Introduction of Rapid Methicillin-Resistant \textit{Staphylococcus aureus} Polymerase Chain Reaction Testing and Antibiotic Selection Among Hospitalized Patients With Purulent Skin Infections

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Over the past decade, methicillin-resistant \textit{Staphylococcus aureus} (MRSA) has emerged as the most frequent cause of purulent skin and soft tissue infection (SSTI) in many settings [1, 2]. Simultaneously, empiric use of MRSA-active agents, including vancomycin, has increased dramatically [2]. In a 2008 US multicenter study, 90% of patients hospitalized with SSTIs were treated with MRSA-active antibiotics; however, only 43% had cultures positive for MRSA [2].

Use of antibiotics discordant with pathogen susceptibility places patients at risk of treatment failure and promotes antimicrobial resistance [3]. Recent introduction of polymerase chain reaction (PCR) assays for \textit{S. aureus} detection in general, and MRSA specifically, offers potential for rapid and accurate pathogen identification and reduction of discordant antibiotic use among patients with purulent SSTI. With results available in approximately an hour, PCR assays may facilitate initiation of targeted antibiotics 1–2 days before reporting of culture results.

The primary objective of this study was to compare rates and durations of discordant antibiotic use in patients admitted from the emergency department (ED) to the hospital with purulent SSTI before and after introduction of a rapid MRSA PCR assay, following physician education regarding test characteristics and then active physician guidance by a pharmacist. The secondary objective was to determine whether availability of a rapid MRSA PCR assay impacted hospital length of stay (LOS). We hypothesized that availability and use of the PCR assay would reduce rate and duration of discordant antibiotic use.

METHODS

This was a single-center, retrospective, blinded systematic medical records review of patients with SSTI with purulent drainage admitted from the ED to a public teaching hospital (Olive View–UCLA Medical Center, Sylmar, California). Patients aged ≥18 years hospitalized with purulent SSTI were identified for study inclusion. Rates of discordant antibiotic use were compared for 3 consecutive phases related to the introduction of a rapid MRSA PCR assay. Phase I (March–August 2009) was prior to introduction of the assay. Phase II (September 2009–March 2010) followed ED physician instruction to order a rapid MRSA PCR assay for all admitted patients with purulent SSTI for whom wound cultures were sent, and ED and admitting physician education regarding test characteristics and encouragement to use the test results in antibiotic selection. During phase III (April–November 2010), a pharmacist was assigned during regular weekday hours to track assay results and to page and advise admitting physicians regarding alternative antibiotic(s) when prescribed antibiotics were discordant with assay results.

During phase I of the study, sterile Dacron swab wound cultures were processed in the hospital laboratory according to standard culture techniques [4]. During phases II and III, specimens were obtained using a simultaneous double Dacron swab. One swab was used for standard cultures, and the other was...
used for the Xpert MRSA/SA SSTI test, a PCR assay processed using the Cepheid GeneXpert system [5].

Potential subjects were identified by review of the automated ED patient log for admissions with SSTI diagnoses. Exclusion criteria were history of vancomycin allergy or intolerance, presence of an additional site of infection requiring treatment (eg, pneumonia), admission to the intensive care unit or for a condition other than SSTI, and prior treatment for the identified SSTI at an outside facility.

Consistent with current Infectious Diseases Society of America (IDSA) clinical practice guidelines, the following MRSA-active antibiotics were defined as appropriate for complicated or purulent MRSA SSTI: vancomycin, linezolid, daptomycin, te- lavancin, clindamycin, doxycycline, minocycline, and trimetho- prim/sulfamethoxazole (TMP-SMX) [6]. For non-MRSA SSTIs, the use of an antibiotic to which the organism was susceptible, except for vancomycin, linezolid, daptomycin, te- lavancin, doxycycline, minocycline, and TMP-SMX, was considered appropriate. Clindamycin was considered appropriate for non-MRSA infections as it is well tolerated, inexpensive, and provides adequate coverage for both methicillin-susceptible S. aureus (MSSA) and streptococcal infections. Due to cost and unfavorable side effect profiles, the MRSA-active agents vancomycin, daptomycin, and linezolid are typically not preferred for non-MRSA SSTIs, and antistaphylococcal penicillins, cephalosporins, or clindamycin are generally preferred based on cost, tolerability, and clinical experience. IDSA SSTI treatment guidelines list TMP-SMX and doxycycline as MSSA treatment options [7]. However, limited clinical data support their use and, therefore, both were defined as discordant for non-MRSA infections.

All data were collected by trained research assistants blinded to the study objectives and hypothesis. Antibiotic initiation and completion times were extracted from inpatient records. On the basis of pilot data, we estimated that >80% of subjects would be empirically treated with vancomycin, but only 30% would have MRSA cultured. Assuming a baseline rate of discordant vancomycin use of 60%, and a hypothesized rate reduction of 50%, we estimated that 49 patients per phase would be required to obtain an α of .05 and power of 80%. Differences in proportions and 95% confidence intervals [8] were calculated, and χ² and Fisher exact test were used to compare discordant antibiotic use between phase I and subsequent phases. The Mann-Whitney U test was used to compare median days of discordant antibiotic use, vancomycin use, and hospitalization between phase I and subsequent phases. The local institutional review board approved the study.

RESULTS

Of 169 patients assessed, 165 (98%) were determined to be eligible for study inclusion. Demographic characteristics of subjects were similar between study phases. Overall, the median age was 51 years, two-thirds were men, and 42% were diabetic. MRSA was isolated by culture from 47 of 165 (28%) subjects. In phases I, II, and III, MRSA was detected by culture in 28% (15 of 53), 26% (13 of 50), and 31% (19 of 62), and MSSA in 21% (11 of 53), 38% (19 of 50), and 37% (23 of 60) subjects, respectively. Compared with standard wound culture, the rapid PCR assay was 100% sensitive and 89% specific for MRSA detection, and 100% sensitive and 68% specific for S. aureus detection.

The proportion of subjects treated with discordant antibiotics, overall, and by presence of MRSA, and median days of discordant antibiotic use and hospital LOS in phases I, II, and III are summarized in Table 1. In phases I, II, and III, 31 of 53 (58%), 31 of 50 (62%), and 28 of 62 (45%) subjects were treated with discordant antibiotics, and the median duration of discordant antibiotic use was 0.6, 1.1, and 0.2 days, respectively. Neither the proportion treated with discordant antibiotics nor duration of discordant antibiotic use differed significantly between study phases.

Among subjects with a culture positive for MRSA, only 6.3% (3 of 47) received discordant antibiotics upon admission. Of 118 subjects with negative MRSA cultures, 87 (74%) received MRSA-active agents. Vancomycin was the principal antibiotic prescribed for subjects receiving anti-MRSA empirical treatment, used for 96% in the ED and 91% in the hospital. Median LOS (days) was 2.8 in phase I, 3.9 in phase II (P = .04), and 3.1 in phase III (P = .38). At time of hospital discharge, 33% (16 of 49) of phase I, 30% (14 of 47) of phase II (P = .93), and 21% (12 of 56) of phase III (P = .21) subjects were sent home with a prescription for discordant antibiotics. If the PCR assay had been consistently used to guide antibiotic selection, the rate of discordant antibiotic use would have been reduced from 58% to 6.5% (P < .001), with all MRSA-positive patients receiving appropriate antibiotics.

DISCUSSION

This study highlights the frequent use of MRSA-active antibiot- ics among patients hospitalized with MRSA-negative purulent SSTI and the challenges in implementing a potentially useful rapid molecular assay–based treatment strategy. As observed in a recent US multicenter study [2], we found that most subjects had wound cultures negative for MRSA, yet three-quarters of these MRSA-negative subjects were treated with MRSA-active agents. Delays in appropriately directed antibiotics are imposed by the timeliness of routine culture testing. Whereas theoretical best-practice use of the rapid PCR assay would have reduced the overall rate of discordant antibiotic use from 58% to 6.5%, even with physician education and active pharmacist guidance, we found only a nonstatistically significant trend toward reduction to a rate of 45%. 
Epidemiological and clinical characteristics are insufficiently predictive of MRSA SSTI etiology [1]. Until recently, physicians had little choice but to provide empiric MRSA coverage until cultures had resulted. Rapid molecular diagnostic tests, such as the Cepheid Xpert MRSA/SA SSTI assay, allow a shift from overly broad empirical treatment to targeted therapy that may reduce cost and adverse effects, and generally improve antibiotic stewardship. PCR assays provide rapid and accurate pathogen identification, and, with an effective implementation strategy, would facilitate initiation of targeted antibiotics days before reporting of wound culture and susceptibility results.

This study has a number of limitations. This was a single-site study, thus limiting its generalizability. Conducting the study at a teaching hospital may have reduced the effectiveness of physician education, for example, because of frequent rotation of trainee physicians. The impact of pharmacist intervention may have been greater had availability not been limited to regular weekday hours. Some might consider TMP-SMX and doxycycline to be overly broad empirical treatment for MSSA infections; however, these were rarely used, with 95% of inappropriate use ascribed to vancomycin. Some subjects may have appropriately received antibiotics defined as “discordant” if medication contraindications existed.

Our study demonstrates that introducing a rapid molecular diagnostic test in absence of an effective implementation strategy to ensure appropriate use of results may be insufficient to produce intended results. Further study into strategies to overcome barriers to physicians incorporating test results into routine practice is warranted.

### Notes

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#### Potential conflicts of interest

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