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ORIGINAL ARTICLE

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Transmission of methicillin-resistant *Staphylococcus aureus* in an acute care hospital in Japan

Kaori Matsumoto MD[1] | Seisho Takeuchi MD[1,2] | Yoshio Uehara PhD[1,2] | Masahide Matsushita MD[3] | Kazumi Arise BSN[2] | Norihito Morimoto MT[2,4] | Yusuke Yagi Pharm D[2,5] | Hiromi Seo MD[1]

[1]Department of General Medicine, Kochi Medical School Hospital, Nankoku, Japan

[2]Department of Infection Control and Prevention, Kochi Medical School Hospital, Nankoku, Japan

[3]Department of Family Medicine, Kochi Medical School, Nankoku, Japan

[4]Department of Clinical Laboratory, Kochi Medical School Hospital, Nankoku, Japan

[5]Department of Pharmacy, Kochi Medical School Hospital, Nankoku, Japan

Correspondence
Seisho Takeuchi, Department of General Medicine, Kochi Medical School Hospital, Nankoku, Japan.
Email: takeuti@kochi-u.ac.jp

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Abstract

Background: Asymptomatic carriers of methicillin-resistant *Staphylococcus aureus* (MRSA) are important sources of nosocomial transmission. However, the route of transmission of MRSA is not completely understood. The purpose of this study was to calculate MRSA transmission rates in a hospital with a high MRSA infection/colonization density and inadequate hand hygiene compliance.

Methods: The prevalence of MRSA colonization among 157 patients at the time of admission to and discharge from a medical school hospital in Japan was determined by performing surveillance cultures. All MRSA isolates were evaluated using multilocus sequence typing (MLST) to identify the transmission routes.

Results: Methicillin-resistant *S. aureus* was prevalent in 1.9% of our study population. MRSA was acquired during hospitalization at a rate of 4.0/1000 patient-days. At discharge, 5.1% of the patients exhibited MRSA colonization; this was significantly higher than the prevalence noted upon admission ($P < 0.001$). MLST documented three possible nosocomial transmission events. MRSA colonization was detected using surveillance cultures prior to being identified by conventional, clinically oriented examinations.

Conclusions: Multilocus sequence typing results suggested that patients who were colonized with MRSA acquired it during hospitalization. These results reinforce the importance of infection control for preventing nosocomial MRSA transmission in hospitalized patients.

KEYWORDS

infection control, methicillin-resistant *Staphylococcus aureus*, multilocus sequence typing, nosocomial transmission, surveillance

1 | INTRODUCTION

Control of healthcare-associated infections remains a major clinical concern related to improving mortality and morbidity rates. Since its discovery in 1961, methicillin-resistant *Staphylococcus aureus* (MRSA) continues to be an important healthcare-associated pathogen. MRSA bacteremia, skin and soft tissue infection, and surgical site infections are associated with longer hospitalizations, greater mortality, and higher

healthcare costs.[1] To date, several different hospital-based strategies have been proposed by infection control personnel and hospital administrators to mitigate the spread and impact of MRSA. Nonetheless, the incidence of MRSA infections remains high in Japan.[2,3]

Methicillin-resistant *S. aureus* infections typically occur in individuals who are colonized with MRSA.[4] Implementing contact precautions for MRSA carriers is essential for preventing healthcare-associated infections. To implement effective precautions for avoiding MRSA infections, it is important to clarify when, how, and from whom MRSA is transmitted. In other words, early detection of MRSA infections in hospitalized patients is critical. Prior hospital admission is a risk factor for MRSA infection, suggesting that MRSA is acquired during hospitalization.[2,5]

When MRSA is prevalent in hospitals, it can be transmitted by undetected carriers to uninfected patients in the hospital.[6] However, MRSA transmission rates and routes in the hospital are not completely understood. Multilocus sequence typing (MLST) is useful in clarifying the diversity and epidemiology of MRSA in healthcare settings.[7] The purpose of this study was to evaluate MRSA transmission rates in a hospital, where MRSA infection/colonization density was relatively high and hand hygiene compliance was inadequate. The prevalence of MRSA colonization in patients at the time of hospital admission to and discharge from a medical school hospital in Japan was determined using surveillance cultures.

2 | MATERIALS AND METHODS

2.1 | Study setting and design

This study was conducted at Kochi Medical School Hospital, a 605-bed tertiary care general hospital with 13 wards. All patients admitted to one of the 50-bed wards from June 2008 to June 2009 were analyzed. Samples were collected from 157 patients at the time of admission and on the day of discharge. Data from clinical medical records were retrospectively reviewed (Table 1). Contact precautions were implemented over standard precautions for patients with MRSA.

2.2 | Isolation and identification of *Staphylococcus aureus* and MRSA

After obtaining written informed consent, we used wet (0.85% NaCl) cotton swabs to obtain bilateral anterior cultures of the nares of all participants. These swabs were immediately inoculated in Staphylococcus Medium 110 (Becton Dickinson & Co, Sparks, MD, USA) supplemented with 5% egg yolk (Kyokuto, Tokyo, Japan) and Trypticase soy agar containing 5% sheep blood (Nippon Becton Dickinson & Co, Tokyo, Japan). Selective plates were cultured for MRSA for 48 hours at 36°C. *Staphylococcus aureus* was identified using API Staph (Sysmex-bioMérieux, Tokyo, Japan), and *fem*A and *fem*B gene detection was performed using polymerase chain reaction (PCR). The presence of *mecA* gene was confirmed using a real-time PCR assay as previously described.[8]

TABLE 1 Demographic characteristics of the 157 patients included in this study

Characteristic	
Age, mean, y	64
Male gender, N (%)	91 (58)
Length of stay, mean days	26
Hospitalization history within 1 y, N (%)	79 (50)
Use of antibiotics within 1 mo, N (%)	17 (11)
Diabetes mellitus, N (%)	29 (18)

2.3 | Laboratory methods

During the study period, MRSA strains collected from participants were stored and evaluated. DNA extraction and MLST were performed according to the methods described by Enright et al.[7] Sequence types were determined by accessing the MLST website (http://www.mlst.net/). MLST was performed using a 3130 Genetic Analyzer (Applied Biosystems, Carlsbad, CA, USA).

2.4 | Nosocomial transmission events of MRSA

Transmission events in the ward were defined as the transfer of MRSA with the same MLST type from a colonized patient to another patient who was previously negative, hospital stays that overlapped with the stay of a colonized patient, and instances of epidemiological linkage. The linkage was defined as either being a roommate of the index patient in a multibed room or being treated by the same attending doctors.

2.5 | Methicillin-resistant *Staphylococcus aureus* prevalence proportion in the ward

We retrospectively analyzed MRSA isolation data from all patients admitted to the ward. MRSA point prevalence proportion refers to the total number of patients with MRSA divided by the total number of patients admitted to the ward in each month. The MRSA prevalence proportion expresses MRSA transmission pressure in the ward; therefore, we used it as a parameter in this study.

2.6 | Hand hygiene practices

Monthly alcohol-based hand rub utilization (volume in mL) was measured during the study period, and the number of times hand hygiene was practiced was calculated from these data.

2.7 | Ethical disclosure

The study protocol was approved by the Ethics Committee of Kochi Medical School, and written informed consent was obtained from all participants in this study.

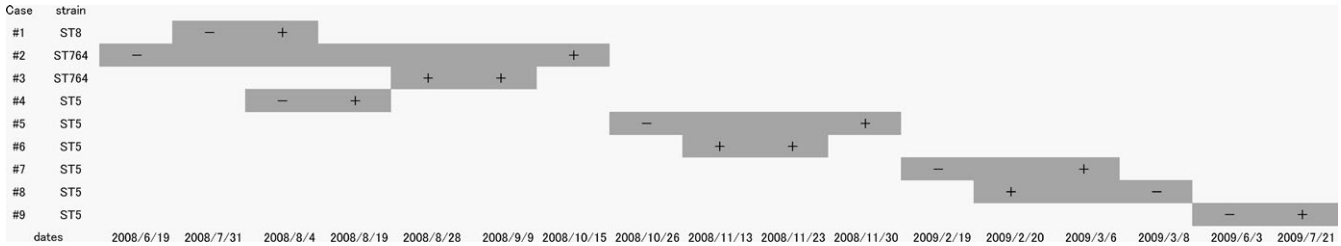

FIGURE 1 Tracing transmission routes of methicillin-resistant *Staphylococcus aureus* (MRSA) among hospitalized patients. Horizontal bars represent the length of hospital stay. Minus signs and plus signs represent the time point at which patients tested negative or positive for MRSA

TABLE 2 Clinical characteristics of nine patients with methicillin-resistant *Staphylococcus aureus*

Case	#1	#2	#3	#4	#5	#6	#7	#8	#9
Age, y	29	56	77	29	50	79	75	79	69
Male gender	−	+	+	−	+	−	+	+	+
Hospitalization history within 1 y	−	+	+	+	+	+	−	−	−
Use of antibiotics within 1 mo	−	+	−	−	−	−	−	−	−
Presence of infection at the time of admission	−	−	−	+	−	+	−	−	−
Diabetes mellitus	+	−	−	+	−	+	−	−	+
Primary disease	Skin ulcer	Esophageal cancer	Mediastinal tumor	Skin ulcer	Lung cancer	Thoracic aortic aneurysm	Lung cancer	Lung cancer	Colon cancer
MRSA colonization on admission	−	−	+	−	−	+	−	+	−
MRSA colonization at discharge	+	+	+	+	+	+	+	−	+

MRSA, methicillin-resistant *S. aureus*.

2.8 | Statistical analysis

Proportions of MRSA colonization were analyzed using the chi-square test.

3 | RESULTS

Methicillin-resistant *S. aureus* colonization was evaluated in 314 samples obtained from 157 patients both at the time of admission to and at the time of discharge from the ward of our hospital. In total, 11 samples from nine patients were positive for MRSA (Figure 1). MRSA colonization was confirmed in three patients at admission; therefore, the MRSA prevalence proportion on admission was 1.9%. MRSA remained at discharge in two patients (cases #3 and #6) but disappeared in the third patient (case #8). All three MRSA-positive patients were previously admitted to our hospital. The number of times these patients were admitted to the hospital was 1 (case #3), 2 (case #6), and 2 (case #8).

Six patients (3.8%) (cases #1, #2, #4, #5, #7, and #9) were negative for MRSA colonization at the time of admission; however, they were detected positive for MRSA at discharge (Figure 1). Hence, we concluded that they acquired MRSA during hospitalization. Hospital stay lengths for these cases were 4 (case #1), 15 (case #2), 15 (case #4), 35 (case #5), 48 (case #7), and 118 (case #9) days. The mean length of hospital stay in these six patients was 39.2 days; therefore, the MRSA incidence rate was 4.0/1000 patient-days. At discharge, 5.1% of the patients exhibited MRSA colonization; this was significantly higher than the prevalence noted upon admission ($P < 0.001$).

In total, nine of the 157 (5.7%) patients were positive for MRSA. Clinical characteristics of these nine patients are summarized in Table 2. All patients presented at least one risk factor for MRSA colonization. MLST was performed on 11 MRSA isolates obtained from these patients at both admission and discharge (Figure 1). Identical

TABLE 3 Nosocomial methicillin-resistant *Staphylococcus aureus* transmission events

Transmission event	#3 to #2	#6 to #5	#8 to #7
Same MLST type	+	+	+
Overlap in hospital stay	+	+	+
Roommate	−	−	−
Same attending doctor	+	+	+

MLST, multilocus sequence typing.

TABLE 4 Hand hygiene practices and methicillin-resistant *Staphylococcus aureus* prevalence proportions

Month	June 2008	July 2008	August 2008	September 2008	October 2008	November 2008	December 2008	January 2009	February 2009	March 2009	April 2009	May 2009	June 2009
Hand hygiene practices (times per patient-day)	4.7	3.7	4.0	4.9	4.0	3.2	4.0	4.2	3.2	3.3	3.6	3.9	5.6
MRSA prevalence proportions (%)	19.0	12.5	12.8	17.1	21.1	14.3	8.7	11.1	11.6	11.6	7.3	16.7	10.8

MRSA, methicillin-resistant *S. aureus*.

MRSA strains were obtained from both samples (admission and discharge) in two patients (cases #3 and #6). As confirmed by MLST, one patient had strain ST8, two had ST764, and the remaining six had ST5. Since case #2 was positive for ST764 after case #3 was detected to be positive for the same strain, MRSA transmission could have occurred from case #3 to case #2. Both cases #3 and #2 were treated by the same attending doctors (Table 3). Similarly, two possible transmission events of ST5 strains occurred: from case #6 to case #5 and from case #8 to case #7. In total, three possible transmission routes were documented.

We investigated whether the nine patients who were positive for MRSA on surveillance culture underwent clinical examinations during their hospitalization period. We found that bacterial cultures were not obtained from six of these patients. MRSA infection was detected in case #2 via clinically ordered wound culture on August 11, 2008, and in case #4 via clinically ordered sputum culture on August 14, 2008, both of which were obtained prior to receiving the discharge surveillance cultures. The last patient (case #6) was already known to be a MRSA carrier because MRSA was isolated during previous admission. Overall, of the nine MRSA-positive patients confirmed by surveillance culture, six were detected prior to being identified by conventional clinically oriented examinations.

We calculated the MRSA prevalence proportion in the ward. In total, 42 patients were admitted to the ward on June 5, 2008, and eight of them were MRSA carriers; therefore, the MRSA prevalence proportion was 19.0%. Similarly, the average MRSA prevalence proportion from June 2008 to June 2009 was 13.3% (Table 4).

We calculated the number of times hand hygiene was practiced on the basis of the number of times alcohol-based hand rubs were utilized. On average, there were 4.0 instances of hand hygiene per patient-day (Table 4).

4 | DISCUSSION

Methicillin-resistant *S. aureus* transmission events were analyzed by examining surveillance cultures of 157 participants in a tertiary care general hospital in Japan. Results were compared among clinically oriented conventional cultures, MRSA prevalence rates, and hand hygiene compliance data.

Multilocus sequence typing of 11 MRSA isolates was performed to clarify the diversity and epidemiology of MRSA in this healthcare setting. The most frequently detected strain was ST5, accounting for 67% of the isolates; this is consistent with previous findings, with ST5 being the most prevalent clone in Japan.[8] Both ST5 and ST764 strains are closely related and are classified as clonal type CC5, while ST8 is classified as clonal type CC8. Most of the recently isolated healthcare-acquired MRSA (HA-MRSA) isolates in Japan were clonal types CC5 and CC8.[9] These findings suggest that all 11 MRSA isolates were prevalent HA-MRSA strains in Japan and that these patients did not acquire MRSA in community settings.

The MRSA prevalence proportion on admission was 1.9%, and all three MRSA-positive patients were previously admitted to our

hospital, suggesting that previous hospital admission was a risk factor for MRSA infection: this is in agreement with the findings of previous studies.[2,5] Our results suggest that patients who were colonized with MRSA acquired it during a previous visit to our hospital. The MRSA prevalence proportion in our hospital was 13.3%, which is similar to that reported (19.9%) at other facilities in Japan.[2] The prevalence of MRSA colonization in Japanese hospitals is much higher than that observed in American or European hospitals.[10,11]

In our study, MRSA incidence rate was 4.0/1000 patient-days. MLST revealed three possible nosocomial transmission routes of MRSA—one case with ST764 strain and two cases with ST5 strains—suggesting that patients who were negative for MRSA at the time of admission acquired nosocomial infections during their respective hospitalizations. The mean number of times hand hygiene was practiced was 4.0 times per patient-day. The hand hygiene compliance rate, which was evaluated using direct observation, was not high during this period.[12] MRSA infections could have occurred due to insufficient infection control practices. Hence, to prevent the transmission of MRSA, quality control practices should be improved by implementing multifaceted interventions, including hand hygiene, contact precautions, and universal decolonization of inpatients.[13–15]

Methicillin-resistant *S. aureus* colonization was detected on active surveillance cultures prior to being detected on clinically oriented conventional examinations in six of the nine patients, indicating that some MRSA infections were missed during clinically oriented bacterial cultures.[16] Some MRSA infections were transmitted by yet-unknown MRSA colonization.[6] Therefore, active surveillance cultures are an important strategy for elucidating MRSA transmission.

The MRSA prevalence in all patients in the ward was 13.3%, indicating that MRSA transmission pressure was high. Additionally, this proportion (13.3%) was higher than the proportion of MRSA carried within the nares of 157 patients (5.1%), suggesting that MRSA carriage did not often involve the nares. On an average, ward personal exhibited only four instances of hand hygiene per patient-day. Such a poor compliance increases the risk of nosocomial MRSA transmission. Since we only measured monthly alcohol-based hand rub utilization, we could not separately analyze hand hygiene between patients and staff. Future investigations should use direct observations to separately analyze this.

The present study has several limitations. First, only nasal swabs were used. A substantial percentage of MRSA carriers are missed if only the nares are swabbed.[17] Second, the discriminatory power of MLST may not be sufficient to determine the diversity of MRSA. Inclusion of multiplex PCR-based SCCmec typing would increase the relevance of these data. Third, MRSA strains obtained during hospitalization were not analyzed; therefore, it is not clear when MRSA colonization occurred in these patients. More frequent sampling is necessary to accurately investigate the dynamics of MRSA transmission.

In conclusion, our findings suggest that patients who were colonized with MRSA acquired it during hospitalization. This reinforces the central role of infection control practices for preventing nosocomial MRSA transmission in hospitalized individuals. The pronounced risk of transmission emanating from undetected MRSA carriers suggests that increasing the frequency of microbiological diagnosis could help reduce MRSA transmission.

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CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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