Prediction of Methicillin-Resistant Staphylococcus aureus Involvement in Disease Sites by Concomitant Nasal Sampling

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Nasal colonization with methicillin-resistant Staphylococcus aureus (MRSA) is believed to precede disease. It is therefore reasonable to expect that testing for nasal MRSA colonization could provide guidance in the choice of empirical therapy for infections. We conducted a retrospective review of 5,779 nasal MRSA tests performed within a 24-h period before or after a clinical culture showed the growth of any organism. A positive nasal MRSA test strongly predicted MRSA involvement at a clinical site (relative risk, 12.9 times higher than in the remainder of the population; 95% confidence intervals [CI], 10.4, 16.1). Nasal MRSA colonization also strongly predicted antimicrobial resistance in other organisms. A negative nasal test was less useful; only 217 of 323 patients (67.2%; 95% CI, 61.8, 72.3) with clinical cultures involving MRSA had detectable, concomitant nasal MRSA colonization. Patients with clindamycin-susceptible MRSA infections were less likely (59%) to have nasal colonization than those with clindamycin-resistant MRSA infections (71%; P = 0.042). Patients nasally colonized with MRSA were substantially more likely to have antibiotic-resistant floras in clinical specimens, and this should be considered when initiating therapy. However, nearly a third of MRSA-infected patients were not nasally colonized, suggesting that nasal colonization need not precede disease and that a negative test for nasal colonization would not rule out MRSA disease in settings of moderate or high prevalence.

It is common for physicians to encounter patients with clinical evidence of infection but to have no microbiological data for them; such is the case for any infection prior to culture availability and often remains the case throughout the therapeutic encounter for infections such as cellulitis, osteomyelitis, and pneumonia. In such instances, empirical therapy must be chosen based on a clinician’s judgment. Often, a key element of the empirical treatment decision will be whether or not to include antibiotics active against methicillin-resistant Staphylococcus aureus (MRSA). This poses a dilemma. Treatments active against MRSA are not first-line therapies for non-MRSA organisms, being more costly and potentially less effective and more toxic (1, 13). However, a patient who does have a MRSA infection may be endangered by the decision not to use anti-MRSA therapy (19).

Endogenous nasal colonization is believed to be the source for most staphylococcal diseases (21). Physicians treating a culture-negative infection may therefore reason that a surrogate for a pathogen from the infected site might be a test for nasal MRSA colonization; a positive test ought to predict MRSA involvement in a clinical infection, while a negative test could rule out the pathogen. High-sensitivity PCR-based tests of nasal colonization (7), which can yield results in several hours, might be of particular use in guiding empirical therapy, providing results several days before the susceptibilities of clinical isolates have been determined. We therefore undertook to examine whether MRSA nasal colonization predicts MRSA involvement in a patient with positive clinical cultures from sites of suspected infection elsewhere in the body. We also examined whether MRSA nasal colonization predicts resistance to common antibiotics in nonstaphylococcal clinical isolates.

MATERIALS AND METHODS

Data acquisition. Evanston Northwestern Healthcare is an 850-bed, three-hospital healthcare organization in the northern suburbs of Chicago, IL. On 1 August 2005, the organization began a universal admission surveillance program for MRSA in which all patients were tested for nasal colonization on admission and again upon transfer to intensive care or chronic care units. The laboratory database system was used to identify all patients who had a clinical culture positive for any pathogen from 1 August 2005 through 31 January 2007. Viral cultures and surveillance cultures were excluded, as were cultures labeled “stool,” “rectal,” “vaginal,” “genital,” “throat,” “nares,” and “nasal,” since these were considered unlikely to represent sites for which MRSA disease is a significant consideration. Only the first positive culture in a 30-day period was used for each patient. The included cultures were then matched to nasal MRSA tests to identify those cultures that were obtained within 1 day before or after a nasal surveillance test. For all patients with positive clinical cultures for MRSA, patient records were reviewed to determine whether the cultures represented true infection (defined below). To examine the effect of MRSA-active antimicrobial agents on nasal test results, records of all patients with positive MRSA clinical cultures from 1 August 2005 through 30 April 2006 (n = 154) were reviewed for the receipt of these agents in the 14 days prior to nasal testing. This study was approved by the Evanston Northwestern Healthcare institutional review board.

Laboratory methods. Nasal MRSA testing was performed by swabbing both anterior nares; the swab was processed by using the BD-GeneOhm real-time PCR test (Becton Dickinson, Franklin Lakes, NJ) (6, 7). We modified the preanalytical specimen processing to facilitate high-volume testing (15). In our center, we have found this assay to have a sensitivity of 98.2% and a specificity of 97.5% (14). Susceptibility testing of all organisms was carried out according to the guidelines of the Clinical Laboratory Standards Institute; clindamycin susceptibilities reflect disk approximation test results (4).

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TABLE 1. Nasal-MRSA-colonization status of patients with MRSA recovered from clinical cultures

<table>
<thead>
<tr>
<th>MRSA culture site</th>
<th>No. of patients with indicated nasal-colonization test result</th>
<th>% of clinically positive patients who were nasally positive (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Bloodstream</td>
<td>11</td>
<td>31</td>
</tr>
<tr>
<td>Extremity</td>
<td>39</td>
<td>62</td>
</tr>
<tr>
<td>Other*</td>
<td>30</td>
<td>45</td>
</tr>
<tr>
<td>Respiratory</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>Ulcer</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Urine</td>
<td>14</td>
<td>47</td>
</tr>
<tr>
<td>Total</td>
<td>106</td>
<td>217</td>
</tr>
</tbody>
</table>

* Most frequently, “other” cultures were obtained from the abdominal wall, buttock, or breast.

Definitions. A culture involving MRSA was a clinical culture in which MRSA was at least one of the recovered organisms. In the context of such cultures, nasal tests also positive for MRSA were considered concordant. Antimicrobial agents active against MRSA were clindamycin, fluoroquinolones, linezolid, mupirocin, tetracyclines, rifampin, trimethoprim-sulfamethoxazole, daptomycin, tigecycline, and vancomycin. True MRSA infections were defined as follows. Bloodstream infection required a positive blood culture. Respiratory tract infection required a positive respiratory culture, a compatible chest X ray, and a decision to treat. Urinary tract infection required a positive urine culture and either a decision to treat or the growth of >100,000 CFU/ml plus at least 50 leukocytes per high-power field. Surgical-site infection required a positive culture from the surgical site. All other sites required a positive culture and a decision to treat.

Statistical analysis. Exact binomial 95% confidence intervals (CI) were calculated for all proportions. Fisher’s exact test was used for group comparisons. The performance of nasal MRSA colonization as a predictor of MRSA involvement in the setting of positive clinical cultures was evaluated using standard formulae for sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, and negative likelihood ratio.

RESULTS

In 18 months of universal admission surveillance, 57,089 nasal tests were performed. A total of 5,779 of these tests were performed within 24 h of a positive nonsurveillance clinical culture that met inclusion criteria. Of those clinical cultures, 323 (5.6%) involved MRSA.

Nasal tests to rule out MRSA infection. To function as an ideal rule-out test, nasal MRSA tests would be consistently positive in the presence of clinical MRSA. We found that 217 of 323 patients (67.2%; 95% CI, 61.8, 72.3) whose clinical cultures involved MRSA had a positive nasal real-time PCR test. The degree of nasal concordance was highest in the setting of positive urine cultures (77%) and lowest in the setting of positive cultures from “other” body sites (generally nonextremity skin and soft tissue sites) (60%; P = 0.043) (Table 1).

Nasal concordance was not higher when only patients with true MRSA infections were considered (177 of 260 cultures; 68.1%). Nasal concordance was not affected by the receipt of antimicrobials. Levels of concordance were 69.0% among 42 patients who had received antimicrobials active against MRSA, including mupirocin for decolonization therapy, in the 14 days prior to nasal testing and 67.0% among 112 patients who had not (P = 0.85). Concordance was higher when clinical cultures grew clindamycin-resistant MRSA (149 of 209; 71.3%) than when they yielded clindamycin-susceptible MRSA (54 of 91; 59.3%; P = 0.042).

Overall, 5.6% of the clinical cultures involved MRSA (Table 2). In this context, the NPV of a nasal MRSA test for MRSA involvement in the clinical site was 0.98 (95% CI, 0.97, 0.98). The NPV for bloodstream, respiratory, and urine infections was ≥0.98. Owing to the higher prevalence of MRSA involvement in skin and soft tissue infections (Table 2), the NPV was lower for infections of extremities, ulcers, or other sites (Table 3).

Nasal tests to rule in MRSA infections. For all body sites, a positive nasal MRSA test significantly increased the risk of MRSA recovery from a clinical culture site; the mean risk ratio was 12.9 (95% CI, 10.4, 16.1) (Table 4). The PPV of nasal MRSA infections varied widely, from 0.11 for urine infections to 0.76 for infections of an extremity (Table 3).

MRSA nasal-colonization status as a marker of antibiotic resistance. Within 24 h of a nasal test for MRSA, 1,448 cultures grew Escherichia coli, 533 cultures grew Enterococcus spp., 355 cultures grew Klebsiella spp., 254 cultures grew Candida spp., and 87 cultures grew Enterobacter spp. The impact of a positive nasal culture on the risk of antibiotic resistance for the selected bacteria is shown in Table 5. The risk of recovering Candida glabrata was 1.7 times higher (95% CI, 0.9, 2.9) than for other candidal species.

DISCUSSION

The incidence of MRSA infections in the developed world has increased in recent years (18). A clinician usually does not know at the time that therapy is begun whether a patient is infected with MRSA and often never knows for certain. Unfortunately, the optimal antibiotic for the treatment of MRSA disease is generally not the best choice for non-MRSA infections (5). Vancomycin is therapeutically inferior to β-lactams for the treatment of methicillin-susceptible S. aureus bacteraemia and endocarditis (3, 20) and has relatively poor pulmonary penetration (12). Vancomycin’s negligible oral bioavailability necessitates intravenous administration, which is associated with cost and morbidity. Additionally, its extensive use may drive increases in the prevalence of vancomycin-resistant enterococci. Newer agents are expensive and potentially toxic (1). Despite this, the choice to use an empirical regimen that is not active against MRSA must be made carefully; MRSA can be a dangerous organism if not properly treated (19). The dilemma of empirical coverage for MRSA, particularly in the setting of...
TABLE 3. Test characteristics of nasal MRSA colonization as a predictor of MRSA involvement in a clinical culture from any body site

<table>
<thead>
<tr>
<th>MRSA culture site</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>LR+</th>
<th>LR−</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloodstream</td>
<td>0.74 (0.59, 0.85)</td>
<td>0.88 (0.86, 0.90)</td>
<td>0.21 (0.15, 0.29)</td>
<td>0.99 (0.98, 0.99)</td>
<td>6.23 (4.85, 7.98)</td>
<td>0.30 (0.18, 0.49)</td>
</tr>
<tr>
<td>Extremity</td>
<td>0.61 (0.52, 0.70)</td>
<td>0.94 (0.92, 0.96)</td>
<td>0.76 (0.65, 0.84)</td>
<td>0.90 (0.86, 0.92)</td>
<td>10.93 (6.95, 17.19)</td>
<td>0.41 (0.32, 0.53)</td>
</tr>
<tr>
<td>Other</td>
<td>0.60 (0.49, 0.70)</td>
<td>0.96 (0.95, 0.97)</td>
<td>0.61 (0.49, 0.71)</td>
<td>0.96 (0.95, 0.97)</td>
<td>16.32 (10.92, 24.41)</td>
<td>0.42 (0.32, 0.55)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>0.75 (0.55, 0.88)</td>
<td>0.99 (0.96, 0.97)</td>
<td>0.30 (0.20, 0.43)</td>
<td>0.98 (0.97, 0.99)</td>
<td>7.18 (4.97, 10.37)</td>
<td>0.28 (0.14, 0.56)</td>
</tr>
<tr>
<td>Ulcer</td>
<td>0.70 (0.48, 0.86)</td>
<td>0.89 (0.77, 0.95)</td>
<td>0.70 (0.48, 0.86)</td>
<td>0.89 (0.77, 0.95)</td>
<td>6.07 (2.71, 13.58)</td>
<td>0.34 (0.17, 0.67)</td>
</tr>
<tr>
<td>Urine</td>
<td>0.77 (0.65, 0.86)</td>
<td>0.87 (0.86, 0.89)</td>
<td>0.11 (0.09, 0.15)</td>
<td>0.99 (0.99, 1.00)</td>
<td>6.13 (5.18, 7.24)</td>
<td>0.26 (0.17, 0.42)</td>
</tr>
<tr>
<td>Total</td>
<td>0.67 (0.62, 0.72)</td>
<td>0.90 (0.89, 0.90)</td>
<td>0.27 (0.24, 0.31)</td>
<td>0.98 (0.97, 0.98)</td>
<td>6.38 (5.72, 7.11)</td>
<td>0.37 (0.31, 0.43)</td>
</tr>
</tbody>
</table>

a LR+, positive likelihood ratio; LR−, negative likelihood ratio.

b Most frequently, “other” cultures were obtained from the abdominal wall, buttock, or breast.

skin and soft tissue infections, has become a daily one for many clinicians.

Published guidelines aim to help physicians choose empirical therapy well (2), but such general guidelines cannot address the particularities of a unique patient or the prevalence of MRSA in a specific institution or region. Recently, the practice of nasally testing patients for MRSA colonization has increased in popularity. While such testing is generally performed for reasons of infection control (i.e., to protect other patients from MRSA carriers), it is reasonable to suppose that the knowledge of a patient’s MRSA colonization status might be used to guide empirical therapy if an infection arises in that patient. In fact, if the nasal-colonization status is informative in this respect, it could be used as a dedicated diagnostic test in its own right when MRSA infection is a consideration. The availability of nasal-colonization assays with turnaround times of less than 30 min would make these tests particularly useful in this situation.

The presumption that a patient’s nasal-colonization status might provide clues about the source of his or her infection is a reasonable one. The anterior nares are the principal reservoir for S. aureus in humans (22), and most infections caused by this organism are thought to be endogenous. For example, von Eiff and colleagues found that when S. aureus-colonized individuals developed an invasive disease, more than 80% of the instances were with their colonizing strain (21). It is the “endogenous-source” hypothesis that has fueled the practice of nasal-decolonization therapy on numerous occasions. Among the remaining two-thirds of infected patients who were concomitantly nasally colonized with MRSA, this suggests that about a third—at least—of MRSA infections did not originate from organisms colonizing the anterior nares. Among the remaining two-thirds of infected patients who were concomitantly nasally colonized, whether the MRSA originated in the infection or the nares cannot be determined from this study.

Can a nasal MRSA test be used to rule out MRSA disease? It depends. Applied to our general patient population, the NPV for bloodstream and respiratory disease was ≥0.96—likely good enough to guide empirical therapy. However, this performance relies on a relatively small prevalence (about 5%) of MRSA in blood and respiratory isolates. In an intensive care unit in which MRSA accounts for 30% of culture-positive respiratory isolates, as has recently been reported (10), the NPV would be only 0.89. Conversely, for any body site in which MRSA is expected to account for 10% or less of all isolates, the NPV would be ≥0.96. Thus, given the relatively high false-negative rate (a negative MRSA infection result from nares despite MRSA infection), estimating the pretest probability that a given infection involves MRSA is a key step in using nasal MRSA as a rule-out test.

Notably, the false-negative rate of this test was unaffected by whether the patient had recently been treated for MRSA. This may support the idea that antimicrobial agents have only weak activity against nasal staphylococcal colonization; it may also be a product of the fact that we used an assay to detect MRSA DNA rather than viable organisms. While the anterior nares are established as the reservoir of traditional MRSA subtypes, it has been suggested that the reservoir for community-associated (CA) MRSA may lie elsewhere (11). Clindamycin susceptibility is a simple phenotypic marker for CA MRSA (17). In our study, clindamycin-susceptible MRSA organisms were significantly less likely to be associated with nasal colonization than clindamycin-resistant MRSA (59% versus 71%; P =
TABLE 5. Positive nasal MRSA test result as a predictor of resistance to antimicrobial agents

<table>
<thead>
<tr>
<th>Organism (no. of cultures)</th>
<th>Ceftazidime</th>
<th>Levofloxacin</th>
<th>Gentamicin</th>
<th>TMP-SMX</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli (1,448)</td>
<td>1.31 (0.52, 3.28)</td>
<td>2.12 (1.71, 2.62)</td>
<td>1.76 (1.13, 2.74)</td>
<td>1.53 (1.22, 1.92)</td>
<td>1.95 (0.26, 14.7)</td>
</tr>
<tr>
<td>Klebsiella spp. (355)</td>
<td>4.13 (1.02, 16.71)</td>
<td>5.17 (1.88, 14.2)</td>
<td>9.19 (2.12, 39.71)</td>
<td>3.71 (1.56, 8.8)</td>
<td>14.81 (2.89, 75.96)</td>
</tr>
<tr>
<td>Enterobacter spp. (87)</td>
<td>3.29 (1.38, 7.83)</td>
<td>6.58 (1.28, 66.76)</td>
<td>14.81 (2.89, 75.96)</td>
<td>1.95 (0.26, 14.7)</td>
<td>3.62 (1.47, 8.89)</td>
</tr>
</tbody>
</table>

* TMP-SMX, trimethoprim-sulfamethoxazole. Data indicate the numbers of times that it is more likely for a MRSA-colonized patient to harbor a resistant organism than it is for a non-MRSA-colonized patient.

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REFERENCES


In conclusion, we have examined the relationship between nasal MRSA colonization and MRSA disease. We found the presence of nasal MRSA colonization to be a strong predictor of MRSA involvement and of antibiotic resistance in patients with ongoing infections. The absence of nasal MRSA colonization, however, was useful for ruling out MRSA involvement only if the prevalence of MRSA as a pathogen in the clinical infection being assessed was low (e.g., <10%).

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