < 0.01 cases versus controls.

Patients not meeting the criteria for healthcare-associated MRSA bacteremia

A total of three patients with MRSA bacteremia detected within 24 h of hospital admission did not meet the strict criteria, although all three had previous exposure to a healthcare setting or intervention. These patients were fully ambulatory men with a mean age (± S.D.) of 81.6 ± 16.4 years and were admitted from home. The mean (± S.D.) Charlson score was 3 ± 2.6. The first patient had a past medical history of bladder neoplasm diagnosed in 1987 and received a diagnosis of nephrolithiasis. His last hospital visit was 302 days prior to study entry. The second patient had metastatic prostate carcinoma and was admitted with a diagnosis of pneumonia. He received daily care from a nursing assistant. Since the nursing care was not specialized, criteria for ‘healthcare-associated’ were not met. The third patient underwent a transurethral prostate resection as an outpatient 42 days before study enrolment and was seen in an ambulatory care clinic at BIDMC 31 days before study enrolment. His admitting diagnosis was epididymoorchitis.

Risk factors for healthcare-associated MRSA bacteremia

Risk factors associated with healthcare-associated MRSA bacteremia, on univariate analysis, included male sex, a non-ambulatory status, hospitalization(s) in the previous 6 months, requirement for chronic haemodialysis, presence of a CVC, a hospital history of prior MRSA infection or colonization, diabetes mellitus, skin ulcers or cellulitis at hospital admission and quinolone exposure in the previous 30 days (Table 2).

Two logistic regression models were generated (Table 3). The first model included a previous history of MRSA infection or colonization, the strongest unadjusted predictor as identified by univariate analysis. In this model, previous MRSA infection or colonization, presence of a CVC, documentation of skin ulcers or cellulitis at hospital admission were independently associated with MRSA bacteremia. This model correctly identified 75% of the cases with a sensitivity of 76% and specificity of 73%.

Since prior MRSA colonization or infection status may not be known at the time of hospital admission, a second model was generated that excluded prior history of MRSA colonization or infection. This model identified the presence of a CVC, hospitalization(s) within the previous 6 months, diabetes mellitus and use of quinolones within the previous 30 days as independent risk factors for healthcare-associated MRSA bacteremia. This model correctly identified 66% of the cases with a sensitivity of 68% and specificity of 65%.

The power of the two models to predict healthcare-associated MRSA bacteremia at hospital admission, expressed by the area under the ROC curve, was 73% and 71% for the first and second model, respectively.

Discussion

This study characterized the epidemiology of MRSA bacteremia from the community, defined as recovery of MRSA from blood cultures within the first 24 h of hospital admission. The main findings were as follows: 1) true community-acquired MRSA bacteremia was not recovered throughout the study period; 2) unique risk factors identifying a subgroup of patients with healthcare-associated MRSA bacteremia at hospital admission among patients with a recent exposure to a healthcare setting were identified; 3) MRSA bacteremia at hospital admission increased significantly over the study period.

Despite recent reports of unique community-acquired MRSA clones,<sup>7,19</sup> this study did not identify community-acquired MRSA over the 5.5 year study period. Concordant with these findings, a meta-analysis of MRSA infections identified within 24–72 h of hospitalization, documented a prevalence of community-acquired MRSA infections, defined as patients without any known risk factors for harbouring MRSA, of ≤0.24%.<sup>11</sup> The findings of this study and others<sup>11</sup> imply that the great majority of MRSA isolates recovered at hospital admission to an adult tertiary care centre were acquired during a prior exposure to a healthcare setting or intervention, and were not acquired in the community. Thus, using the term ‘community-acquired’ MRSA among patients with a recent exposure to a healthcare setting at the time of hospital admission may lead to confusion. A more accurate term for these infections would be ‘healthcare-associated’.<sup>20</sup> The recent documentation of true community-acquired MRSA infections recovered from patients with no prior exposure to a healthcare setting and no other known risk factors for MRSA emphasizes the importance of this distinction. These truly community-acquired MRSA strains tend to be susceptible to more antibiotics and genetically distinct from healthcare-associated strains.<sup>6,21–23</sup> Future studies should consider using more specific terms to differentiate between true community-acquired MRSA strains and healthcare-associated strains recovered at hospital admission.
In this study, three patients did not meet the strict study criteria for healthcare-associated MRSA bacteraemia, although all three were exposed to a healthcare setting in the past. These isolates therefore cannot be categorized as community-acquired. The time limits used to define healthcare-associated MRSA bacteraemia, in this study, required a hospitalization in the previous 6 months, or exposure to an out-of-hospital setting or intervention in the previous 30 days. Owing to the prolonged duration of MRSA colonization, criteria for categorizing healthcare-associated MRSA infection may warrant extending the period for prior exposure to a healthcare setting or intervention to at least 1 year if not longer. A similar principle may apply to studies focusing on vancomycin-resistant enterococci since colonization with the same strain can persist for over a year.

In the tertiary care institution of this study, the incidence of MRSA bacteraemia at hospital admission increased from 0.3/1000 patient admissions in 1998 to 1.3/1000 patient admissions in 2002. This rise may represent a move towards healthcare delivery to the out-of-hospital setting. For example, it is estimated that 250,000 patients currently receive parenteral therapy at home, a number that is rising by 10% per year, and that ~32% of antibiotic therapy is administered in outpatient centres. As a direct result, home care organizations have increased by 85% in the last 10 years.

Identifying the subgroup of patients at high risk of MRSA bacteraemia at hospital admission among patients with a recent exposure to a healthcare setting is important, since once admitted to the hospital, these patients contribute substantially to the dissemination of MRSA. Independent risk factors associated with MRSA bacteraemia at hospital admission in this patient population included a history of previous MRSA colonization or infection, the presence of a CVC and documentation of a skin ulcer or cellulitis at hospital admission. To extend the clinical applicability of the study results, a second analysis was performed that excluded prior history of MRSA colonization or infection, since knowledge of this information may not always be available at the time of hospital admission. In this second analysis, although the presence of a CVC was once again a risk factor, prior hospitalizations, diabetes mellitus and prior quinolone therapy were also associated with MRSA bacteraemia at hospitalization. The differences between the two analyses suggest that a prior history of MRSA colonization or infection may be an indicator of the other risk factors identified in the second analysis, all of which have been previously recognized to increase the likelihood of harbouring MRSA. These simple patient characteristics identified in this study are easily obtained during the clinical assessment of a patient at hospital admission and can identify a subgroup of patients who are at high risk of MRSA bacteraemia at the time of hospital admission.
among all patients admitted from out-of-hospital settings or who have recently had exposure to a healthcare intervention. Empirical use of vancomycin in this group of patients may be warranted when presenting with symptoms and signs consistent with bacteraemia. This group of patients may also require prompt institution of infection control interventions to limit cross-transmission of MRSA or targeted MRSA surveillance screening efforts.

Several studies focusing on different patient populations have addressed potential risk factors for MRSA infection at hospital admission. Charlebois et al.3 studied a population of the urban poor in San Francisco and identified prior intravenous drug use, prior hospitalization within 1 year and prior endocarditis as independent risk factors for MRSA colonization. Another study, which excluded San Francisco and identified prior intravenous drug use, prior hospitalization in the previous 6 months and quinolone therapy in the previous 30 days, among all patients admitted from out-of-hospital settings or who have recently had exposure to a healthcare intervention. Empirical use of vancomycin in this group of patients may be warranted when presenting with symptoms and signs consistent with bacteraemia. This group of patients may also require prompt institution of infection control interventions to limit cross-transmission of MRSA or targeted MRSA surveillance screening efforts.

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A retrospective case-control study design was chosen to obtain a sufficient number of outcomes of MRSA bacteraemia in the first 24 h of hospital admission. Potential bias in the retrospective measurement of predictor variables or selection of cases and controls was minimized by using strict definitions for variables and a comprehensive database.

Preventing transmission of MRSA is important since infections caused by this antimicrobial-resistant pathogen are associated with considerable morbidity and mortality, and excess hospital costs.29 Rising rates of MRSA infections also result in a greater use of vancomycin with an increased risk of emergence of glycopeptide-resistant pathogens.10,12 In this study, all the cases of MRSA bacteraemia admitted from the community had recent exposure to a healthcare setting or intervention. This high-risk group can be identified using simple characteristics outlined in this study and can assist the clinician in targeting preventive measures and streamlining vancomycin use.

### Table 3: Two logistic regression analyses of risk factors associated with healthcare-associated MRSA bacteraemia within 24 h of hospitalization, including (first model) and excluding (second model) a history of previous MRSA infection or colonization

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
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<tbody>
<tr>
<td><strong>First model</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>previous MRSA infection or colonization</td>
<td>17.04</td>
<td>4.98–58.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>cellulitis at hospital admission</td>
<td>4.27</td>
<td>1.52–11.94</td>
<td>0.006</td>
</tr>
<tr>
<td>presence of a central venous catheter</td>
<td>3.30</td>
<td>1.71–6.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>skin ulcers at hospital admission</td>
<td>3.12</td>
<td>1.37–7.11</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Second model</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>presence of a central venous catheter in the previous 6 months</td>
<td>3.24</td>
<td>1.76–5.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>quinolone therapy in the previous 30 days</td>
<td>1.99</td>
<td>1.07–3.69</td>
<td>0.02</td>
</tr>
<tr>
<td>diabetes mellitus</td>
<td>1.84</td>
<td>1.05–3.22</td>
<td>0.03</td>
</tr>
</tbody>
</table>

References


