Reversion of Methicillin-Resistant *Staphylococcus aureus* Skin Infections to Methicillin-Susceptible Isolates

Anisha B. Patel, MD; Emma Hill, BA; Eric L. Simpson, MD; Jon M. Hanifin, MD

**IMPORTANCE** The rise of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the outpatient setting has led to a growing trend of empirical antibiotic treatment for MRSA. The limited oral antibiotics available and the growing resistance to these antibiotics make this a controversial practice.

**OBJECTIVE** To determine the frequency of patients with MRSA skin and soft-tissue infections (SSTIs) reverting to methicillin-susceptible *Staphylococcus aureus* (MSSA) positivity.

**DESIGN AND SETTING** Retrospective medical record review of inpatients and outpatients from our university hospital and clinics between January 1, 2000, and December 31, 2010.

**PARTICIPANTS** Patients in our institutional microbiological database were included if they had a MRSA-positive SSTI and subsequent culture-proven *S aureus* SSTI more than 1 month later. No sociodemographic restrictions were applied. A sample of at least 200 patients meeting the above criteria was desired. The database was sorted by ascending medical record number, with the first 1681 patients’ medical records reviewed. Of these, 215 patients met our criteria.

**MAIN OUTCOMES AND MEASURES** Whether a patient remained MRSA positive in subsequent SSTIs or reverted to MSSA-positive infections.

**RESULTS** Of the total 215 patients, 64 (29.8%) had at least 1 incident of MSSA reversion, and 55 (25.6%) reverted to MSSA infections for the remainder of the study. We assessed various factors that might increase or decrease the likelihood of reversion. The presence of an invasive device was the only factor to demonstrate a statistically significant risk (relative risk, 1.20; 95% CI, 1.02-1.41; *P* = .03) toward remaining MRSA positive in subsequent infections.

**CONCLUSIONS AND RELEVANCE** Patients with MRSA SSTIs demonstrated the ability to revert to subsequent MSSA SSTIs with a significant frequency. Further study regarding MRSA risk factors and their effects on subsequent infections would be valuable in guiding empirical treatment. Reculturing new infections in previously MRSA-positive patients is a prudent management strategy as we recognize that susceptibilities of the *S aureus* organisms change.
**Methods**

Data, derived from culture record log sheets at the Oregon Health & Science University microbiological laboratory, included both inpatient and outpatient culture results. Institutional review board approval from Oregon Health & Science University was obtained before the study for the use of the microbiological and patient medical records. All MRSA-positive microbiological results between January 1, 2000, and December 31, 2010, were included in the initial database. This database was edited to include cultures with documented sites from skin, wound, or soft tissue. All suspected SSTI MRSA-positive cultures were verified by medical record review and then served as an index case. Only patients who had at least 1 additional *S aureus* culture-positive SSTI at least 1 month after the index case were included in the analyses. Sentinel colonization cultures were identified via medical record review as cases in which the documented infection site differed from the culture site or no active infection was noted. These colonization cultures were verified by medical record review and then served as a case. The medical records were reviewed for all subsequent MRSA and MSSA SSTIs through June 1, 2011, when data collection concluded. All sentinel MRSA cultures were obtained, however, between January 1, 2000, and December 31, 2010.

Medical records were also reviewed for other factors that might be predictive of MSSA reversion, including the following: basic demographics (age and sex), dermatologic information (diagnoses related to skin, mucosa, or wounds and whether the culture was associated with a flare of the cutaneous disease), health status (comorbidities, medications, and recent antibiotic use), hospital-acquired MRSA risk factors (procedures or hospitalizations since the first culture, history of an invasive device [an indwelling catheter, prosthesis, port, or other implanted stimulator or pain control device], and previous positive MRSA cultures), community-acquired MRSA risk factors (high-risk residence, participation in contact sports, and men having sex with men), and for each culture (site, date, culture result, infection vs colonization, relation to skin diagnosis, inpatient vs outpatient, and invasive device status).

Patients were then classified into 2 groups: those who remained MRSA positive in all subsequent infections and those who reverted to MSSA in at least 1 subsequent infection. Those who reverted to MSSA were further divided into a group that remained MSSA positive for all subsequent SSTIs available in the Oregon Health & Science University microbiological database and those who switched back to MRSA positivity at least once in future culture screenings during the study.

Relative risks were calculated and 2-tailed Fisher *t* tests were performed to determine the *P* values and 95% confidence intervals.

**Results**

Among 1681 culture records reviewed in our database, 215 patients had at least 2 culture-positive SSTIs meeting our criteria. Demographic information is included in Table 1.

Patients with MRSA SSTIs demonstrated the ability to revert to subsequent MSSA SSTIs with a significant frequency. Of the 215 total patients, 160 (74.4%) had a final status of MRSA positivity, while 55 (25.6%) reverted to MSSA infections for the remainder of the study. The last culture within this 10-year period was considered the patient's final MRSA status.

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**Table 1. Demographic Information**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>45.9 (15.5)</td>
</tr>
<tr>
<td>Sex, F/M, No.</td>
<td>109/106</td>
</tr>
<tr>
<td>Primary skin diagnosis, No.</td>
<td>36</td>
</tr>
<tr>
<td>Patient location at first culture</td>
<td>36 inpatients, 179 outpatients</td>
</tr>
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</table>

*Diagnoses included the following: psoriasis (n = 9), atopic dermatitis (n = 6), recurrent furuncles (n = 3), pressure ulcers (n = 2), bullous hand dermatitis (n = 1), calciphylaxis (n = 1), CREST (calcinosi, Raynaud phenomenon, esophageal dysmotility, scleroderma, and telangiectasia) syndrome (n = 1), dermatitis herpetiformis (n = 1), recurrent folliculitis (n = 1), Klippel-Trénaunay-Weber syndrome (n = 1), neurofibromatosis I (n = 1), nephrogenic systemic fibrosis (n = 1), inten التر (n = 1), genital herpes (n = 1), stasis ulcers or lymphedema (n = 1), lichen simplex chronicus (n = 1), pemphigus vulgaris (n = 1), perioral dermatitis (n = 1), pyoderma gangrenosum (n = 1), and seborrheic dermatitis (n = 1).
A total of 151 (70.2%) remained MRSA positive in all subsequent cultures, while 64 (29.8%) had at least 1 incident of MRSA reversion. Nine of these patients went on to develop future MRSA infections. Eighty-six percent of the patients showing a reversion to MSSA remained MRSA free throughout the study.

Patients with atopic dermatitis showed about the same reversion rate to MSSA as the larger sample, with 2 of 6 (33%) patients reverting. Patients with flaring atopic dermatitis showed similar incidence rates of MSSA reversion to the larger sample and their nonflaring counterparts (1 of 3 patients reverted). The small number of patients with atopic dermatitis analyzed, however, makes firm conclusions difficult.

We next assessed various factors that might increase or decrease the likelihood of reversion (Table 2). Among a variety of possible factors, only 1, the presence of an invasive device, demonstrated a statistically significant risk (relative risk [RR], 1.20; 95% CI, 1.02-1.41; \( P = .01 \)) toward remaining MRSA positive in subsequent infections. Three other factors demonstrated trends toward remaining MRSA positive: taking immunosuppressive medications (RR, 1.19; 95% CI, 1.00-1.41; \( P = .17 \)), inpatient at time of sentinel culture (RR, 1.15 [0.97-1.36]; \( P = .21 \)), and antibiotic use within 1 week of first culture (RR, 1.13 [0.96-1.33]; \( P = .25 \)).

### Table 2. Factors Related to Remaining MRSA Positive

<table>
<thead>
<tr>
<th>Factor</th>
<th>Relative Risk (95% CI)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive device (n = 110)</td>
<td>1.20 [1.02-1.41]</td>
<td>.01</td>
</tr>
<tr>
<td>Immunosuppressive medications (n = 29)</td>
<td>1.19 [1.00-1.41]</td>
<td>.17</td>
</tr>
<tr>
<td>Inpatient at time of sentinel culture (n = 36)</td>
<td>1.15 [0.97-1.36]</td>
<td>.21</td>
</tr>
<tr>
<td>Antibiotic use within 1 week of first culture (n = 44)</td>
<td>1.13 [0.96-1.33]</td>
<td>.25</td>
</tr>
<tr>
<td>IV drug use (n = 38)</td>
<td>1.08 [0.83-1.48]</td>
<td>.55</td>
</tr>
<tr>
<td>Past non-SST MRSA infection (n = 18)</td>
<td>1.13 [0.91-1.41]</td>
<td>.57</td>
</tr>
<tr>
<td>Atopic dermatitis (n = 6)</td>
<td>0.89 [0.50-1.58]</td>
<td>.65</td>
</tr>
<tr>
<td>History of malignant neoplasm (n = 11)</td>
<td>1.11 [0.83-1.48]</td>
<td>.73</td>
</tr>
<tr>
<td>Hospitalization or invasive procedure subsequent to first culture (n = 117)</td>
<td>0.97 [0.83-1.39]</td>
<td>.76</td>
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<tr>
<td>Hepatitis C positive (n = 39)</td>
<td>1.04 [0.86-1.26]</td>
<td>.84</td>
</tr>
<tr>
<td>History of connective tissue disease (n = 14)</td>
<td>1.06 [0.80-1.41]</td>
<td>&gt; .99</td>
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<tr>
<td>HIV positive (n = 11)</td>
<td>0.98 [0.67-1.41]</td>
<td>&gt; .99</td>
</tr>
<tr>
<td>Diabetes mellitus (n = 67)</td>
<td>1.00 [0.85-1.89]</td>
<td>&gt; .99</td>
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</tbody>
</table>

**Abbreviations:** HIV, human immunodeficiency virus; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; SST, skin and soft tissue.

Discussion

This study demonstrates the tendency of patients with MRSA SSTIs to revert to MSSA infections with considerable frequency (29.8%). The findings reinforce the importance of cultivating recurrent purulent infections whenever possible, even in patients with a history of MRSA infections.

Little is known about the basic microbial mechanisms that promote reversion. One possibility is that both MRSA and MSSA strains persist, but that antimicrobial use promotes the growth of MRSA over MSSA, making it the dominant organism in laboratory cultures. After the antimicrobials are withdrawn, MSSA colonies regain dominance. Our data, however, did not show any correlation between antibiotic use within 1 week of culturing and MRSA persistence.

Similarly, a phenomenon has been described with MRSA susceptibility to glycopeptides, in which vancomycin hydrochloride exposure causes the development of a glycopeptide-resistant strain of bacteria, which reverts to glycopeptide susceptibility when vancomycin is discontinued. A proposed mechanism for the observed reversion is one of extreme selection in which exposure to antibiotics generates colonies that are 100% MRSA, but the withdrawal of antibiotics favors reversion to the MSSA phenotype, with the bacteria mutating back to this state. This has been demonstrated both in vitro and in vivo with glycopeptide-resistant *S aureus*. In 1 study, the resistant strains of bacteria reverted to glycopeptide susceptibility when exposed to nonsensitive media. No identifiable colonies of glycopeptide-resistant bacteria remained among the reverted populations.

The mechanism for reversion may, alternatively, be that patients clear their MRSA colonization and are reinfected with a new organism. Patients who remain MRSA positive may have persistent colonization or are prone to MRSA reinfection. Contributing to MRSA persistence could be differing host immune responses to MRSA and MSSA, as well as variations in host immunity that predispose certain patients to a MRSA infection. The length of time between the first and second cultures can have implications as to the patients’ comorbidities and immune status as well as the virulence of the MRSA strain.
The shorter mean time between first and second cultures in patients who remained MRSA positive may indicate an immunologic vulnerability to more frequent MRSA infections. Although much research has been done on the immune response to \textit{S aureus} infections, the differences, if any, between the immune response to MRSA and MSSA have yet to be delineated.\cite{25}

Also adding to the predisposition to or the persistence of MRSA infections could be the patient’s skin microbiome. Grice and Segre\cite{16} demonstrated the importance and effect of commensal organisms on subsequent cutaneous infections in patients with chronic wounds.

In an outpatient setting, during a 10-week observation, Fernandez et al\cite{17} demonstrated that colonization is associated with an increased risk of infection and suggest a higher conversion rate in patients colonized with MRSA compared with those colonized with MSSA. In addition, molecular similarity between \textit{S aureus} strains isolated from nasal carriers and their infected wounds has been shown.\cite{18} In contrast, Kauffmann et al\cite{19} were unable to relate a decrease in the colonization rate to a drop in the infection rate, although this may have been due to a low rate of infections overall. In summary, the relationship between colonization and infection in outpatient SSTIs is still being delineated.

Other studies tracking systemic infections and colonization in hospitalized patients showed that more than 80% of MRSA carriers decolonized without active treatment,\cite{20,21} although those patients who were actively treated decolonized at a faster rate\cite{20} and those with skin wounds had a higher risk of remaining colonized.\cite{21} Approximately 50% of MRSA carriers decolonized in 1 year. The rate of decolonization slows after this first year, but 80% of patients can decolonize by 5 years.\cite{21} This ability of patients to decolonize at a significant rate without treatment may be evidence that subsequent infections are due to a new rather than a persistent organism, particularly when the time between infections is more than 1 year. Interestingly, our data showed that patients reverted to MSSA infections a mean 29.7 months after the sentinel MRSA culture, when the suspected colonization rate would be about 30%, favoring the likelihood of a new colonizing or infecting organism for infections at this point.\cite{21} As MRSA carriers decolonize, they are more likely to become colonized by MSSA, as shown in the general population.\cite{16} For those patients remaining MRSA positive, it could be hypothesized that they are clearing their MRSA colonization more slowly than average and are being reinfected by the same organism or, alternatively, this might relate to host immune response or their skin microbiome, making them more susceptible to MRSA reinfection.

Speciating the organisms in future studies would clarify whether subsequent MRSA infections were recurrent or new bacterial strains.

While the original observations occurred in patients with atopic dermatitis, few were detected in this retrospective medical record review, making it difficult to draw any conclusions regarding their MRSA reversion rates. This may reflect the culturing and treatment practices of our dermatologists, combined with the small number of patients with atopic dermatitis who were MRSA positive. Trends noted in San Diego, California, and Toronto, Canada, suggest that pediatric patients with atopic dermatitis have a lower infection rate with MRSA,\cite{24,25} and the rate of increase of MRSA infections is slower than in the general pediatric population.\cite{25}

The clinical observation that patients are able to revert to subsequent MSSA infections after having an index MRSA SSTI raises many questions discussed earlier. How this should affect clinician practices remains to be seen, but at this time, re culturing new infections in previously MRSA-positive patients is a prudent management strategy as we recognize that susceptibilities of the organisms change, particularly as elapsed time from the last MRSA culture increases. Miller et al\cite{26} demonstrated that it is not possible to predict serious MRSA SSTIs based on the presence or absence of risk factors. This is consistent with our evidence that few, if any, MRSA risk factors showed trends toward persistence. Future areas of research include exploring potential differences in host immune responses to MRSA and MSSA, characterization of the human microbiome of patients with recurrent MRSA vs MSSA infections, and molecular typing of the \textit{mec} resistance genes for each infection to help indicate if these are recurrent or new infections. Epidemiologic studies that would be of interest include tracking a cohort of patients’ susceptibility patterns of their cutaneous \textit{S aureus} infections. Furthermore, a cohort of patients with dermatologist-diagnosed atopic dermatitis would be of interest to study \textit{S aureus} colonization and subsequent infection rates. One of the difficulties in the current study was identifying patients with atopic dermatitis in the database. Having a central database with culture information for patients with atopic dermatitis would greatly aid in the research of their infections.

Limitations of our study include the retrospective medical record review method and access only to university system records. We had hoped to identify patterns of infection in patients with atopic dermatitis but found infrequently documented dermatologic diagnoses, and few patients had seen a dermatologist.

In conclusion, this study demonstrates the ability of patients with MRSA to have subsequent MSSA SSTIs, although the mechanism of this change and whether it demonstrates a reversion or new infection remains to be clarified. We can conclude, however, that SSTIs should be cultured when possible and that further research into this topic could help identify risk factors for subsequent MRSA infections.

\textbf{Author Contributions:} Drs Patel and Hanifin had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Patel, Simpson, Hanifin. Acquisition of data: Patel, Hill. Analysis and interpretation of data: Patel, Simpson, Hanifin. Drafting of the manuscript: All authors. Critical revision of the manuscript for important intellectual content: Patel, Simpson, Hanifin. Statistical analysis: Patel.
Obtained funding: Patel.
Administrative, technical, and material support: Hill, Hanfin.
Study supervision: Hanfin.
Conflict of Interest Disclosures: Dr Hanfin reported serving as a consultant to Chugai Pharma USA, GlaxoSmithKline, Leerink Swann, LEO Pharma, Meda Pharmaceuticals, Merck Sharp & Dohme, Novartis, Pfizer, Valeant Elidel Advisory Board, and Zyngenetics/BMS. Dr Simpson reported serving as a consultant to Alcimed, Auvio, Brickell Biotech, Clarion Healthcare, Galderna Laboratories, L.E.K. Consulting, Medicis Pharmaceutical Corp, Panmira Pharmaceuticals LLC, Regeneron, and Versant Ventures. Dr Simpson reported serving as a speaker for Galderna Laboratories.

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REFERENCES