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Original Article

Active Surveillance of Methicillin-Resistant *Staphylococcus aureus* with the BD GeneOhm MRSA™ Assay in a Respiratory Ward in Nagasaki, Japan

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SUMMARY: The utility of active surveillance cultures (ASCs) in respiratory wards, that do not have an associated intensive care unit (ICU), and the usefulness of the BD GeneOhm MRSA™ system for rapid detection of methicillin-resistant *Staphylococcus aureus* (MRSA) have not been previously evaluated in Japan. ASCs using conventional culture methods and the BD GeneOhm MRSA™ assay were conducted in adult inpatients between May 11, 2009 and November 10, 2009 in a respiratory ward, without an associated ICU, in Nagasaki University Hospital. The infection and colonization rates of MRSA acquired in this respiratory ward were both investigated. A total of 159 patients were investigated. Of these, 12 (7.5%) were found positive for MRSA by the BD GeneOhm MRSA™ assay and 9 (5.7%) were found positive by a conventional culture test upon admission. All cases were MRSA-colonized cases and cross-transmission was not found to occur during hospitalization. The BD GeneOhm MRSA™ assay had a sensitivity of 100% and a specificity of 98%. ASCs in our respiratory ward revealed that MRSA was brought in from other sites in some cases, and that current infection control measures in Nagasaki University Hospital are effective. The BD GeneOhm MRSA™ assay was proven to be a useful and rapid detection tool for MRSA.

INTRODUCTION

Hospital-acquired infections are a major clinical concern and their management and control are strictly required in order to improve hospital-related mortality and morbidity rates (1). Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most prominent drug-resistant pathogens responsible for nosocomial infection and the incidence of MRSA is almost 60% of overall *S. aureus* infections in Japan (2,3).

Active surveillance cultures (ASCs) were first recommended by the Society for Healthcare Epidemiology of America for preventing nosocomial transmission of multidrug-resistant *S. aureus* and *Enterococcus* (4). Although the primary objective of ASCs is to control increasing number of MRSA infection cases, their efficacy and cost-effectiveness have been questioned. The utility of ASCs has been evaluated in many studies with different designs, evaluation methods, and interventions, and their effectiveness is still controversial (5,6). Many ASC studies of MRSA were conducted in intensive care facilities and surgery wards in Europe and the United States (6–10), since the major risk factors for MRSA infection, including recent surgical procedures, exposure to broad-spectrum antibiotics, hemodialysis, and indwelling percutaneous medical devices and catheters (11–13), are well recognized in such facilities. However, there are other medical settings, such as hospitals in which intensive care unit (ICU) is not equipped and long-term care facilities, where MRSA can be endemic. To date, no ASC studies have been conducted in common respiratory wards without ICU, or in Japanese medical facilities, even though such hospitals and wards are not less common in Japan than elsewhere.

Conventional methods for the detection and identification of MRSA are Gram staining and bacterial culture. Such methods require at least 1 day for detecting MRSA and additional days to determine drug-susceptibility. The BD GeneOhm MRSA™ assay (Nippon Becton Dickinson Co., Tokyo, Japan) has been recently developed as a rapid detection system for MRSA that gives results in 2 h (14). The BD GeneOhm MRSA™ assay

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uses multiplex real-time polymerase chain reaction (PCR) to detect the staphylococcal cassette chromosome (SCC) *mec* insertion site in MRSA and the chromosomal *orfX* of *S. aureus*. Its high performance for detecting MRSA isolates in clinical samples from Japanese patients has been reported previously (15).

In this study, we conducted the first ASCs in a respiratory ward without an associated ICU in Japan using the BD GeneOhm MRSA™ assay and compared the results obtained with those of a standard detection technique to evaluate its usefulness.

MATERIALS AND METHODS

Setting: This observational study was conducted between May 11, 2009 and November 10, 2009 in Nagasaki University Hospital (NUH). All adult inpatients (age, $\geq$16 years) in the respiratory ward were eligible for inclusion in this study. Approximately 350–500 patients, including 150–200 new patients per year, are admitted to this respiratory department ward, with the most common lung disease being cancer. There is no ICU associated with this respiratory ward. This study was approved by the ethical committee of NUH and informed consent from each patient was acquired prior to performing the ASCs.

Microbiological surveillance: Microbiological surveillance of colonization with methicillin-sensitive *S. aureus* (MSSA) and MRSA was performed. Nasal swab specimens from all registered patients were obtained within 48 h after admission, or transfer, to the respiratory ward in NUH. All specimens were plated directly on MRSA selective agar with oxacillin (Nippon Becton Dickinson) and blood agar (Nippon Becton Dickinson) and were tested by the BD GeneOhm MRSA™ assay. The BD GeneOhm MRSA™ assay was performed according to the manufacturer's instructions, and the PCR step was performed within 36 h after sample acquisition. The same nasal swab specimen was also incubated in trypticase soy broth (Nippon Becton Dickinson) as a backup culture and microbial identification was subsequently performed if the BD GeneOhm MRSA™ assay showed a positive result but no microorganisms were initially detected from the MRSA-selective agar or blood agar. The Clinical and Laboratory Standards Institute definition was used for confirmation of MRSA (16). If both conventional culture and the BD GeneOhm MRSA™ assay indicated negative results at the initial screening upon entry to the respiratory ward, subsequent screening for MRSA by culture and BD GeneOhm MRSA™ assay was continued once per week until the time of patient discharge (maximum 7 weeks from admission). When MRSA was identified within the first 48 h after respiratory ward admission, subsequent culture and BD GeneOhm MRSA™ assay in following weeks were discontinued. In cases where MRSA was identified at the initial screening of first admission with active symptoms, such as fever and elevation of inflammatory markers, including leukocyte counts, C-reactive protein, and procalcitonin, MRSA was considered as having been introduced into the respiratory ward with active infection. In the absence of such symptoms and signs, it was considered as having been introduced into the respiratory ward without active infection. When MRSA was found with active symptoms, such as fever and elevation of inflammatory markers, after the first 48 h after admission to the respiratory ward, it was considered to be a hospital-acquired infection. It was considered to be a hospital-acquired colonization if there were no such symptoms and signs.

Data analysis of infection rate: Patient information was acquired at the time of registration for this study. Sex, age, and status of admission to the respiratory ward were recorded. The route of admission, i.e., if the patient was (i) transferred from another ward of NUH, (ii) transferred from another medical facility, (iii) transferred from a nursing home facility, or (iv) admitted directly from home, was noted. History of admission to other medical facilities or nursing homes within the previous year was also recorded. Pulmonary diseases in patients with MRSA positive results, whether by PCR assay or culture methods, were recorded. The endpoints of this study were (i) infection rates of MRSA acquired in a respiratory ward without ICUs and having been introduced from other sites, (ii) colonization rates of MRSA acquired in a respiratory ward and having been introduced from other sites, and (iii) evaluation of the performance of the BD GeneOhm MRSA™ assay compared to conventional cultures as the gold standard.

Statistical analysis: Categorical variables were studied using McNemar's test. A P-value of <0.05 was considered to be statistically significant.

RESULTS

Characteristics of recruited patients: A total of 159 patients (81 men and 78 women) were enrolled in this study. The mean patient age was 66 years, with most being over 50 years. A total of 147 patients (92.4%) were directly admitted to the respiratory ward from their homes, 9 patients were transferred from other medical facilities, and 3 patients were transferred from other wards in NUH. A total of 71 patients (44.7%) had no history of prior admission to medical facilities within the previous year, while 82 patients (51.6%) had been admitted to a medical facility in the previous year (unknown for remaining 6 patients).

Positive rate of MRSA by BD GeneOhm MRSA™ assay and culture: At the initial screening, 12 (7.5%) patients had positive results when using the BD GeneOhm MRSA™ assay and 9 (5.7%) had positive results when using a conventional culture test. Table 1 shows the numbers of samples positive for MRSA, either by conventional culture or by BD GeneOhm MRSA™ assay, from the 1st to 7th weeks after admission. There were no cases in which either culture or BD GeneOhm MRSA™ assays became MRSA-positive from the 2nd week after admission until discharge (maximum 7 weeks) in patients who were MRSA-negative at the time of admission. Table 2 indicates the characteristics of patients who were MRSA-positive by the BD GeneOhm MRSA™ assay or by conventional culture at the first screening. In 3 PCR-positive cases, no evidence of MRSA was found by conventional culture (Case nos. 9, 10, and 12), and these cases were considered to be false-positives. On the other hand, there were no cases in which PCR-negative but culture-positive results were obtained. None of the MRSA-positive patients indicat-

Table 1. Numbers of nasal swab samples taken and positive results with the BD GeneOhm MRSA™ assay or conventional culture method

Timing of sampling nasal swab weeks after admission	No. of samples	No. of PCR positive	No. of culture positive	No. of patients discharged during week
0	159	12	9	80
1	67	0	0	30
2	37	0	0	15
3	22	0	0	12
4	10	0	0	5
5	5	0	0	0
6	5	0	0	4
7	1	0	0	—

Table 2. Characteristics of patients with MRSA-positive results either by BD GeneOhm MRSA™ assay or conventional culture method

Case no.	Age	Sex	PCR	Blood agar	MRSA selective agar	Subsequent identification of MRSA from TSB culture	Colonization or infection	Underlying disease	Admission from	History of admission within a year
1	56	F	positive	positive	positive	positive	colonization	lung cancer	home	positive
2	73	M	positive	positive	positive	positive	colonization	lung cancer	home	positive
3	84	M	positive	positive	positive	positive	colonization	pneumonia	other ward in NUH	negative
4	56	F	positive	positive	positive	positive	colonization	lung cancer	home	positive
5	86	M	positive	negative	negative	positive	colonization	lung cancer	home	negative
6	53	F	positive	positive	positive	positive	colonization	lung cancer	home	positive
7	75	M	positive	negative	negative	positive	colonization	COPD	home	negative
8	69	M	positive	positive	positive	positive	colonization	lung cancer	home	positive
9	66	F	positive	negative	negative	negative	colonization	NTM	home	negative
10	69	F	positive	positive	negative	negative	colonization	NTM	other medical facility	positive
11	75	M	positive	positive	positive	positive	colonization	lung cancer	home	positive
12	48	M	positive	positive	negative	negative	colonization	IPF	home	positive

TSB, trypticase soy broth; NTM, non-tuberculosis mycobacterium infection; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis.

ed active signs of infection, and therefore, they were considered as being MRSA colonized. There was only 1 MRSA-positive patient with pneumonia, who was transferred from another ward of NUH. However, the causative pathogen in this case was *Pseudomonas aeruginosa* and the patient was MRSA colonized.

Performance evaluation of the BD GeneOhm MRSA™ assay: In this study, the BD GeneOhm MRSA™ assay had a sensitivity of 100%, a specificity of 98.0%, a positive predictive value of 75.0%, and a negative predictive value of 100.0%.

DISCUSSION

S. aureus is a major causative agent in hospital-acquired pneumonia (HAP) (17,18) and almost 50% of *S. aureus* infections involve MRSA. Depending on its severity, patients with HAP may be first admitted to a respiratory ward before being transferred to an ICU. Therefore, ASCs in the primary respiratory ward, as the initial admission place, are worth evaluating. Additionally, to date, no ASC studies from respiratory wards that do not have an associated ICU have been published. Our results indicated that few cases of MRSA were introduced into the respiratory ward from other sites, but all were colonized cases and no definite cases of MRSA infection were identified. Subsequent screening until the time of patient discharge also revealed that there were no cases of cross-transmission of MRSA between patients while in the respiratory ward. Approximately 1,000 *S. aureus* isolates per year are detected from all clinical specimens in NUH, approximately 200 isolates are obtained from sputum, and almost 60% of *S. aureus* isolates are positive for MRSA. Despite this high incidence of MRSA in clinical specimens at NUH, infection control and management by the infection control team appears to be quite effective and cross-transmission of MRSA is well controlled in the respiratory ward. Additionally, patients with MRSA pneumonia are critically ill and tend to be admitted to the ICU, which in NUH is managed by a completely separate medical team to that of the respiratory ward. Further assessment of ASCs in the ICU of NUH will be required to determine if infection control across the whole of the NUH facility is appropriately effective. Furthermore, since methods of infection control in respiratory wards differ between different medical facilities, further surveillances at other facilities in Japan are also required.

The prevalence of community-acquired (CA)-MRSA is quite low in Japan, and few cases have been reported to date (19,20). In this study, we encountered 2 cases in which MRSA was introduced directly from the patient's home. These patients had neither a history of admission to other medical facilities, nor of prior usage of an-

tibiotics. Molecular analysis revealed that these isolates did not possess the type-IV SCC *mec*, or the Panton-Valentine leucocidin genes that are unique to CA-MRSA (21–23). Although no apparent transmission route was identified for these 2 cases, we have to note that such cases exist.

Several rapid tests to detect MRSA have been recently developed, and in particular new real-time quantitative PCR assays that enable its detection within 2 h could provide an alternative to conventional Gram stain or culture technique. The sensitivities of newly available commercial PCR-based assays range from 68% to 100%, and their specificities range from 64% to 99% (24–27). This is the first prospective study to evaluate the performance of the BD GeneOhm MRSA™ assay in Japan. Our data indicate that this assay possesses high sensitivity (100%) and specificity (98%) for detecting MRSA. Although we have not performed a study of its cost-effectiveness, we found the BD GeneOhm MRSA™ assay to be highly useful for detecting MRSA within a very short time.

In conclusion, it might not be necessary to screen all patients in our respiratory ward without an ICU for MRSA as long as infection control management is well-executed. The BD GeneOhm MRSA™ assay was proven to be a useful and rapid detection system for MRSA.

Conflict of interest Nippon Becton Dickinson Co., Ltd. (Tokyo, Japan) supported the study with a grant; the sponsor was not involved in the enrollment of patients, collection, analysis, interpretation of the data, or preparation of the manuscript.

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