Original Article

Countermeasures Against Methicillin-Resistant *Staphylococcus Aureus* Transmission

Non-Screening Preemptive Isolation and Cohorting of Patients With Respiratory Tract Devices

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ABSTRACT

Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) is often isolated in airways of patients with respiratory tract devices (RT-D) after endotracheal intubation or tracheostomy (RT-D patients). Transmission to other patients is frequent. In this study, we investigated the effectiveness of non-screening preemptive isolation and cohorting (NSPEIC) of RT-D patients in our surgical ward. Specifically, we assessed the possibility of preventing transmission to other patients.

Methods: We analyzed data from 433 patients: 217 RT-D patients admitted to our surgical ward and 216 postoperative patients who were hospitalized in the surgical ward during the same period, but had not undergone tracheostomy or endotracheal intubation, and had a positive MRSA result for a nonrespiratory specimen, such as a surgical site infection (SSI) (non-RT-D patients). The indications for isolation and cohorting were as follows. During Phases I (September 1987 to February 1990) and III (September 1997 to February 1999), RT-D patients underwent isolation and cohorting after testing revealed MRSA positivity; during Phases II (March 1990 to August 1997) and IV (March 1999 to May 2014), all RT-D patients underwent NSPEIC regardless of MRSA status. During Phase I, MRSA strains were defined as matching when drug-susceptibility pattern, coagulase type, enterotoxin type, toxic shock syndrome toxin-1 production, and phage type all matched. During Phases II through IV, pulsed-field gel electrophoresis was used for identification and matching.

Results: During Phase I, 93.1% (27/29) of MRSA cases had matched strains, and this period was therefore classified as "with transmission". No strains matched during Phase II. During Phase III, 85.7% (18/21) of MRSA cases had matched strains, and this period was also classified as "with transmission". Similarly, during Phase IV, 4.7% (2/43) of MRSA cases had matched strains, and this period was classified as "with transmission". Matching rates were significantly lower for Phases II and IV than for Phases I and III.

Conclusions: NSPEIC appears effective in preventing MRSA transmission among RT-D patients in a surgical ward.

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KEYWORDS: methicillin-resistant *Staphylococcus aureus* (MRSA), isolation, cohorting, colonization, pulsed-field gel electrophoresis (PFGE)

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The incidence of device-associated methicillin-resistant *Staphylococcus aureus* (MRSA) hospital infection is increasing globally.[1–7] We implemented a MRSA prevention and control strategy at our hospital in 1990, and the number of MRSA-positive patients after gastroenterological surgery decreased to ≤1% (out of all postoperative infection cases in the division).[8–15] Our strategy calls for prophylactic administration of the antibiotics cefazolin or cefotiam for 3 days, including the day of surgery,[8–15] for tracheostomy and endotracheal intubation patients (who are at high risk for MRSA reservoirs), development of a manual for treatment of infectious wounds that clarifies procedures for hand washing and glove wearing[16], and use of non-screening preemptive isolation and cohorting (NSPEIC), regardless of test results for bacterial pathogens such as MRSA. However, the benefits of isolation and cohorting (IC) in patients with respiratory tract devices (RT-D) without MRSA colonization have not been proven.[17–26] We therefore investigated the effectiveness of NSPEIC in preventing MRSA transmission from RT-D patients.

Methods

Patients, study design, and countermeasures

We retrospectively investigated data from 217 RT-D patients who had undergone either tracheostomy or ≥24-hour endotracheal intubation in any department or division and were initially positive for MRSA in our surgical unit during the period from September 1987 through May 2014. We also analyzed data from all 216 patients without respiratory tract devices (non-RT-D patients) who were hospitalized in the surgical ward during the same period and had not undergone tracheostomy or endotracheal intubation but had a positive MRSA result from a sample taken from a non-respiratory surgical site infection (SSI) (Table 1).

The study was a comprehensive retrospective study with predefined study phases. Infection and colonization were not distinguished in either group, and all MRSA-positive patients were included. We examined MRSA strains obtained from isolation and identification of bacteria in specimens that had been collected from patients and stored in skim milk at -80℃ until analysis. Microbiological assessment of airway secretions was performed at least weekly in patients under respiratory management, even if the patient had no signs of systemic infection. Similarly, for infections at non-respiratory sites, bacterial culture was conducted at least weekly when purulent discharge was macroscopically evident, even if the patient had no signs of systemic infection.

Setting

Our surgical unit primarily accommodates postoperative patients from the respiratory surgery and breast surgery departments but also includes those who have undergone gastroenterological surgery, those with postoperative infections, and those receiving chemotherapy. Palliative care for patients with recurrent malignant cancer is also provided in this ward. Five rooms with a total of 56 beds are available for postoperative acute care: 1 intensive care room with 4 beds, 7 rooms with 6 beds each, and 5 rooms used for IC (2 beds each). There are no single rooms.

Patient isolation and cohorting

Isolation is defined as placement of 1 patient in a 2-person room. Cohorting is defined as placement of 2 patients with similar conditions in a 2-person room. NSPEIC is defined as preventative performance of IC, *i.e.*, without screening for MRSA colonization in a patient. For both isolation and cohorting, healthcare workers used barrier precautions (an apron or gown, gloves, and in some cases, a mask as a physical barrier to transmission) while performing airway aspiration. For all other procedures, standard precautions were taken.

The indications for NSPEIC differed depending on the time period. During Phase I (September 1987 to February 1990), RT-D patients were managed by IC after MRSA was detected; during Phase II (March 1990 to August 1997), all RT-D patients underwent NSPEIC, regardless MRSA status; during Phase III (September 1997 to February 1999), IC was not performed for any RT-D patients; and during Phase IV (March 1999 to May 2014), all RT-D patients underwent NSPEIC, as in Phase II. The following MRSA strains were used: Phase I — 4 strains isolated from 45 RT-D patients and 5 strains from 51 non-RT-D patients; Phase II — 6 strains from 28 non-RT-D patients; Phase III — 19 strains from 43 RT-D patients and 13 strains from 66 non-RT-D patients; Phase IV — 71 strains from 93 RT-D patients and 43 strains from 71 non-RT-D patients. When more than 1 MRSA strain was isolated from a single patient, each strain was examined separately; "with transmission" was defined as one or more type matches.

Definition of MRSA transmission

MRSA transmission was defined as isolation of an identical MRSA strain in non-RT-D patients and RT-D patients

Table 1 Definitions of patient groups

RT-D patients	non-RT-D patients
With respiratory tract device ・Tracheostomy patients ・Endotracheal intubation patients	Without a respiratory tract device ・Isolated positive for MRSA from taken from SSI other than respiratory infections

*RT-D patients: patients who underwent endotracheal intubation or tracheostomy
All patients were hospitalized in a surgical ward.
RT-D: respiratory tract devices, MRSA: methicillin-resistant *Staphylococcus aureus*, SSI: surgical site infection

("with transmission"). The matching rates were calculated as follows: the denominator was the number of MRSA-positive non-RT-D patients during a given period and the numerator was the number of these patients that had MRSA strains and types that matched those isolated from RT-D patients.

Method for detecting toxin gene

Coagulase type was determined with *Staphylococcus* coagulase-typing immune serum (Denka Seiken Co. Ltd., Tokyo, Japan), using the method described by Ushioda et al.[27] Enterotoxin type was determined with a staphylococcal enterotoxin detection kit for toxins A through D (SET-RPLA; Denka Seiken Co. Ltd.), using the method of Fujikawa et al.[28] Toxic shock syndrome toxin (TSST)-1 production was determined with a TSST-1 detection kit (TST-RPLA; Denka Seiken Co. Ltd.), using the method of Fujikawa et al.[28]

Assessment of phage typing

Phage type was determined with typing phage sets (manufacturer and model unknown) and by enhancing the bacterial strain.

Typing by pulsed-field gel electrophoresis

Pulsed-field gel electrophoresis (PFGE) was performed according to the method of Ichiyama et al.[29] The sample was cultured overnight, washed, and a bacterial solution of 10^9 cells/ml was embedded in an equal amount of 1.5% low-melting agarose. After bacteriolysis in a lysostaphin and achromopeptidase solution, the sample was treated with proteinase K, after which sections of chromosomal DNA were produced with *Sma*I. These DNA sections were subjected to electrophoresis in a 1% agarose gel. The Genofield system (Atto System Co. Ltd., Tokyo, Japan) was used for PFGE.

Determination of strain similarity was based on differences in the bands obtained. If different bands were seen in 3 or fewer places, they were judged to be from the same strain. Alphabet typing was as follows: "B" indicates Phase II, "C" indicates Phase III, and "D" indicates Phase IV. They were assigned numbers in the order they were discovered.

Analysis of MRSA strains

Methods for determining a match between isolated MRSA pathogens were as follows. During Phase I, MRSA strains were defined as matching when drug-susceptibility pattern, coagulase type, enterotoxin type, TSST-1 production, and phage type all matched. During Phases II through IV, PFGE was used for identification and matching.

For PFGE determination of type, samples were analyzed only when MRSA was identified within an interval of 2 months during the same phase. If no MRSA-positive patients were simultaneously present in the unit, or if MRSA infections appeared at least 2 months apart, cross-infection was considered not to have occurred and strain typing was not conducted.

Statistical analysis

Statistical analysis was performed using JMP version 9 statistical software (SAS Institute Inc., Cary, NC, USA). Statistical significance was defined as a 2-sided p value of 0.05 or lower. Differences in dichotomous outcomes were assessed using the chi-square (χ^2) test.

Ethical condition

This study was approved by the Ethics Review Board of Toho University Ohashi Medical Center (approval number: 13-86).

Results

During Phase I, there were 45 RT-D patients, and 4 MRSA strains were isolated from 20 of these patients. During the same phase, there were 51 non-RT-D patients, and 5 MRSA strains were isolated from 29 of these patients. Among the 51 non-RT-D patients, 27 (matching rate,

Table 2 Identification and matching of MRSA strains during Phase I

Strain types	Coagulase types	Enterotoxin types	TSST-1 production	Phage types	RT-D (45 cases)	non-RT-D (51 cases)	Matched
1	Ⅱ	C	+	NT	14	17	17
2	Ⅲ	B+C	−	Ⅲ	1	7	7
3	Ⅱ	A+B	−	NT	3	1	1
4	Ⅲ	−	−	Ⅲ	2	2	2
5	Ⅱ	A+B	+	NT	0	2	0
		total			20	29	27

Matching rate: 93.1% (27/29)
Among 51 non-RT-D patients, 5 MRSA strains were isolated from 29 patients; 27 non-RT-D patients had strains that matched strains isolated from RT-D patients.
MRSA: methicillin-resistant *Staphylococcus aureus*, TSST-1: toxic shock syndrome toxin-1, RT-D: respiratory tract device, NT: non-typeable

Table 3 Identification and matching of MRSA strain types during Phase Ⅱ

PFGE types	RT-D (36 cases)	non-RT-D (28 cases)	Matched
B1	0	1	0
B2	0	2	0
B3	0	1	0
B4	0	1	0
B5	0	1	0
B6	0	1	0
total	0	7	0

Matching rate: 0% (0/7)
MRSA strains were not identified because all cases developed after an interval greater than 2 months between times of onset.
MRSA: methicillin-resistant *Staphylococcus aureus*, PFGE: pulsed-field gel electrophoresis, RT-D: respiratory tract devices

93.1%) had strains that matched a MRSA strain isolated from RT-D patients (Table 2).

During Phase II, there were 36 RT-D patients and 28 non-RT-D patients. The MRSA strains were not identified (Table 3).

During Phase III, when MRSA infection was frequent, strains from all 43 RT-D patients were analyzed by PFGE, and 19 MRSA strains were identified. There were 66 non-RT-D patients during the same period, and 13 MRSA strains were detected by PFGE analysis of strains from 21 patients with cross-infections. The 10 MRSA strains isolated from 18 of these patients were identical to those isolated from RT-D patients (85.7%) (Table 4).

During Phase IV, there were 93 RT-D patients, and PFGE was used to analyze strains from 12 of these patients. From these 12 patients, 7 MRSA strains were isolated. There were 71 non-RT-D patients during the same period, and PFGE was used to analyze strains from 43 patients. Of the 43 strains analyzed, 2 matched strains isolated from RT-D patients (4.7%) (Table 5).

The overall matching rate for Phases I and III was 90.0%, and the overall matching rate for Phases II and IV was 4.0%. During the period of NSPEIC, the concordance rate was significantly lower ($p<0.0001$).

During Phases II through IV, PFGE was used for MRSA strain typing. However, PFGE was not routinely used during Phase I, when strain typing was usually determined by analyzing coagulase type, enterotoxin type, TSST-1 production, and phage type. Because of the long duration of the study — 27 years — the methods used for patient management frequently changed. However, to the greatest extent possible we attempted to use consistent methods during the various study phases.

Discussion

The use of IC for patients with MRSA colonization is controversial. Cooper et al[17] reviewed isolation measures and found no well-designed studies that assessed the role of isolation measures alone. Nonetheless, some evidence indicates that concerted efforts including isolation can reduce MRSA, even in endemic settings. The authors concluded that current isolation measures recommended in national guidelines should continue to be used until further research establishes otherwise. A recent study[30] reported

Table 4 Identification and matching of MRSA strains during Phase Ⅲ

PFGE types	RT-D (43 cases)	non-RT-D (66 cases)	Matched
C1	1	0	0
C2	1	1	1
C3	2	2	2
C4	1	2	2
C5	1	2	2
C6	3	0	0
C7	2	0	0
C8	3	3	3
C9	4	2	2
C10	3	0	0
C11	5	2	2
C12	1	0	0
C13	3	1	1
C14	2	0	0
C15	2	0	0
C16	1	0	0
C17	5	1	1
C18	2	2	2
C19	1	0	0
C20	0	1	0
C21	0	1	0
C22	0	1	0
total	43	21	18

Matching rate: 85.7% (18/21)
Among 66 non-RT-D patients, 13 MRSA strains were isolated from 21 patients; 10 MRSA strains isolated from 18 of these patients were identical to those isolated from RT-D patients.
MRSA: methicillin-resistant *Staphylococcus aureus*, PFGE: pulsed-field gel electrophoresis, RT-D: respiratory tract devices

Table 5 Identification and matching of MRSA strains during Phase Ⅳ

PFGE type	RT-D (93 cases)	non-RT-D (71 cases)	Matched
D1	0	1	0
D2	0	1	0
D3	0	1	0
D4	0	1	0
D5	3	1	1
D6	0	1	0
D7	0	1	0
D8	0	1	0
D9	0	1	0
D10	2	1	1
D11	0	1	0
D12	0	1	0
D13	0	1	0
D14	0	1	0
D15	0	1	0
D16	0	1	0
D17	0	1	0
D18	0	1	0
D19	0	1	0
D20	0	1	0
D21	0	1	0
D22	0	1	0
D23	0	1	0
D24	0	1	0
D25	0	1	0
D26	0	1	0
D27	0	1	0
D28	0	1	0
D29	0	1	0
D30	0	1	0
D31	0	1	0
D32	0	1	0
D33	0	1	0
D34	0	1	0
D35	0	1	0
D36	0	1	0
D37	0	1	0
D38	0	1	0
D39	0	1	0
D40	0	1	0
D41	0	1	0
D42	0	1	0
D43	0	1	0
D44	1	0	0
D45	2	0	0
D46	0	0	0
D47	1	0	0
D48	2	0	0
D49	1	0	0
total	12	43	2

Matching rate: 4.7% (2/43)
Among 71 non-RT-D patients during the same time period, PFGE was used to analyze samples from 43 patients. Only 2 strains (D5, D10) from these patients were matched among the 43 strains from RT-D patients.
MRSA: methicillin-resistant *Staphylococcus aureus*, PEGE: pulsed-field gel electrophoresis, RT-D: respiratory tract devices

that isolation measures were effective in preventing and controlling MRSA in an intensive burn unit. Another study[31] found that contact precautions with single-room isolation or cohorting in an intensive care unit (ICU) were associated with a 60% reduction in MRSA acquisition. However, assessment of isolation measures in these studies only included patients in an ICU or MRSA-positive patients in a surgical unit, regardless of the site where MRSA was detected.[17, 32]

Rapid screening is performed for MRSA, and Tacconelli et al[33] reported that active screening for MRSA is more important than the type of test used. Furthermore, the authors suggested that because many countries are considering important and costly decisions, such as manda-

tory legislation for MRSA universal screening, policymakers should be informed of the limits and heterogeneity of the available evidence. However, daily active screening is expensive and therefore difficult to perform in a surgical unit.

We believe that RT-D patients in a surgical unit can become a reservoir of transmission; however, limiting isolation to known MRSA-positive patients would mean that no action would be taken until MRSA is detected. We therefore investigated if NSPEIC without MRSA screening was effective for RT-D patients who have high risks of MRSA colonization and becoming an MRSA reservoir.

In our study, MRSA rapidly increased during Phase I, and an effective prevention and control strategy was sought during this period. IC was only applied to MRSA-positive RT-D patients. During Phase II, NSPEIC was performed as part of a comprehensive study of MRSA prevention and control. During Phase III, IC was not performed because infection control measures that lacked sufficient evidence were restricted by the hospital administration. Because MRSA infection increased during Phase III, NSPEIC was resumed during Phase IV. Matching rates for MRSA strains isolated from RT-D patients and non-RT-D patients were significantly higher during Phases I (when only RT-D patients with MRSA colonization underwent IC) and III (when IC was not conducted at all) than during Phases II and IV, when NSPEIC was carried out. These findings suggest that NSPEIC was effective for RT-D patients in a general hospital unit.

A previous report suggested that NSPEIC cannot be performed unless ample hospital rooms are available.[32] However, rooms for NSPEIC do not require specialized equipment; instead, replacement of patients who are already hospitalized is needed. Thus, lack of rooms is not a justification for failing to conduct NSPEIC.

Conclusions

MRSA is often detected in the airways of RT-D patients, who often become MRSA reservoirs. Furthermore, MRSA cannot be detected when colonization occurs unless screening is frequent, which is extremely expensive. The present findings indicate that NSPEIC is an effective strategy for preventing MRSA transmission from RT-D patients in a surgical unit.

Conflicts of interest: Shinya Kusachi received payments for lectures given to Taisho Toyama Pharmaceutical Co., Ltd., Shionogi & Co., Ltd. and MSD K.K. (a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA), Daiichi Sankyo Co., Ltd. and Astellas Pharma Inc.

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