

Antiseptic Body Washes for Reducing the Transmission of Methicillin-Resistant *Staphylococcus aureus*: A Cluster Crossover Study

Patrick N. A. Harris,^{1,2,3} Bich Diep Le,¹ Paul Tambyah,^{1,2} Li Yang Hsu,^{1,2} Surinder Pada,^{1,2,4} Sophia Archuleta,^{1,2} Sharon Salmon,⁵ Amartya Mukhopadhyay,² Jasmine Dillon,⁶ Robert Ware,⁷ and Dale A. Fisher^{1,2}

¹Division of Infectious Diseases, University Medicine Cluster, National University Hospital, and ²Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore; ³UQ Centre for Clinical Research, University of Queensland, Brisbane, Australia; ⁴Department of Medicine, Alexandra Hospital, Jurong Health Services, and ⁵Nursing Administration, National University Hospital, Singapore; ⁶School of Medicine, University of Queensland, St Lucia, and ⁷School of Population Health, University of Queensland, Brisbane, Australia

Background. Limiting the spread of methicillin-resistant *Staphylococcus aureus* (MRSA) within healthcare facilities where the organism is highly endemic is a challenge. The use of topical antiseptic agents may help interrupt the transmission of MRSA and reduce the risk of clinical infection. Octenidine dihydrochloride is a topical antiseptic that exhibits in vitro efficacy against a wide variety of bacteria, including *S aureus*.

Methods. We conducted a prospective cluster crossover study to compare the use of daily octenidine body washes with soap and water in patients identified by active surveillance cultures to be MRSA-colonized, to prevent the acquisition of MRSA in patients with negative screening swabs. Five adult medical and surgical wards and 2 intensive care units were selected. The study involved an initial 6-month phase using octenidine or soap washes followed by a crossover in each ward to the alternative product. The primary and secondary outcomes were the rates of new MRSA acquisitions and MRSA clinical infections, respectively.

Results. A total of 10 936 patients admitted for ≥ 48 hours was included in the analysis. There was a small reduction in MRSA acquisition in the intervention group compared with controls (3.0% vs 3.3%), but this reduction was not significant (odds ratio, 0.89; 95% confidence interval, .72–1.11; $P = .31$). There were also no significant differences in clinical MRSA infection or incidence of MRSA bacteremia.

Conclusions. This study suggests that the targeted use of routine antiseptic washes may not in itself be adequate to reduce the transmission of MRSA in an endemic hospital setting.

Keywords. colonization; methicillin-resistant *Staphylococcus aureus*; MRSA; octenidine; topical antiseptics.

Controlling the spread of methicillin-resistant *Staphylococcus aureus* (MRSA) within healthcare facilities is important in reducing the impact of healthcare-associated infection. Patients colonized with MRSA during hospital admission serve as a reservoir for further spread and

may develop subsequent clinical infection themselves [1, 2]. Infection with MRSA carries a considerable burden in terms of patient morbidity, length of stay, additional healthcare costs, and quality of life [3, 4]. It has been estimated that in the United States, at least 80 000 people annually experience severe infections with MRSA, leading to more than 11 000 deaths [5]. Bacteremia due to MRSA is also associated with increased mortality and morbidity compared with methicillin-susceptible *S aureus* [6]. Furthermore, MRSA infection and colonization may be associated with increased rates of overall clinical disease, rather than simply replacing methicillin-susceptible strains [7]. Infection control measures to prevent MRSA transmission in hospitals usually involve the rapid identification of MRSA-colonized patients and the subsequent instigation of contact precautions, antimicrobial stewardship, and adherence to good hand

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Correspondence: Dale A. Fisher, MBBS, FRACP, National University Health System, Level 10 Tower Block, Department of Medicine, 1E Kent Ridge Road, Singapore 119228 (mdcfda@nus.edu.sg)

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hygiene practice [8–10]. Although, the efficacy of individual infection control measures are debated [11, 12], intensive multifaceted and evidence-based interventions can lead to significant reductions in healthcare-related MRSA infections [13, 14]. Measures to reduce transmission within healthcare facilities have reduced the incidence of hospital-acquired infection [15].

Several strategies have been used over the years to decolonize patients with MRSA [16] with variable efficacy, and the optimal strategy remains unclear [15]. Intranasal mupirocin has been most commonly used, and it reduces the risk of MRSA colonization [17], although the effect on subsequent infection in some studies is limited [18] unless combined with antiseptic bathing [19]. Targeted decolonization with mupirocin and chlorhexidine before surgery reduces subsequent *S aureus* surgical site infections by approximately 60% [20]. It is estimated that approximately 80% of MRSA surgical site infections are caused by the same strain colonizing patients at the time of surgery [16].

There has been debate as to whether decolonization strategies should be applied to targeted groups of patients or whether a universal approach is more effective, especially in high-risk areas such as intensive care units (ICUs). A recent cluster randomized trial including 74 ICUs and more than 74 000 patients concluded that universal decolonization resulted in significant reductions of clinical MRSA infections and bloodstream infections from any pathogen, although the positive effect on MRSA bloodstream infections was not significant [21].

Although most decolonization strategies have used chlorhexidine as the body wash component, other topical antiseptic agents may also be effective. Octenidine dihydrochloride is a positively charged bispyridinamine that exhibits antimicrobial activity against a wide range of Gram-positive and Gram-negative bacteria, including *S aureus*, and has been studied as a topical antiseptic for several decades [22]. When combined with nasal mupirocin, it is effective in reducing MRSA colonization from various clinical sites [23]. Previous clinical studies in the ICU have shown octenidine to be effective in reducing rates of MRSA acquisition, but without a significant effect on bacteremia events [24]. Although octenidine has never been compared head-to-head in a randomized trial, it seems to have less adverse effects (such as skin reactions) than chlorhexidine [25] and greater efficacy in vitro [26].

At the National University Hospital (NUH) in Singapore, an MRSA interventional bundle incorporating numerous strategies has been implemented for several years. This includes universal active surveillance (including a single swab from the nares, axilla, and groin for MRSA screening at ward entry and exit), use of prompt microbiological identification with chromogenic agar, improved adherence to infection control practices by publicly displayed feedback of MRSA acquisition, and hand hygiene compliance rates as well as isolation and cohorting of MRSA patients [14].

This study aimed to assess the utility of a topical antiseptic agent (octenidine), in addition to current strategies, to reduce MRSA colonization and subsequent clinical infection in patients admitted to hospital. Given the potential effect of decolonization strategies beyond the level of the individual patient, we used a cluster design to assign the intervention at a ward level.

METHODS

Trial Design

We undertook a prospective cluster-controlled crossover trial to compare the efficacy of targeted octenidine body washes in the reduction of MRSA colonization and subsequent infection in hospitalized patients. The study setting was NUH, a large tertiary referral hospital in Singapore. The study ran from November 2011 until January 2013.

The null hypothesis of the study was that daily octenidine body washes would be ineffective in controlling the transmission of MRSA when applied daily to those with a positive entry swab.

This study involved 5 general wards and 2 ICUs at NUH. All wards continued to undertake active surveillance by the use of entry and exit MRSA swabs for all patients and maintained contact isolation or cohorting of MRSA-positive patients, in accordance with hospital policy. The study was conducted over 2 phases. In the first phase, the intervention arm saw 1 ICU and 2 general wards commence daily octenidine washes for all patients. The other ICU and 3 general wards continued their usual practice with only soap and water wash. In ICU, the intervention arm consisted of daily washing with octenidine impregnated cloths as described below for all patients from the time of admission. In the general wards, octenidine was given to all patients during showering as a full body wash (with detail including contact time as a written instruction) or as a full body wipe during bathing with a regular plain sponge. This universal approach continued for 48 hours (when the active surveillance culture result was available) at which time patients who were identified to be MRSA-positive were continued on the daily octenidine bathing regimen and cohorted or isolated according to standard hospital procedures. Those negative for MRSA ceased octenidine washes once admission screening swab results were available and continued normal washing with soap. All rooms with MRSA-positive patients underwent terminal cleaning with a bleach-based solution including change of curtains upon patient discharge. All patients who were MRSA negative on entry had repeat swabs taken weekly until discharge. If subsequently found to be MRSA positive, these patients were transferred to the protocol with octenidine if this occurred in a ward in the intervention arm. After 6 months of the first phase of the protocol, an interim analysis was performed to assess safety. The 2 arms (intervention and control) then underwent crossover with a 2-month washout period. In all wards,

standard hospital MRSA infection control policies of active surveillance, isolation, and standard precautions were maintained. Data collection continued for all wards throughout both intervention and control phases. A summary of the study protocol is demonstrated in Figure 1, and a summary of the ward workflow is detailed in Figure 2. The requirement for full ethics approval was waived by the hospital administration because the efforts were based on standard hospital procedures, which at the time were diverse between wards. Patients were entitled to refuse any bathing procedures.

Participants

All adult patients admitted to the target wards during the study period were included. Octenidine was administered initially to all patients on wards during the intervention phase, unless they had broken skin or a known hypersensitivity to the product. Patients admitted to the ward for less than 48 hours were excluded and had no further data collected.

Methicillin-Resistant *Staphylococcus aureus* Screening Methods

All adult patients admitted to the target wards received MRSA screening swabs at entry, unless known to be previously colonized with MRSA in the preceding 12 months. All patients who remained on the ward for ≥ 48 hours also received exit MRSA screening swabs on discharge or ward transfer. If a patient was admitted for more than 48 hours but subsequently

died, exit swabs were still taken. Screening tests for MRSA were performed using sterile bacterial swabs from the anterior nares and groin, or any open wounds, inoculated onto MRSA-Select (Bio-Rad Laboratories, Redmond, WA) chromogenic media, and incubated for 24 hours, per the manufacturer's instructions. Bacterial identification was confirmed by routine laboratory methods, and susceptibility was determined according to European Committee on Antimicrobial Susceptibility Testing standards [27].

Intervention

Full body washing with octenidine lotion or sponging with octenidine mitts (Octenisan Schülke & Mayr GmbH, Norderstedt, Germany) was performed daily, with at least 1-minute contact time. A clean towel was used after each wash. There was a change of bed linen after the first wash, then changed as per usual hospital practice. A daily change and laundering of underwear and nightclothes was also required. Patients received their first octenidine wash within 24 hours of admission. The frequency of washes and use of octenidine or normal soap were recorded by the study team. Patients received written, pictorial, and verbal instructions on correct usage of the product, including the required contact time. No nasal or systemic decolonization was attempted.

Outcomes

The primary outcome measure was the number of patients newly acquiring MRSA, either via culture-confirmed asymptomatic colonization or microbiologically confirmed clinical infection. A secondary outcome measure was the effect of octenidine washes on the rate of clinical MRSA infections in patients identified as colonized at the time of entry to the ward.

Definitions

We define known MRSA colonization at admission as follows: a patient with a positive culture of nasal, groin, and axilla swab at admission screening or clinical specimen up to day 2 or known MRSA within 12 months prior to admission. There are two possible outcomes for such patients. The first is MRSA colonized, subsequent MRSA infection >48 hours after admission: MRSA cultured from sterile, operative site or other clinical specimens, with antimicrobial treatment for MRSA infection commenced. Only MRSA isolated from specimens on day 3 or more of ward admission were considered to represent an event relevant to the study intervention, with clinical isolates prior to this defined as reflecting prior colonization or infection. The second is MRSA colonized, no MRSA infection >48 hours subsequent to admission: MRSA colonized without evidence of clinical infection (as defined above) during admission to the study ward.

We define no prior MRSA colonization on admission as follows: a patient with negative admission MRSA surveillance swabs, and no prior history of MRSA in preceding 12 months.

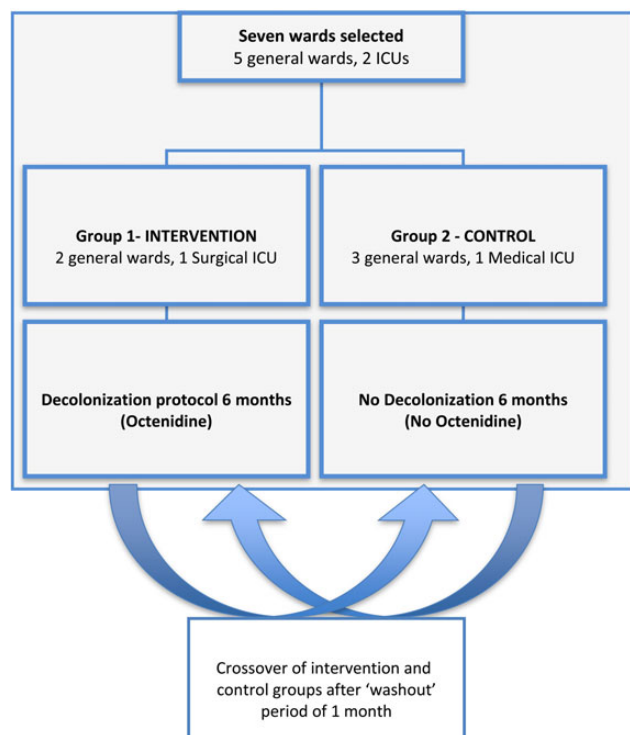


Figure 1. Study design. Abbreviation: ICU, intensive care unit.

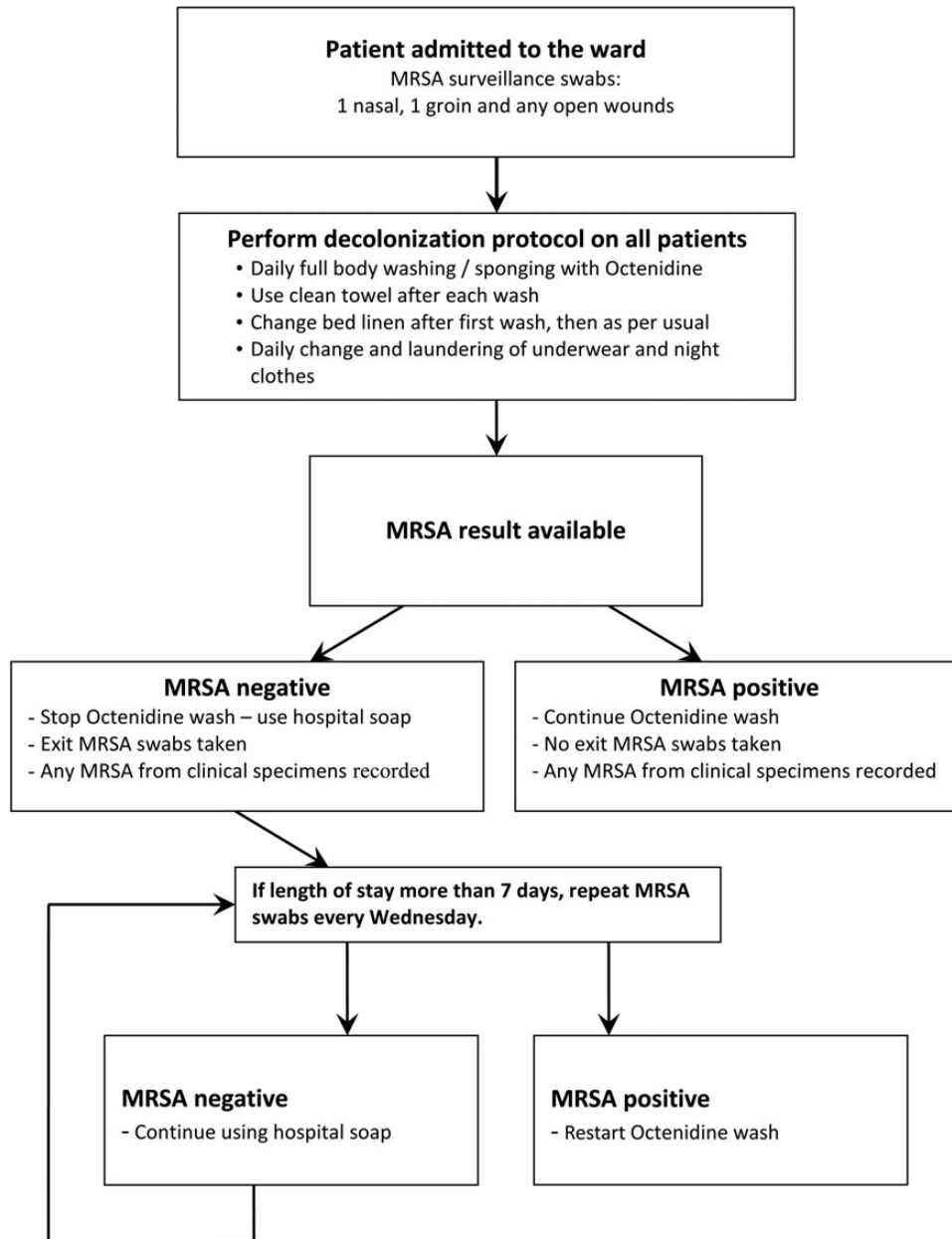


Figure 2. Study protocol and workflow. Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

There are 3 possible outcomes. The first is MRSA negative, and subsequently no MRSA colonization or infection: patients with no MRSA infection from any clinical site up to the time of discharge from the target ward *and* negative exit screening swabs. The second is MRSA negative, but subsequent MRSA infection: patients with no prior history of MRSA and negative entry screening swabs who develop clinical MRSA infection during admission to study ward (as defined above). The third is MRSA negative, subsequent MRSA colonization: patients with no prior history of MRSA and negative entry screening swabs who subsequently isolate MRSA from screening swabs or from clinical specimens without signs of infection and no

MRSA-active antimicrobial therapy being initiated by the primary team.

We define nosocomial MRSA bacteremia as follows: any positive blood culture collected >48 hours after admission with MRSA isolated. Finally, we define missing swab data as follows: patients for whom exit or entry swabs were required but were not collected. As such, the MRSA status could not be established.

Data Collection and Statistical Analysis

All patients admitted to the study wards for ≥ 48 hours during the study period had clinical, demographic, microbiological, and nursing data prospectively collected by the research team.

Table 1. Clinical and Demographic Variables for Intervention and Control Groups

Variable	Intervention Group (%)		Control Group (%)		P Value
Admissions (total)	8619	(50.5)	8433	(49.5)	
Admissions (≥48 h)	5277	(48.3)	5658	(51.7)	
Service type					<.001
Medical	3291	(62.4)	3467	(61.3)	
Surgical	901	(17.1)	1127	(19.9)	
Others	1085	(20.6)	1064	(18.8)	
Length of hospital stay (days)					
Median (25th–75th percentile)	6 (4, 12)	...	6 (3, 13)08
Length of ward stay (days)					
Median (25th–75th percentile)	5 (3, 8)	...	4 (3, 8)	...	<.001
Age (years)					
Mean (SD)	63.6 (17.6)	...	63.8 (17.6)52
Female	2308	(43.7)	2399	(42.4)	.29
Comorbid conditions					
Diabetes	1938	(37.1)	2158	(38.3)	.14
Renal disease	824	(15.8)	957	(17.0)	.06
Liver disease	471	(9.0)	327	(5.8)	<.001
Solid organ malignancy	635	(12.2)	553	(9.8)	<.001
Hematological malignancy	35	(0.7)	14	(0.3)	.001
History of previous MRSA	908	(17.2)	742	(13.1)	<.001
Surgery during admission	1500	(28.4)	1206	(21.3)	<.001
Antibiotic use during admission	3584	(67.9)	3465	(61.2)	<.001
Mobility					.08
Ambulant	3943	(74.7)	4291	(75.8)	
Assisted	616	(11.7)	694	(12.3)	
Bedbound	302	(5.7)	276	(4.9)	
Chair bound	395	(7.5)	373	(6.6)	
Unknown	21	(0.4)	24	(0.4)	
Use of intravenous line	4151	(78.7)	4160	(73.5)	<.001
Use of urinary catheter	966	(18.3)	1037	(18.3)	.39
Use of endotracheal tube	521	(9.9)	466	(8.2)	<.001
Use of percutaneous drain	1504	(28.5)	1277	(22.6)	<.001
APACHE II scores (ICU)					
(median, 25th–75th percentile)	22 (16, 27)	...	19 (14, 25)	...	<.001
Charlson scores					
(median, 25th–75th percentile)	1 (0, 3)	...	1 (0, 3)05

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; SD, standard deviation.

This included age, sex, ethnicity, admitting clinical service, hospital admission/discharge dates, ward admission/discharge dates, in-hospital mortality, MRSA status at entry and exit, all MRSA-positive clinical specimens, use of antimicrobial therapy, surgical procedures, days of octenidine/normal soap washes, bed linen changes, Acute Physiology and Chronic Health Evaluation (APACHE II) scores [28] (if admitted to ICU), and Charlson comorbidity scores [29]. All included patients were observed for the duration of their hospital admission.

Sample size calculations assumed that 4% of patients would have new MRSA infections in the control wards. To detect a

decrease in new MRSA infections of 20%, with 80% power, approximately 8500 patients needed to be enrolled in each of the control and intervention groups, with $\alpha = 0.05$. Data describing clinical and demographic variables for all patients were tabulated, with proportions expressed as percentages. Median, 25th and 75th percentiles or mean and standard deviation were calculated as appropriate for scale variables. The association between the treatment (intervention/control) and MRSA acquisition and clinical infection outcomes was investigated using univariable mixed-effects logistic regression models, with treatment included as the main effect and ward included

Table 2. Primary and Secondary Outcomes for Intervention and Control Groups^a

Outcome	Intervention N (%)		Control N (%)		OR (95% CI)	P Value
All new MRSA	156	(3.0)	187	(3.3)	0.89 (.72, 1.11)	.31
New MRSA colonization	146	(2.8)	180	(3.2)	0.87 (.69, 1.08)	.21
New MRSA clinical infections ^b	36	(0.7)	40	(0.7)	0.99 (.63, 1.55)	.96
MRSA infections in previously colonized patients ^b	26	(0.5)	34	(0.6)	0.83 (.50, 1.39)	.48
MRSA bacteremia ^b	7	(0.1)	6	(0.1)	1.25 (.42, 3.73)	.69

Abbreviations: CI, confidence interval; MRSA, methicillin-resistant *Staphylococcus aureus*; OR, odds ratio.

^a Number of admissions greater than 48 hours: control = 5658, intervention = 5277.

^b Only if MRSA isolated >48 hours after admission.

as a random intercept, to account for the possibility of correlated acquisition outcomes within each ward. Subgroup analyses of ICU and non-ICU wards were also performed. Analyses were conducted using Stata statistical software, version 12.0 (StataCorp, College Station, TX).

RESULTS

During the study period, there were a total of 17 052 admissions to the study wards over the 2 study phases, of which 10 935 (64.1%) were admitted for 48 hours or more and were therefore included in the analysis. The clinical and demographic characteristics of the 2 comparison groups are summarized in Table 1. In the intervention group, bed linen changes were performed on day one of admission in 94% of patients, and 80.2% of patients were recorded as having received octenidine washes on day 1 of admission. There were a total of 343 (3.1%) new MRSA acquisitions (either colonization or infection) overall. Of these, 187 (3.3%) occurred in the control group compared with 156 (3.0%) in the intervention group. The reduction in MRSA acquisitions seen in the octenidine arm was not significant (odds ratio [OR], 0.89; 95% confidence interval [CI], .72–1.11; $P = .31$). There were also no significant differences in MRSA clinical infections (OR, 0.99; 95% CI, .63–1.55; $P = .96$) or MRSA bacteremia events (OR, 1.25; 95% CI, .42–3.73; $P = .69$) between the

octenidine and control groups, respectively (Table 2). When stratified by ICU and non-ICU wards, there were again no significant differences in outcome observed (Tables 3 and 4). There were no reported or noted reactions to octenidine. In addition, there were no reports of patients refusing to use octenidine during the project. Failure to have a full set of MRSA screening swabs collected at entry and exit was more common in the control group (10.5% vs 14.7%; $P < .01$).

DISCUSSION

In this large quasi-experimental study, targeted use of daily octenidine body washes for MRSA-colonized patients, in addition to standard MRSA contact precautions and cohorting, was not associated with a significant reduction in MRSA transmission, MRSA infections, or MRSA bacteremia. There may be several reasons for the lack of an observed effect. During the study period, overall rates of MRSA acquisition were higher than those reported in other countries, such as the United States. By including postdischarge MRSA detection in an analysis of >1.2 million at-risk hospital admissions in California, Avery et al [30] reported an incidence of hospital-onset MRSA infection of 35.7 cases per 10 000 admissions (or half the value of 0.7% encountered in patients admitted to the nonintervention wards during our study). High background prevalence of MRSA may

Table 3. Primary and Secondary Outcomes for Intervention and Control Groups—ICU Wards Only^a

Outcome	Intervention N (%)		Control N (%)		OR (95% CI)	P Value
All new MRSA	9	(1.5)	13	(2.0)	0.76 (.32, 1.78)	.53
New MRSA colonization	8	(1.4)	13	(2.0)	0.67 (.28, 1.64)	.38
New MRSA clinical infections ^b	4	(0.7)	8	(1.2)	0.55 (.16, 1.83)	.33
MRSA infections in previously colonized patients ^b	3	(0.5)	8	(1.2)	0.41 (.11, 1.55)	.19
MRSA bacteremia ^b	0	(0.0)	1	(0.2)	n/c	

Abbreviations: CI, confidence interval; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; n/c, not calculable because no events in intervention group; OR, odds ratio.

^a Number of admissions greater than 48 hours: control = 649, intervention = 589.

^b Only if MRSA isolated >48 hours after admission.

Table 4. Primary and Secondary Outcomes for Intervention and Control Groups—Non-ICU Wards Only^a

Outcome	Intervention N (%)		Control N (%)		OR (95% CI)	P Value
All new MRSA	147	(3.1)	174	(3.5)	0.90 (.72, 1.13)	.37
New MRSA colonization	138	(2.9)	167	(3.3)	0.88 (.70, 1.11)	.28
New MRSA clinical infections ^b	32	(0.7)	32	(0.6)	1.10 (.67, 1.81)	.70
MRSA infections in previously colonized patients ^b	23	(0.5)	26	(0.5)	0.97 (.55, 1.70)	.90
MRSA bacteremia ^b	7	(0.1)	5	(0.1)	1.50 (.47, 4.72)	.49

Abbreviations: CI, confidence interval; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; OR, odds ratio.

^a Number of admissions greater than 48 hours: control = 5009, intervention = 4688.

^b Only if MRSA isolated >48 hours after admission.

make decolonization strategies less effective. Methicillin-resistant *S aureus*-colonized patients were targeted for bacterial load reduction with octenidine, whereas MRSA-negative patients were given normal soap washes. It may be that octenidine could help prevent MRSA acquisition and that use in noncolonized individuals would have been protective. The effect of decolonization strategies may be more effective in high-risk areas, during outbreaks or in targeted populations, such as the ICU. Furthermore, given that the anterior nares is the most common site for MRSA colonization, the intervention may have been more effective if combined with nasal decolonization (eg, with topical mupirocin). Nasal carriage of *S aureus* has been shown to increase the risk of nosocomial *S aureus* bacteremia 3-fold [31] and may also lead to an increased risk of surgical site infection, particularly after cardiac or orthopedic surgery [32, 33]. In one study, 86% of MRSA bloodstream infections reflected strains colonizing the patient's anterior nares [34]. A Cochrane review of 9 randomized trials concluded that decolonization with mupirocin was effective in reducing subsequent infection, although the quality of studies was limited [35]. However, nasal decolonization was not used in this study for several reasons. We aimed to test a strategy that could be up-scaled easily and applied to all hospitalized patients with limited complexity and cost. Nasal application of mupirocin to all patients would add considerably to both nursing time as well as prescribing costs. Furthermore, high-level mupirocin resistance in *S aureus* is high in Singapore and rising (11% of all isolates in 2010) [36]. Mass administration across the institution would be likely to negatively impact these figures.

Strengths of this study include the large numbers of patients included, the varied patient mix (including patients from different ward locations and clinical specialties), and the crossover cluster design. However, limitations are acknowledged. As a crossover study, we were surprised that some imbalances between the intervention and control groups were observed for key factors such as antibiotic use, use of an intravenous line, prior MRSA colonization, surgical procedures, and comorbidities such as liver disease or malignancy. Other variables were significantly different (driven by the large sample size) but

with the absolute magnitude of the difference being negligible (eg, median length of ward stay 5 vs 4 days). The lack of benefit in the intervention group may have been due to imbalance between the groups in terms of some of the known risk factors for MRSA infection and colonization, but this cannot be proven.

A proportion of patients failed to have complete screening swabs collected (both at entry and exit), and this was more frequent in the control group. As such, the rate of MRSA acquisition may have been underestimated in this group. Furthermore, additional potentially colonized body areas (such as the throat or rectum) were not sampled, so some MRSA-colonized patients may have been missed. The rate of recorded octenidine use on day 1 of admission was less than required by the protocol (80.2% were recorded as receiving octenidine on day 1 of admission); all patients during the intervention phase were supposed to have octenidine administered until MRSA screening results were available. However, the adherence rate was reasonable given the busy clinical situation, which is comparable to most routine clinical settings. The lack of intervention effect could reflect the real-world difficulties involved in the universal provision of a labor-intensive nursing intervention. Previous studies have shown significant reductions in other non-MRSA bacteremic events (eg, coagulase-negative staphylococci, Gram-negative bacilli) with the use of topical antiseptic agents. Non-MRSA culture data were not collected in this study, so beneficial effects of octenidine on other infections are also not known.

Other factors, such as adequate hand-hygiene adherence, may also affect the rate of MRSA transmission. However, NUH maintains a strong focus on infection control and prevention, and hand-hygiene compliance on the wards targeted during the study remained high at 73%.

We did not test for resistance to octenidine in patients infected or colonized with MRSA, but this phenomenon is thought to be rare. Methicillin-resistant *S aureus* exposed to octenidine at low levels for up to 3 months did not develop resistance [37], whereas chlorhexidine resistance has been described [38], mediated by mechanisms such as plasmid-borne *qacA/B* efflux pump genes [39].

CONCLUSIONS

In conclusion, this large prospective study compared 2 groups of hospitalized patients using a cluster crossover design to assess the effect of octenidine body washes on MRSA acquisition and infection. The intervention was not found to have any significant additional beneficial effect beyond our routine infection control practices. As such, in a general ward population of mixed specialties and acuity, targeted daily octenidine body wash cannot currently be recommended as an infection control intervention on the basis of our findings. The major question that remains unanswered as a result of this study is the value of universal antiseptic body washes in the general ward setting to decrease transmission, applying the treatment to those uncolonized.

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