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The Role of Methicillin-Resistant *Staphylococcus aureus* Polymerase Chain Reaction Nasal Swabs in Clinical Decision Making

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a Gram positive, round bacterium. The bacteria has evolved to withstand attacks from antibiotics and has made MRSA resistant to traditional antibiotics, such as β-lactams, resulting in difficult-to-treat infections. The presence of a genetic mutation within the *mecA* gene, which codes for the penicillin-binding protein 2a (PBP2a), differentiates MRSA from methicillin-susceptible *Staphylococcus aureus* (MSSA). Presence of the PBP2a protein allows *Staphylococcus aureus* (*S aureus*) to overcome β-lactam antibiotics' method of killing by allowing the bacteria to continue to divide and grow.

β-lactam antibiotics cause cell death in susceptible isolates by binding to penicillin-binding proteins, which inhibits transpeptidation within the cell wall via inactivation of the penicillin-binding protein. By inhibiting cell wall synthesis, the cell loses its integrity and leaks its contents, causing cell death. Penicillin-binding protein 2a is a modified protein that has a low affinity for β-lactam antibiotics, allowing MRSA to survive and making it dangerous and difficult to eradicate.

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First described in 1961, MRSA's prevalence steadily increased in the following decades. It is the most common cause of skin and soft tissue infections presenting to emergency departments in the U.S.[1] About 20% of bloodstream infections are caused by *S aureus*, and in 2003, nearly two-thirds of hospital-onset *S aureus* infections were methicillin-resistant in U.S. intensive-care units (ICUs).[2] It has been shown that patients with MRSA bacteremia have worse overall outcomes, including increased mortality, greater lengths of stay, and increased costs, compared with those with MSSA infections.[2,3] In 2011, MRSA infections caused an estimated 11,000 deaths, making fast and accurate detection of MRSA a crucial step in appropriate antimicrobial therapy selection.[4]

Currently, the Clinical and Laboratory Standards Institute (CLSI) recommends testing for MRSA by using phenotypic or genotypic methods. Phenotypic methods test for the observable characteristics of an organism, whereas a genotypic method identifies the specific gene that the organism carries. Recommended phenotypic methods include the latex agglutination test for PBP2a, the cefoxitin disk screen test, and a plate containing 6 µg/mL of oxacillin in Mueller-Hinton agar supplemented with sodium chloride.[5] These methods have varying sensitivity and specificity and take between 48 to 72 hours to provide a result.

Within the past 15 years, a newer, genotypic, method of MRSA detection was approved by the FDA with high sensitivity and specificity. This method uses polymerase chain reaction (PCR) to identify the *mecA* gene. Polymerase chain reaction is a technique used to copy and amplify a specific segment of DNA, making thousands to millions of copies. If present, the MRSA PCR amplifies the *mecA* gene that makes *S aureus* resistant to methicillin and other β-lactams, which confirms that the specimen contains MRSA. The FDA has approved the use of MRSA PCR nasal swabs to detect MRSA in patients at risk of nasal colonization. While previously discussed methods may take between 2 and 3 days to confirm presence of MRSA, PCR can identify MRSA in about 1 hour.[6]

If a *S aureus* infection is suspected, empiric therapy often includes coverage of both MSSA and MRSA, due to the high morbidity and mortality associated with these infections. However, continuing an unneeded or unduly broad antibiotic, such as those that cover MRSA, can cause unintended consequences, such as toxicities, emerging resistance, or selection for pathogenic organisms.[7] Therefore, empiric broad antibiotic therapy should be de-escalated as soon as possible, which further

emphasizes the need for quick and accurate detection of the infecting organism. De-escalation of therapy can lead to a shorter length of stay and decreased mortality.[8,9] Conversely, quick identification of infections caused by MRSA would allow therapy to be broadened to cover MRSA in infected patients, which could potentially decrease patient morbidity and mortality.

NASAL MRSA PCR COLONIZATION

Rapid identification of a causative organism is crucial to determine appropriate antibiotic therapy. Fortunately, PCR is a very rapid method of detecting MRSA, and the use of MRSA PCR nasal swabs may be an effective way to predict whether MRSA is the organism causing an infection at various anatomical sites. If a patient has a suspected infection on admission, a MRSA PCR nasal swab often is completed to determine whether a patient's nares are colonized with MRSA. However, there is no clear consensus in the literature regarding the correlation between MRSA nasal colonization and an infection caused by MRSA, making it difficult for clinicians to confidently de-escalate therapy on a negative MRSA PCR or broaden therapy on a positive result. The purpose of this literature review was to determine whether a MRSA PCR nasal swab can be used as a surrogate marker for MRSA infections at various sites.

Pneumonia has many potential causative organisms, many of which are covered empirically with guideline-directed therapy. The predictive power of MRSA PCR nasal swabs may allow clinicians to prescribe earlier directed therapy. A retrospective cohort study performed at a tertiary care center looked at the clinical usefulness of a MRSA PCR nasal swab in the treatment of pneumonia.[10] Patients were included in the trial if they had a MRSA PCR nasal swab within 1 month of their blood or sputum culture as well as confirmed pneumonia. After analysis of 435 patients, the MRSA PCR nasal swab showed the following performance characteristics for detecting culture-proven MRSA: 88.0% sensitivity, 90.1% specificity, 35.4% positive predictive value (PPV), and 99.2% negative predictive value (NPV). Due to the high negative predictive value, the results indicated that discontinuation of MRSA antibiotic coverage would be appropriate for noncritically ill patients with pneumonia who had a negative MRSA PCR nasal swab.

Another retrospective study was performed by Johnson and colleagues to determine the association between MRSA PCR nasal swabs and the causative organism in pneumonia.[11] Patients were included in the trial if they had a MRSA PCR nasal swab and a lower respiratory culture yielding *S aureus* within 48 hours of hospital admission. After analysis of 72 patients, MRSA PCR nasal swabs demonstrated the following diagnostic characteristics for detecting culture-proven MRSA: 93.3% sensitivity, 95.2% specificity, 93.3%PPV, and 95.2% NPV. These results suggest that early nasal swab MRSA PCR tests can predict the absence of MRSA reliably and may help guide the discontinuation of MRSA-directed empiric antibiotic therapy.

In addition, Giancola retrospectively studied the relationship between MRSA PCR nasal swabs and the likelihood of pneumonia caused by MRSA in intensive and intermediate care units.[12] An analysis of 200 patients revealed high concordance between respiratory cultures and MRSA PCR nasal swab results with the following characteristics: 90.5% sensitivity, 79.9% specificity, 34.5% PPV, and 98.6% NPV. These test characteristics suggested that MRSA PCR nasal swabs might be a useful stewardship tool to allow for discontinuation of anti-MRSA therapy in critically ill patients with confirmed pneumonia.

Another retrospective analysis conducted by Baby and colleagues took a different approach to determine the clinical usefulness of MRSA PCR nasal swabs in the treatment of pneumonia.[13] The primary outcome, mean duration of MRSA-targeted therapy, was reduced by 46.6 hours in the group who received a pharmacist-ordered MRSA PCR nasal swab compared with the group that did not receive a MRSA PCR nasal swab ($P < .01$) Per protocol, pharmacists were authorized to order a MRSA PCR nasal swab for patients who were prescribed vancomycin or linezolid for pneumonia. On receipt of the MRSA PCR nasal swab results, pharmacists were instructed to recommend discontinuation of anti-MRSA therapy if the PCR was negative for MRSA.

Results of this study indicated there were no significant differences in time to clinical improvement between preprotocol and postprotocol implementation (1.8 days vs 2.3 days, respectively; $P = .54$), length of stay (11.0 days vs 8.2 days, respectively; $P = .22$), or mortality (14.8% vs 6.7%, respectively; $P = .41$). The MRSA PCR nasal swabs allowed for a reduction in duration of anti-MRSA therapy without adverse effects on outcomes and provided a statistically significant reduction in the incidence of acute kidney injury during therapy in the postprotocol implementation group (26% vs 3.3%; $P = .02$), likely due to decreased exposure to vancomycin.

Collectively, these studies indicate that MRSA PCR nasal swabs can be clinically useful in making decisions regarding discontinuation of MRSA-targeted therapy in pneumonia when MRSA PCR nasal swabs are negative.

A wider variety of infection sites were studied in a 2008 retrospective review of nearly 5,800 MRSA PCR nasal swabs taken within 24 hours (before or after) of a clinical culture that resulted growth of any organism.[14] The goal of this study was to determine whether MRSA nasal colonization could predict MRSA involvement at various suspected infection sites. Overall, 217 patients (67.2%) with positive MRSA clinical cultures had a positive MRSA PCR nasal swab. The concordance between MRSA PCR nasal swabs and infection sites was highest with positive urine cultures (77%) and lowest in "other" infection sites (60%, primarily abdomen, buttock, and breast). Respiratory infections showed a 75% concordance between MRSA PCR nasal swabs and infection sites, as well as the following characteristics: 75% sensitivity, 90% specificity, 30% PPV, and 98% NPV. Additionally, infection site concordance was higher when clinical cultures grew clindamycin-resistant MRSA (71.3%) vs clindamycin-susceptible MRSA (59.3%; *P* = .04).

Overall, a positive MRSA PCR nasal swab increased the likelihood of MRSA at the primary infection site but was not clinically significant or consistent across infection sites. As seen in other studies, a negative MRSA PCR nasal swab could be useful for lowering concern for MRSA involvement in the primary infection, as evidenced by the following characteristics for all infection sites: 67% sensitivity, 90% specificity, 27% PPV, and 98% NPV.

Sarkionda and colleagues evaluated the clinical usefulness of MRSA PCR nasal swabs in the ICU setting in patients with a lower respiratory tract infection (RTI) or bloodstream infection.[15] A total of 749 patients received a MRSA PCR nasal swab before admission to the ICU and were included in this study. The concordance between MRSA PCR nasal swabs and the causative organism was analyzed in patients who developed a MRSA lower respiratory infection (N = 120) and a MRSA bloodstream infection (N = 78) and demonstrated the following characteristics: 24.2% sensitivity, 78.5% specificity, 17.7% PPV, and 84.4% NPV; and 23.1% sensitivity, 78.2% specificity, 11.0% PPV, and 89.7% NPV, respectively. The authors concluded that the MRSA nasal swab results are not useful for making decisions regarding the need of empiric antimicrobial therapy targeting MRSA infections in lower respiratory infections and bloodstream infections. However, due to the high NPV in this study, one might conclude that negative MRSA PCR nasal swabs could still be used to de-escalate therapy, which is in agreement with the results from Dangerfield and Johnson.[10,11]

Similarly, results from a retrospective chart review demonstrated a lack of predictive value by the MRSA PCR nasal swab.[16] Of 1,203 adult patients admitted to an ICU at a single center, 57 positive MRSA colonized and 122 negative MRSA colonized patients' charts were randomly selected. The presence of MRSA lower RTI or bloodstream infections was found to be 3.51% vs 2.46% in the colonized and noncolonized groups, respectively (*P* = .46). These results led to the conclusion that a positive MRSA PCR nasal swab alone should not be used to make decisions regarding empiric MRSA antibiotic coverage.

An alternative approach to MRSA surveillance was taken by Harris in a prospective cohort of 12,080 adults with a suspected infection on admission to a non-ICU.[17] Patients were screened with a 2-question tool to determine whether they were high risk for a MRSA infection. The 2 questions were "Have you been admitted to any health care facility in the last 12 months?" and "Do you have a skin infection (eg, boil, abscess, spider bite, or cellulitis) at this time?" If patients answered yes to either question, they were considered high risk, and a MRSA PCR nasal swab was ordered.

Patients who answered no to both questions were considered low risk and did not receive a MRSA PCR nasal swab. In total, 623 of 5,609 patients (11.1%) identified as high risk had a positive MRSA PCR nasal swab, and 148 of these 623 patients (23.8%) developed a MRSA-positive clinical culture. Only 121 of 4,986 patients (2.4%) who were high risk and had a negative MRSA PCR nasal swab went on to develop a MRSA-positive clinical culture (98% NPV). Additionally, 104 of 6,741 patients (1.6%) who answered no to both screening questions developed a MRSA-positive clinical culture (98% NPV). Results indicated that a high percentage of patients who were at high risk for MRSA (yes response to either question) and had a positive MRSA PCR nasal swab also had a positive clinical culture for MRSA. Conversely, a very small percentage of high-risk patients with a negative MRSA PCR nasal swab developed a positive clinical culture for MRSA.

The screening tool proved very effective as the low-risk group had the lowest number of patients (1.6%) develop a positive clinical culture for MRSA. It may be deduced that combination use of MRSA colonization testing via PCR nasal swabs in

conjunction with a screening tool may be an effective method to identify patients in whom anti-MRSA therapy can be safely discontinued.

CONCLUSION

Based on the results of previously described studies, sufficient data may exist to support the discontinuation of MRSA-targeted therapy in noncritically ill patients with confirmed or suspected pneumonia and a negative MRSA PCR nasal swab. Insufficient evidence exists, however, to support a broadening of antimicrobial therapy to include anti-MRSA coverage in individuals with a positive MRSA PCR nasal swab, regardless of the infection site.

Clinical judgment should be used when determining empiric antimicrobial therapy and for appropriateness of de-escalation of therapy in critically ill patients. Once a patient stabilizes, a negative MRSA PCR nasal swab could be considered as supporting evidence to discontinue anti-MRSA therapy, especially in patients with lower respiratory infections, such as pneumonia. ●

Author disclosures

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