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CLINICAL THERAPEUTICS

Utility of Methicillin-Resistant *Staphylococcus aureus* Nares Screening for Patients with a Diabetic Foot Infection

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ABSTRACT Treatment of suspected methicillin-resistant *Staphylococcus aureus* (MRSA) is a cornerstone of severe diabetic foot infections; however, antibiotics can be associated with toxicity. The objective of this study was to determine the negative predictive value (NPV) of MRSA nares screening in the determination of subsequent MRSA in patients with a diabetic foot infection. This was a retrospective cohort study across Veterans Affairs (VA) medical centers from 1 January 2007 to 1 January 2018. Data from patients with an International Classification of Diseases (ICD) code for a diabetic foot infection with MRSA nares screening, and subsequent cultures were evaluated for the presence of MRSA. NPVs were calculated for the entire cohort, as well as for a subgroup representing deep cultures. Additionally, the distribution of all pathogens isolated from diabetic foot infections was determined. A total of 8,163 episodes were included in the analysis for NPV. The NPV of MRSA nares screening for MRSA diabetic foot infection was 89.6%. For the deep cultures, the NPV was 89.2%. The NPV for cultures originating from the foot was 89.7%, and the NPV for those originating from the toe was 89.4%. There were 17,822 pathogens isolated from the diabetic foot cultures. MRSA was isolated in 7.5% of cultures, and methicillin-susceptible *S. aureus* was isolated in 24.8%. *Enterococcus* was identified in 14.7% of cultures, *Proteus* in 7.3%, and *Pseudomonas* in 6.8% of cultures. Given the high NPVs, the use of MRSA nares screening may be appropriate as a stewardship tool for deescalation and avoidance of empirical anti-MRSA therapy in patients who are not nasal carries of MRSA.

KEYWORDS methicillin-resistant *Staphylococcus aureus*, antimicrobial stewardship, vancomycin, diabetic foot infection, stewardship

Diabetes affects 9.4% of the population in the United States, which equates to about 30.3 million individuals (1). In 2014, there were 108,000 lower-extremity amputations due to diabetes (1). Coverage of methicillin-resistant *Staphylococcus aureus* (MRSA) is a foundation of many empirical antibiotic regimens (2, 3). Guidelines recommend empirical MRSA coverage in patients who have had MRSA previously, if the local incidence of MRSA is high, or if the infection is severe (4).

Studies have indicated that MRSA can infect 15% to 30% of diabetic foot ulcers (5). A small study performed in Texas found that even though only 15% of patients with diabetic foot infections had a positive MRSA culture, as much as 86% of the sample received antibiotics that covered MRSA. Vancomycin, which was the antibiotic that was most frequently prescribed, was given in 78% of all antibiotic regimens (6). There is toxicity related to the use of antibiotics, especially vancomycin, for empirical MRSA coverage (7). Safe and effective use of antimicrobial agents is the foremost concern of antimicrobial stewardship programs (ASP). Patients are often exposed to broad-

Citation Mergenhagen KA, Croix M, Starr KE, Sellick JA, Lesse AJ. 2020. Utility of methicillin-resistant *Staphylococcus aureus* nares screening for patients with a diabetic foot infection. Antimicrob Agents Chemother 64:e02213-19. https://doi.org/10.1128/AAC.02213-19.

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Received 3 November 2019
Returned for modification 15 December 2019
Accepted 18 January 2020
Accepted manuscript posted online 27 January 2020
Published 24 March 2020

TABLE 1 Efficacy characteristics of MRSA nares screening for diabetic foot infections

Screening parameter	No. of isolates	% sensitivity	% specificity	PPV	NPV
Whole cohort	8,163	50.2	89	48.7	89.6
Deep culture	5,499	48.8	89.2	48.7	89.2
Superficial culture	2,664	53.2	88.6	48.7	90.3
Northeast	1,190	53.4	89.6	53.7	89.5
South	2,727	50.4	87.4	46.4	89.0
Midwest	1,658	54.1	91.9	57.8	90.8
West	2,588	45.7	88.6	43.6	89.4
2007–2012	2,947	53.4	86.4	44.5	90.1
2013–2018	5,216	48.5	90.5	51.7	89.3
Culture from foot	5,563	51.2	88.2	47.4	89.7
Culture from toe	2,600	48.2	90.7	51.9	89.4
Duplicates removed	5,403	51.8	90.0	51.0	90.3

spectrum antibiotics, including vancomycin, potentially putting them at risk for adverse effects and resistance (8).

The MRSA Preventative Initiative was begun in 2007 by the Department of Veterans Affairs (VA). It consists of MRSA nares screening at admission, transfers, and discharge (9). In 2010, 96% of patients were screened at admission (9).

The objective of this study was to determine, using a large national database, if the absence of MRSA nasal carriage predicts the absence of MRSA in cultures from patients with diabetic foot infections.

RESULTS

Characteristics of facilities and patients. This cohort yielded 8,163 unique episodes in 5,403 patients with cultures taken from below the ankle. Fifty-six percent of episodes had an International Classification of Diseases code of 9 (ICD-9) for a diabetic foot infection, and 44% had an ICD-10 code. Nasal screening was performed via PCR in 72.3% of the cohort and by standard culture techniques in 27.7%. The majority (98.9%) of the population were men. The mean age of the cohort was 65.0 $\pm$ 9.2 years. A positive screen for nares MRSA occurred in 17.8% of the cohort.

There were 17,822 isolates from the 5,403 patients. MRSA was identified in 7.5% (n = 1,345). Methicillin-susceptible *S. aureus* (MSSA) was identified in 24.8% (n = 4,420). There were 50 other isolates besides *S. aureus* identified in our cohort. Coagulase-negative *Staphylococcus* was identified in 11.5%, *Enterococcus* in 14.7%, *Escherichia* in 4.9%, *Klebsiella* in 3.1%, *Morganella* in 2.5%, *Proteus* in 7.4%, *Pseudomonas* in 6.9%, and *Streptococcus* in 5.1%.

The negative predictive value (NPV) of MRSA nares screening for excluding MRSA infection in any diabetic foot infection was 89.6% for the whole cohort (Table 1). The NPV was 89.2% for those with deep cultures, whereas the NPV was 90.3% for those with superficial cultures. The NPV was 89.7% for cultures originating from the foot and was 89.4% for those originating from the toe. Cultures from the foot accounted for 68% of the cultures, and cultures from the toe accounted for 32% of the cultures.

Geography did not alter the NPVs for the cohorts. The Northeast cohort had an NPV of 89.5%, the South cohort an NPV of 89.0%, the Midwest cohort an NPV of 90.8%, and the West cohort an NPV of 89.4%. We also examined the predictive values based on time frame to determine if there were any differences in the early years of MRSA nares screening. The NPV was 90.1% in 2007 to 2012, and the NPV was 89.3% in 2013 to 2018. Finally, duplicates were removed and each patient was included in the analysis only once. This yielded an NPV of 90.3%. Positive predictive values (PPVs) ranged from 43% to 53%; thus, the presence of MRSA on a nares swab does not indicate the patient would have MRSA in subsequent clinical cultures.

DISCUSSION

Our nationwide study included a large cohort of patients with a diabetic foot infection who had a MRSA nares surveillance swab and a subsequent culture within

7 days of the nares swab. These data confirmed that a negative MRSA nares swab result was consistently associated with NPVs of approximately 90% representing the absence of clinical MRSA infection across cultures from below the ankle. This suggests that a negative MRSA nares screen done within 7 days of the clinical culture can be used to deescalate or avoid the use of empirical anti-MRSA agents for treatment of patients with a diabetic foot infection who are not critically ill.

Studies have indicated that MRSA is the causative pathogen in 15% to 30% of diabetic foot infections (5, 6). Surprisingly, the rate of MRSA was much lower in our veteran population (7.5%). MSSA was the pathogen most frequently isolated in our cohort. Similarly, one study found that the overall incidence of MRSA was 15% and that, given the low likelihood of MRSA infection, vancomycin and other anti-MRSA antibiotics were overused. In that study, 86% of patients received antibiotics directed against MRSA, resulting in a 71% rate of unnecessary anti-MRSA therapy (6).

Another small study found that prior diagnosis of MRSA infection was associated with a higher likelihood of MRSA diabetic foot infection. In that study, patients who were found to have MRSA in their diabetic foot wound were more likely to have had a prior infection with MRSA (15% versus 6%; $P = 0.04$) (6). A recent large cohort study of veterans found similar NPVs for all wound sites. That study included 136,078 wound isolates and reported a 90.4% NPV when only the first isolate was included in the calculation (10). That study was not, however, specific to patients with diabetic foot infections.

MSSA, *Enterococcus*, coagulase-negative *Staphylococcus*, MRSA, *Proteus*, *Pseudomonas*, *Streptococcus*, *Escherichia*, *Klebsiella*, and *Morganella* were the most prevalent pathogens identified in veterans with diabetic foot infections. Similarly to other studies, *S. aureus* was the pathogen most commonly isolated in our study (11, 12, 13). Culturing diabetic foot infections can be challenging, and such infections are often polymicrobial, involving both aerobic and anaerobic bacteria (14). Cultures should ideally be obtained from tissue, since results obtained using tissue samples are more reliable than those obtained using swabs (11, 14). In our study, we distinguished deep cultures (cultures taken from an abscess, fluid, surgical sample, aspirates, or bone culture) from superficial cultures (cultures taken from any other site such as via a swab). The NPV calculated for "nonsterile" isolates (89.6%) for the absence of MRSA in patients who were not colonized with MRSA was not different from that calculated for isolates taken via deep culture (89.2%).

Less than 20% of the population carried MRSA in the nares, and MRSA accounted for less than 10% of infections in the cohort. According to the results of a study that was performed between 2001 and 2002, the rates of prevalence of colonization with *S. aureus* and MRSA in nonhospitalized patients were 31.6% and 0.84%, respectively (15). MRSA infections have substantial morbidity and mortality, making empirical anti-MRSA treatment a foundation of many severe diabetic foot infection regimens (16). This empirical antibiotic use is not benign. Vancomycin is associated with nephrotoxicity—particularly when coupled with the presence of other nephrotoxic agents or piperacillin-tazobactam (7). Vancomycin is also problematic regarding its variable pharmacokinetics and tedious monitoring. The use of MRSA nares screening to detect colonization can be an impactful stewardship tool to deescalate or avoid empirical anti-MRSA therapy in patients with diabetic foot infections who are not colonized nasally with MRSA.

This study had several limitations. Deep culture was classified based on culture labels and free text culture comments, and those classifications may have introduced misclassification bias. Our methodology may have neglected some true infections that were taken from nonsterile sites. Data from patients who were colonized with MRSA in other body sites, such as the rectum and axilla, would not have been captured by this study. Additionally, we could not determine if the patient had been recently decolonized. This study was done in inpatients with diabetic foot infections, and all outpatients were excluded.

Conclusion. The results from this study suggest that a negative MRSA nares swab, taken within 7 days of culture, is useful to predict the absence of MRSA in a subsequent culture from a diabetic foot infection. Stewardship teams may use this information to avoid the use of or deescalate anti-MRSA therapy in non-critically ill patients.

MATERIALS AND METHODS

Setting. In October 2007, all VA inpatient facilities were directed to obtain an anterior nares swab screening for MRSA carriage from every patient who gave consent upon admission, transfers between units, and discharge. The use of PCR testing for MRSA enabled swift identification of MRSA carriers. When PCR was unavailable, culture was done using chromogenic agar. Admission swabs were taken from both anterior nares of each veteran within 24 h, and the results were reported directly to the nursing units (9). These data are stored in the Department of Veterans Affairs' Corporate Data Warehouse (CDW), which houses VA patient medical data. Information was comprised of 121 station numbers, which is the methodology by which the VA classifies facilities or groups of facilities.

Informatics approach. Patients who had had MRSA nares screening performed upon admission or at transfer were identified in the CDW using Structured Query Language (SQL) via the use of the SQL Server Management Studio (SSMS). Data collection and analysis were conducted on the VA Informatics and Computing Infrastructure (VINCI) workspace. Acquisition and analysis of these data were approved by National Data Systems and the VA Western New York Healthcare System Institutional Review Board.

Patient selection. VA patients 18 years of age or older who were tested for MRSA nares colonization upon admission or transfer to a VA inpatient facility between 1 January 2007 and 1 January 2018 were included in the cohort. Transfer cultures were used if the collection time was closer to the collection time of a clinical culture. Each patient had an ICD code consistent with diabetic foot infection. The ICD-9 and ICD-10 codes for diabetic foot infection are 250.8 and 11.621, respectively.

Identification of culture-confirmed MRSA infections. Clinical cultures were identified in the CDW. All culture results were classified by collection site as those likely collected via superficial culture or those taken via deep culture. A positive MRSA culture was defined as a culture obtained after but within 7 days of the time of MRSA nasal swab collection. If MRSA was present in a mixed culture, the MRSA isolate was included preferentially over the other organisms for calculation of the NPV. For determination of the distributions of cultured organisms, all organisms were included. For the purpose of this study, those cultures that included abscess, fluid, surgical, aspirate, and bone culture samples were considered deep cultures. Free text comment fields were manually reviewed to define the anatomical site of the culture.

Geography of diabetic foot infections. The Northeast cohort represented the following geographic regions: Maine, New Hampshire, Vermont, Massachusetts, Rhode Island and Providence Plantations, Connecticut, New York, New Jersey, and Pennsylvania.

The South cohort represented the following geographic regions: Maryland, Delaware, West Virginia, Virginia, Kentucky, North Carolina, Tennessee, Arkansas, Oklahoma, South Carolina, Georgia, Alabama, Mississippi, Louisiana, Texas, Florida, and Puerto Rico.

The Midwest cohort represented the following geographic regions: Ohio, Michigan, Indian, Illinois, Wisconsin, Minnesota, Iowa, Missouri, North Dakota, South Dakota, Nebraska, and Kansas.

The West cohort represented the following geographic regions: Montana, Idaho, Washington, Wyoming, Oregon, Colorado, Utah, Nevada, California, New Mexico, and Arizona.

Statistics. The NPVs were calculated to evaluate the use of the MRSA nasal swab in predicting the absence of MRSA in a clinical culture. NPVs, PPVs, sensitivity, and specificity were calculated for the entire cohort, for deep cultures, for superficial cultures, for the geographic regions listed above, and for the time frames of 2007 to 2012 and 2013 to 2018. They were also calculated for cultures originating from the foot and for cultures originating from the toe. Duplicates were removed for the final analysis of NPV; only the first isolate (in chronological order) was included. Statistics analyses were conducted using JMP Pro version 12.

ACKNOWLEDGMENTS

This material is the result of work supported with resources provided by and use of facilities at the Veterans Affairs Western New York Healthcare System. The contents of the manuscript are not intended to represent the views of the Department of Veterans Affairs or the United States government.

We report no conflicts of interest.

This research was not funded.

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