Major article

Community-onset invasive methicillin-resistant *Staphylococcus aureus* infections following hospital discharge


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**Background:** The majority of invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the United States are community-onset and occur in persons with recent health care exposure.

**Methods:** We performed a matched case-control study to identify risk factors for invasive MRSA infection among recently discharged patients. Cases had MRSA cultured from a normally sterile body site within 100 days following hospital discharge. Controls were matched on hospital, week of admission, and age.

**Results:** Among 77 cases, the most common types of invasive MRSA infection were bloodstream infection and osteomyelitis. Independent risk factors were a history of a MRSA-positive clinical culture from a superficial body site in the 12 months preceding the invasive infection (matched odds ratio [mOR], 23; 95% confidence interval [CI]: 3.7-142), hemodialysis (mOR, 21; 95% CI: 1.7-257), prior hospitalization length of stay >5 days (mOR, 4.5; 95% CI: 1.6-12), and male sex (mOR, 2.9; 95% CI: 1.1-7.9).

**Conclusion:** Risk factors for postdischarge invasive MRSA infections can be identified prior to discharge and remain with the patient after the hospitalization ends. Measures to prevent community-onset invasive MRSA infections might start in the hospital but should also be evaluated in postdischarge settings.

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In 2004, the Centers for Disease Control and Prevention (CDC) began population-based surveillance for invasive MRSA infections in the United States through the Emerging Infections Program’s Active Bacterial Core surveillance system (ABCs). Of the 5,528 invasive MRSA infections reported to ABCs in 2008, 59% were health care-associated community-onset (HACO), which was defined as isolation of MRSA from a normally sterile body site in a resident of the surveillance area, and the culture was obtained in an outpatient setting or before the fourth calendar day of hospitalization, and the patient had 1 or more of the following: (1) a history of hospitalization, surgery, dialysis, or residence in a long-term care facility in the previous year or (2) the presence of a central vascular catheter within 2 days prior to MRSA culture. From 2005 through 2008, the incidence of hospital-onset invasive MRSA infections decreased by 28%, while HACO invasive MRSA infections only decreased by 17% during the same period. Much research has been done to assess risk factors for hospital-onset MRSA, but less is known about the factors that lead to HACO MRSA infections. Encounters with health care settings are hypothesized to play a key role in the development of HACO infections. We sought to identify risk factors for the most
common type of HACO invasive MRSA infection—those that occur following hospital discharge—to inform future research and guide prevention efforts.

METHODS

We conducted a matched case-control study to assess the association of various health care-related exposures with the development of community-onset invasive MRSA infection among patients recently discharged from the hospital. The study population was composed of patients discharged from 2 tertiary care teaching hospitals located in Monroe County, NY, that participated in ABCs. Cases had to meet the ABCs definition for HACO invasive MRSA infection and were identified using the ABCs surveillance database.8 To be included in this case-control study, the ABCs HACO MRSA cases also had to meet the following criteria: (1) culture collected from January 1, 2008, through June 30, 2009; (2) culture represented the first documented episode of HACO invasive MRSA infection for that patient; and (3) the patient had been discharged from 1 of the 2 participating hospitals in the 100 days prior to the culture. We focused this study on patients with hospital discharge in the prior 100 days because ABCs data for 2008 revealed that recent hospitalization was the most common health care exposure among patients with HACO invasive MRSA infection, with approximately 56% having been hospitalized in the 3 months prior to infection (CDC unpublished data). The study size was dictated by the number of cases available.

Controls were selected from among the population of patients who were residents of Monroe County, were discharged from 1 of the 2 participating hospitals, and did not develop invasive MRSA infection by the end of the study period. One control was matched to each case by hospital, week of admission, and age in 10-year intervals. Patients admitted to a psychiatric or rehabilitation ward were not eligible to be controls. This investigation was determined to be a public health evaluation by human studies oversight personnel at the CDC and the New York State Department of Health.

Data collection

We abstracted clinical and laboratory data from hospital medical records, including all documentation for the hospitalization preceding the onset of invasive MRSA for cases and for the control’s date-matched admission. Records for other health care encounters and microbiology culture results were reviewed for each matched pair for the 12 months prior to their index date, which was the date of the case’s invasive MRSA-positive culture.

Variable definitions

We calculated patients’ Charlson comorbidity index score.10,11 We classified patients’ admitting diagnosis into categories based on the disease process or organ system involved. “Long-term care” (LTC) included admissions of any duration to skilled nursing facilities, nursing homes, and rehabilitation facilities. Usual residence in a LTC facility was defined as being admitted from and discharged to a LTC facility in relation to hospitalization. MRSA-positive cultures from superficial body sites were classified as clinical cultures unless they were designated as screening cultures in the laboratory report. Each hospital performed routine MRSA screening on different subsets of patients (eg, upon admission to intensive care units or prior to surgery), but not all study patients were screened for MRSA. Two mutually exclusive MRSA exposure variables were created: (1) positive on clinical culture and (2) positive only on screening. A third variable combining these 2 groups was also analyzed. “Procedures” was defined to include gastrointestinal, pulmonary, or other endoscopy; interventional cardiology or radiology procedures; and bedside procedures other than central line placement. We evaluated inpatient antimicrobial use (≥1 day of therapy). Any antimicrobial use, cephalosporin use, and quinolone use were each analyzed separately as dichotomous variables. Antimicrobials were additionally categorized into 2 groups: (1) those with activity against MRSA (anti-MRSA), ie, vancomycin, linezolid, daptomycin; (2) all others (non-MRSA). Corticosteroid exposure (≥1 day of therapy) included only oral and intravenous routes of administration. “Home health care” was defined as an order for services placed at the time of hospital discharge. Chronic wounds included decubitus ulcers, ulcers because of vascular insufficiency, or nonhealing surgical wounds. The type of wound, location, stage, treatment, or duration was not assessed. Ambulatory status during hospital admission was based on routine nursing assessments that classified patients into 3 categories: independent, required assistance, or dependent.

Statistical analysis

Conditional logistic regression was used to calculate matched odds ratios (mOR) and P values. Candidate variables for multivariate modeling were selected from among variables with a P value <.1 on bivariate analysis that had been examined during the hospitalization preceding infection onset, with the exception of MRSA culture history, which was examined during the preceding 12 months. Variable clustering was assessed using principal components analysis with an eigenvalue of 1, and the number of candidate variables was reduced based on the following considerations. The Charlson score was chosen instead of individual medical conditions. When choosing between several variables representing the same type of exposure at different points in time, the variable representing the most recent time period was chosen, eg, at the time of discharge rather than during the hospitalization. Variables that represent patient factors were chosen over correlated variables that represent treatment decisions, eg, MRSA culture history over anti-MRSA antimicrobial exposure. There were no missing data for any candidate variables. The final model was determined using a backward selection procedure. All candidate variables were considered as multiple exposures and were eligible for elimination from the model. A 2-tailed P value <.05 in the multivariate model was considered statistically significant. Statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC).

RESULTS

Between January 1, 2008, and June 30, 2009, 108 patients of the 2 participating hospitals developed their first episode of HACO invasive MRSA, of which 77 (71%) had been hospitalized in the 100 days prior to infection and were included in the study as cases: 35 from one hospital and 42 from the other. The normally sterile body sites from which MRSA was cultured from the cases were as follows: blood, 60 (78%); bone, 9 (12%); internal abscess, 3 (4%); joint, 2 (2.5%); peritoneal fluid, 2 (2.5%); and pleural fluid, 1 (1%). The cases had the following types of infection: bloodstream infection (BSI) alone, 34 (44%); BSI with another focus of infection, 26 (34%); and other types of infection without BSI, 17 (22%).

The age matching of cases and controls was successful, with the median (range) age for cases 66 (22-91) years and for controls 68 (20-98) years. Clinical characteristics differed significantly between cases and controls (Table 1). Cases had more hospitalizations in the past year. During the most recent hospitalization preceding the invasive MRSA infection (hereafter referred to as the hospitalization preceding infection onset), cases had greater severity of underlying conditions according to the Charlson comorbidity index and a longer length of stay. Cases were more likely than controls to have been
admitted because of an infectious disease process (25% vs 12%, respectively; $P = .059$). For cases, these infectious processes included abscess (11%), cellulitis (37%), osteomyelitis (11%), pneumonia (11%), sepsis (5%), urinary tract infection (16%), and fever (11%). However, most of these infections were not related to MRSA; 7 cases had a MRSA-positive clinical culture during the hospitalization but only 3 were diagnosed with a noninvasive MRSA infection. The other most common admitting diagnosis categories for cases were cardiovascular (20%), gastrointestinal (14%), and orthopedic/trauma (13%).

Cases and controls differed in their odds of exposure to many factors during the hospitalization preceding infection onset (Table 2). Factors positively associated with being a case on bivariate analysis included being discharged with a central venous catheter (CVC) (mOR, 14), receiving hemodialysis (mOR, 11), having a chronic wound (mOR, 12), receiving anti-MRSA antimicrobials (of which 90% were vancomycin) (mOR, 10), receiving systemic corticosteroids (mOR, 6.5), a physical therapy evaluation (mOR, 3.4), having dependent ambulatory status (mOR, 2.9), length of the hospitalization preceding infection onset $< 5$ days (mOR, 3.9), and being discharged to LTC (mOR, 2.1).

Eleven cases received hemodialysis during hospitalization, among whom 10 (91%) were previously on chronic dialysis. Invasive MRSA infections among dialysis patients were not limited to vascular access-related infections; 2 had osteomyelitis, and 1 had BSI associated with a decubitus ulcer.

Being discharged with a CVC was the strongest risk factor for invasive MRSA infection on bivariate analysis. Of these 16 (21%) cases, the most common catheter types were peripherally inserted central catheters (10, 63%), tunneled catheters (4, 25%) and ports (2, 12%). The indications for outpatient CVC among cases were as follows: antibiotics (5, 31%), hemodialysis access (4, 25%), chemotherapy (2, 13%), diuretics (1, 6%), hydration (1, 6%), nutrition (1, 6%), and not documented (2, 13%).

Having a surgery or procedure performed during the hospitalization preceding infection onset was not associated with case status, although cases more frequently had multiple surgeries, and their surgery types were more often orthopedic and cardiothoracic.

Potential risk factors were also evaluated during the 12 months prior to the index date used for matching (Table 3). During this period, 26 cases had a MRSA-positive clinical culture, which was the strongest risk factor for a subsequent invasive MRSA infection (mOR, 13). The culture was obtained at some time before the hospitalization preceding infection onset for 19 (73%) cases and was obtained upon presentation to the hospitalization for 5 (19%); the other 2 had their earliest MRSA-positive culture taken during or after the hospitalization. In 7 (27%) of these 26 cases, the culture history suggests a progression from a superficial to invasive MRSA infection: 5 had wound infections and later developed osteomyelitis, 1 had a superficial surgical site infection that later became a deep infection, and 1 had cellulitis and developed BSI.

Multivariate modeling results showed that a history of an MRSA-positive clinical culture from a superficial body site in the 12 months prior to invasive MRSA infection, receipt of hemodialysis, duration of the hospitalization preceding infection onset $> 5$ days, and male sex were independently associated with invasive MRSA infection postdischarge (Table 4).

**DISCUSSION**

We studied patients who developed invasive MRSA infections in the 100 days following discharge from an acute care hospitalization. Their invasive infections involved a variety of anatomic sites; however, most (78%) of the patients had bacteremia. Our findings showed that these patients are a heterogeneous group with a variety of underlying medical conditions and reasons for admission to the hospital.
hospital. However, on average, these patients have a greater severity of chronic illness, a history of more frequent and longer hospital stays, and impaired ambulatory ability compared with age-matched controls. We identified prior history of MRSA, hemodialysis, long hospital length of stay, and male sex as independent risk factors for developing an invasive MRSA infection during the postdischarge period. Although 72 (94%) of the cases had at least 1 of these factors, they were not present in every case and should not be construed to be the only factors important in this diverse group of infected patients.

The strongest risk factor was having had an MRSA-positive clinical culture from a superficial body site in the 12 months prior to the invasive MRSA infection. Among the 26 cases with this risk factor, 24 (92%) were first positive before the hospitalization preceding infection onset, and the subsequent invasive infection involved the same region of the body from which the superficial MRSA-positive culture had come in only 7 (27%). Only 3 cases had an active noninvasive MRSA infection during the hospitalization preceding invasive infection onset. This suggests that some of these cases could have carried MRSA for some time before they developed an invasive infection and that MRSA contamination from one body site to another could have been involved. MRSA colonization is a well-recognized risk factor for subsequent infection, and patients can have recurrent infections with the same strain.

The majority of our study patients were never screened for MRSA, thus our findings relate most directly to patients with a history of MRSA known from clinical culture obtained from a superficial body site.

Hemodialysis was the second strongest risk factor we identified. Dialysis patients have a 100 times greater risk of invasive MRSA infection than the general population. Their high risk of BSI has been attributed to the use of CVCs for vascular access and to the effects of chronic kidney disease itself, even in patients not receiving dialysis. Dialysis patients likely have both a greater chance of being exposed to MRSA because of their frequent visits to health care facilities and an increased susceptibility to invasive infection because of their comorbid conditions and need for invasive procedures.

MRSA infections have previously been associated with antimicrobial exposure. We did not observe a risk associated with antimicrobials without activity against MRSA, although we did find an association with receipt of vancomycin and other antimicrobials used to treat MRSA. Only 9% of cases had a MRSA-positive clinical culture during admission, whereas 40% received an anti-MRSA drug, indicating that the majority of this drug use was empiric. Patients with a history of MRSA were more likely to receive an anti-MRSA drug. Any possible selective pressure effect of antimicrobial treatment likely occurred prior to the time period we observed in these patients' medical histories.

We did not find significant associations between invasive MRSA infection postdischarge and 2 major categories of health care exposure: history of surgery or LTC admission in the preceding year. Whereas some cases did develop MRSA surgical site infections, the surgery itself was perhaps a necessary but not sufficient factor in the development of infection. In this study, discharge to LTC was correlated with longer hospital length of stay, inpatient orders for physical therapy, and presence of chronic wounds (data not shown), which is consistent with the findings of previous studies looking at risk factors for MRSA among LTC patients. This suggests that patient conditions requiring LTC facility admission and specific exposures within that setting, rather than exposure to a LTC facility per se, might be the factors important in determining onset of MRSA infection.

We found several factors strongly associated with infection on bivariate analysis that were not statistically significant after adjusting for the presence of other variables but are still clinically important predisposing and mediating factors worth consideration. First is discharge from the hospital with a CVC. We found that 21% of cases had been discharged from the hospital with a CVC, of which 81% went on to develop MRSA BSI. A CVC is a potential portal of entry for pathogens, and _S. aureus_ is currently the second most common pathogen of central line-associated BSI in US hospitals (CDC unpublished data). Adherence to evidence-based prevention practices for catheter insertion, maintenance, and timely removal is known to reduce the incidence of central line-associated BSI in hospitals. A similar strict adherence to CVC care and maintenance recommendations in the home and outpatient settings might be needed to prevent community-onset central line-associated BSIs. There were also 3 significant patient conditions: diabetes, chronic wounds, and chronic obstructive pulmonary disease (COPD). Diabetes can lead to the development of chronic wounds and nephropathy requiring dialysis. Chronic wounds offer a site for bacterial colonization and are a potential portal of entry for invasive infections such as osteomyelitis or bacteraemia. Almost one-third of the cases in our study population had chronic wounds, making it one of the most prevalent risk factors. Like previous studies, we found an association between COPD and HACO MRSA infection, although this was no longer significant after adjusting for receipt of corticosteroids.

This was an exploratory study with a small sample size based in a single metropolitan area; however, these findings should help inform the design of more definitive and generalizable studies of postdischarge invasive MRSA infections. Our small sample size relative to the number of variables evaluated limited the statistical power to explore multiple independent associations or risk factors in subgroups of interest, such as those based on anatomic site of infection. Whereas patients of the 2 participating hospitals were expected to have had continuity of care within their respective

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**Table 3**

Bivariate analysis of potential risk factors for community-onset invasive MRSA infection examined during the 12 months preceding infection onset

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases n (%)</th>
<th>Controls n (%)</th>
<th>mOR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodialysis</td>
<td>10 (13)</td>
<td>2 (3)</td>
<td>5 (1.1-23)</td>
<td>.038</td>
</tr>
<tr>
<td>Emergency department visit</td>
<td>30 (39)</td>
<td>11 (14)</td>
<td>4 (1.6-9.8)</td>
<td>.002</td>
</tr>
<tr>
<td>Long-term care stay</td>
<td>25 (32)</td>
<td>14 (18)</td>
<td>1.1 (0.82-1.6)</td>
<td>.45</td>
</tr>
<tr>
<td>MRSA positive</td>
<td>1 (6)</td>
<td>0 (0)</td>
<td>10 (1.1-96)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Any culture</td>
<td>35 (45)</td>
<td>5 (7)</td>
<td>11 (3.4-36)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Clinical culture</td>
<td>26 (34)</td>
<td>3 (4)</td>
<td>13 (3-53)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Screening only</td>
<td>9 (12)</td>
<td>2 (3)</td>
<td>4.5 (0.97-21)</td>
<td>.054</td>
</tr>
<tr>
<td>Outpatient CVC</td>
<td>11 (14)</td>
<td>1 (1)</td>
<td>11 (1.4-85)</td>
<td>.022</td>
</tr>
<tr>
<td>Outpatient urinary catheter</td>
<td>3 (4)</td>
<td>3 (4)</td>
<td>1 (0.20-5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Procedure</td>
<td>13 (20)</td>
<td>19 (26)</td>
<td>0.82 (0.34-2)</td>
<td>.66</td>
</tr>
<tr>
<td>Surgery</td>
<td>18 (24)</td>
<td>11 (14)</td>
<td>1.5 (0.84-4.2)</td>
<td>.123</td>
</tr>
</tbody>
</table>

CI, Confidence interval; mOR, matched odds ratio.

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**Table 4**

Multivariable logistic regression model of independent risk factors for community-onset invasive MRSA infection following hospital discharge

<table>
<thead>
<tr>
<th>Variable</th>
<th>mOR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA-positive clinical culture in prior 12 months</td>
<td>23 (3.7-142)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>21 (1.7-257)</td>
<td>.018</td>
</tr>
<tr>
<td>Hospitalization preceding infection onset</td>
<td>4.5 (1.6-12)</td>
<td>.004</td>
</tr>
<tr>
<td>Length of stay ≥ 5 days</td>
<td>2.9 (1.1-7.9)</td>
<td>.035</td>
</tr>
</tbody>
</table>

CI, Confidence interval; mOR, matched odds ratio.

*Candidate variables for the model were as follows: discharge with a central venous catheter, history of an MRSA-positive clinical culture in prior 12 months, hemodialysis, ambulatory status, chronic wound, sex, hospitalization preceding infection onset length of stay ≥ 5 days, Charlson comorbidity index score, discharge to a long-term care facility, receipt of corticosteroids, and receipt of a quinolone antibiotic. 

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health care networks, if any health care encounters occurred outside of the hospital’s network, we might not have had records of those visits. Invasive culture data were available from all laboratories serving the study catchment area; therefore, the possibility of misclassification of controls was very low. We were not able to compare strain types of different isolates from the same patient over time because this was a retrospective study.

Future studies should examine information that we were not able to collect, including information about exposures that occurred from the time of hospital discharge to infection onset, such as outpatient health care visits or details of home health care services, community-based exposures such as living conditions, socioeconomic status, individual behavioral factors such as personal hygiene or self-care, and body mass index. To build on our finding that a history of MRSA is a strong and prevalent risk factor, a study that matches patients on MRSA colonization status should be done to help identify risk factors for invasive infection specific to MRSA-colonized patients.

We found that the characteristics of patients who develop postdischarge invasive MRSA infections and their risk factors are similar to those previously identified for patients with hospital-onset MRSA infections.10,27,28 Risk factors such as hemodialysis, central lines, and chronic wounds do not end with discharge from the hospital; they persist during the postdischarge period and continue to serve as potential portals of entry for invasive MRSA infection at home or at outpatient or LTC facilities. Many of the risk factors we identified, such as male sex, age, chronic illness, and the need for invasive treatments, cannot be modified; however, they are useful in identifying patients at high risk for postdischarge invasive MRSA infection. Measures aimed at the prevention and control of invasive MRSA infections should continue to be applied to these high-risk patients in the acute care setting. Further research is needed to identify best practices for the prevention of invasive MRSA infections among these patients in the community setting, which might include interventions to decrease MRSA colonization or the introduction of MRSA into normally sterile anatomic sites. Interventions or prevention measures implemented in the inpatient setting alone will likely be insufficient to eliminate health care-associated community-onset infections.

Acknowledgment

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References