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# A Colonization Outbreak of Penicillin-Susceptible *mecA*-Positive *Staphylococcus aureus* in a Neonatal Ward of Children's Hospital

*To the Editor*—We experienced a colonization outbreak of penicillin-susceptible and *mecA*-positive *Staphylococcus aureus* strain in neonatal ward. After implementation of strict precautions and decolonization, the outbreak was terminated. To our knowledge, this is the first report of penicillin-susceptible MRSA outbreak in a neonatal ward.

Nagano Children's Hospital is a tertiary pediatric hospital located in a rural area of Japan with 42 beds in the neonatal ward. Active weekly surveillance cultures of nares of inpatients of the neonatal ward have been carried out since the 1990s, especially for monitoring methicillin-resistant *Staphylococcus aureus* (MRSA). In recent years, the proportion of MRSA carriage in the neonatal ward has been approximately 0 to 5%.

In late July 2016, our surveillance system noticed an unusual surge in the colonization rate of methicillin-susceptible *S. aureus* (MSSA) in the neonatal ward. Detailed investigations revealed that this *S. aureus* strain has unique characteristics; namely, it is uniformly susceptible to penicillin but hetero-resistant to oxacillin and cefoxitin. Genetic analysis also revealed that this strain possesses the *mecA* gene; therefore, this strain was reassessed as MRSA, according to Clinical and Laboratory Standards Institute (CLSI) criteria.[1]

The infection control team had emergency meetings and alerted healthcare workers throughout the hospital about the outbreak. The campaign for reinforcement of hand hygiene with contact precautions, strict isolation, and cohorting the patients was carried out. However, by the end of August, the colonization rate reached its the highest level (12 of 43 patients, 28%). We then decided to implement MRSA decolonization with mupirocin ointment. In total, 17 patients (12 penicillin-susceptible [PS] MRSA patients and 5 'ordinal' MRSA carrier patients) had undergone the decolonization; 10 of 13 patients (76.9%) were confirmed as decolonized (defined as negative results for 2 consecutive cultures). Furthermore, 3 patients were not decolonized, and the other 4 patients were discharged before follow-up cultures were performed.

After these interventions, the carriage rate of PS-MRSA decreased, and no new cases of colonization were reported for 2 consecutive weeks. In late October, we declared that the outbreak had ended. Fortunately, there were no serious infections due to this PS-MRSA during this outbreak.

The outbreak strain of PS-MRSA did not yield typical cultures on MRSA-specific chromogenic media (CHROMagar II, Becton-Dickinson, Japan); on this selective medium, it yielded only a few slow-growing colonies, and sometimes the strain did not yield a culture on the medium. Antimicrobial susceptibility test showed resistance to gentamicin, erythromycin, and levofloxacin but susceptibility to vancomycin. The minimum

TABLE 1. Molecular Characteristics of the Outbreak Strain

| ST | ACME | PVL Genes | Enterotoxins | Adhesins |
|---|---|---|---|---|
| 5 | … | … | *sed, seg, sei, sem, sen, seo, sep, selx, selw* | *icaD, eno, fnbA, ebpS, fib, clfA, clfB, sdrC, sdrD, sdrE, bbp, sak, chp* |

NOTE: ST, sequence type; ACME, arginine catabolic mobile element; PVL, Panton-Valentine leucocidin.

inhibitory concentration (MIC) to oxacillin ranged from 0.25 to 4.0 μg/mL, and the MIC to cefoxitin ranged from 4.0 to 8.0 μg/mL, and the strain was assessed as susceptible to resistant. However, the MIC to penicillin was uniformly low, 0.03–0.12 μg/mL, and the strain was judged as susceptible according to CLSI criteria.[1] These MICs were measured using a broth microdilution test. The MICs to antimicrobial agents were also measured by E-test, and the results showed a similar tendency. The MICs to oxacillin, cefoxitin, and penicillin ranged from 0.25 to 8.0 μg/mL, from 4.0 to 24.0 μg/mL, and from 0.094 to 1.0 μg/mL, respectively.

Molecular subtyping and gene analyses, which were performed as described previously,[2,3] revealed that all the strains belonged to *coa* type IIa, SCC*mec* type I (type-1 *ccr* (A1, B1) and class B *mec*), sequence type (ST) 5, *spa* type t010, and *agr* group II. They did not possess Panton-Valentine leukocidin (PVL) or arginine catabolic mobile element (ACME) genes, but they harbored several hemolysins, enterotoxin gene clusters, and adhesins as shown in Table 1. On the other hand, these strains lacked *mecI*, *mecR1*, and *blaZ* genes.

Genetic analyses of these strains revealed that mobile gene element IS *1182* was inserted within the promoter region of *mecA* gene in the class B SCC*mec*. Therefore, the *mecA* system of this strain was suggested to be nonfunctional. The sequence data were deposited in GenBank under accession nos. MF278653 and MF278654.

To our knowledge, this MRSA outbreak strain, ST5-SCC*mec* type I, has not been reported from clinical isolates in our country. SCC*mec* type I MRSA has seldom been isolated from clinical specimens since the 1990s, and its prevalence might be ~1%–5%.[4]

The emergence of this type of PS-MRSA poses several clinical problems. First, PS-MRSA could not be detected using a routine MRSA selection medium, so PS-MRSA might often be misrecognized as MSSA. Therefore, genetic analysis, such as polymerase chain reaction (PCR), is necessary for the detection of the *mecA* gene from *S. aureus* isolates, at least in serious infections. Second, an appropriate antimicrobial agent for PS-MRSA remains unknown. Moreover, there might be threat of converting from PS-MRSA to true (penicillin- and oxacillin-resistant) MRSA during treatment. The usual treatment regimen for MSSA infection with β-lactam antimicrobials might lead to treatment failure.[5]

Exact prevalence of penicillin-susceptible or oxacillin-susceptible (PS/OS-) MRSA among clinically isolated MSSA is unknown, but it is supposed to be ~3%.[5] Literature on PS/OS-MRSA has been increasing all over the world.[6,7]

The mechanisms of anomalous antimicrobial susceptibility of PS/OS-MRSA have not been fully elucidated.[8] Several hypotheses have been proposed, such as amino acid changes in *Fem* proteins, which are responsible for Staphylococcal cell-wall synthesis,[6] partial excision of *mecA* gene,[9] and *bla* system dysfunction.[10] PS/OS-MRSA strains are also quite diverse; therefore, many other novel mechanisms might be revealed. In consideration of its clinical importance, more attention should be given to penicillin- or oxacillin-susceptible, *mecA*-positive *S. aureus*.

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## Predicting Multidrug-Resistant Gram-Negative Bacterial Colonization and Associated Infection on Hospital Admission: Methodological Issues

*To the Editor*—We read with great interest the article titled "Predicting Multidrug-Resistant Gram-Negative Bacterial Colonization and Associated Infection on Hospital Admission" by Tseng et al[1] published in a recent issue of this journal. We would like to congratulate the authors on their valuable work; however, we think some methodological and statistical issues should be considered to avoid misinterpretation.

As shown in the Table 3 of the article, when a predictor meets a univariate criterion of $P < .01$, the predictor is further considered for multivariable analysis. Here, we are concerned that the authors considered a very conservative $P$ value for univariate screening of candidate predictors. They argued that when a conservative $P$ value (eg, <.01 or <.05) is selected in univariate analysis, only the predictors with relatively large effect will be included in the multivariable analysis. In such a situation, the estimated regression coefficients of selected predictors can have bias away from the null,[2,3] which is known as testimation bias.

Considering a liberal $P$ value (eg, <.10 or <.20) in univariable analysis can effectively compensate for testimation bias.[2] In other words, we can be sure that predictors with relatively large effect (eg, $P < .01$) and predictors with relatively small effect (eg, $.10 < P < .20$) can be tested in multivariable analysis after univariate screening with, for example, $P < .20$. In the study,[1] although long-term hemodialysis appear to be an uninteresting predictor for risk of multidrug-resistant gram-negative bacteria (MDR-GNB) colonization in univariable analysis, it may have a significant effect but only in the presence of other predictors.

We acknowledge that the study provides very interesting results, but the estimated associations for predictors of MDR-GNB colonization may be different from those reported in the study due to testimation bias.

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