ORIGINAL ARTICLE

Effectiveness of Chlorhexidine Wipes for the Prevention of Multidrug-Resistant Bacterial Colonization and Hospital-Acquired Infections in Intensive Care Unit Patients: A Randomized Trial in Thailand

Adhiratha Boonyasiri, MD, Peerapat Thaisiam, MD, Chairat Permpikul, MD, Tepnimitr Judaeng, MNS, Bordeesuda Suiwongsa, MSc, Napaporn Apiradeewajeset, MSc, Teerawan Fakthongphan, BNS, Sunun Suddee, BNS, Wandee Laoagtipparos, MSc, Visanu Thamlikitkul, MD

OBJECTIVE. To determine the effectiveness of daily bathing with 2% chlorhexidine-impregnated washcloths in preventing multidrug-resistant (MDR) gram-positive bacterial colonization and bloodstream infection.

METHODS. A randomized, open-label controlled trial was conducted in 4 medical intensive care units (ICUs) in Thailand from December 2013 to January 2015. Patients were randomized to receive cleansing with non-antimicrobial soap (control group) or 2% chlorhexidine-impregnated washcloths used to wipe the patient's body once daily (chlorhexidine group). Swabs were taken from nares, axilla, antecubital, groin, and perianal areas on admission and on day 3, 5, 7, and 14. The 5 outcomes were (1) favorable events (all samples negative throughout ICU admission, or initially positive samples with subsequent negative samples); (2) MDR bacteria colonization-free time; (3) hospital-acquired infection; (4) length of ICU and hospital stay; (5) adverse skin reactions.

RESULTS. A total of 481 patients were randomly assigned to the control group (241) or the chlorhexidine group (240). Favorable events at day 14 were observed in 34.8% of patients in the control group and 28.6% in the chlorhexidine group ($P = .79$). Median MDR bacteria colonization-free times were 5 days in both groups. The incidence rate of hospital-acquired infection and the length of the ICU and hospital stay did not differ significantly between groups. The incidence of adverse skin reactions in the chlorhexidine group was 2.5%.

CONCLUSION. The effectiveness of 2% chlorhexidine-impregnated washcloths for the prevention of MDR gram-negative bacteria colonization and hospital-acquired infection in adult patients in ICU was not proven.

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Healthcare-associated infections, especially those caused by multidrug-resistant (MDR) bacteria, are associated with increased morbidity, mortality, and healthcare costs and prolonged length of hospitalization.[1] The skin is a major reservoir for pathogens. Patients colonized with MDR bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), extended-spectrum beta-lactamase (ESBL)-producing gram-negative bacteria, MDR *Acinetobacter baumannii*, and MDR *Pseudomonas aeruginosa*, are at increased risk of subsequent infection.[2–6] Chlorhexidine gluconate, which has broad-spectrum activity against both gram-positive and gram-negative bacteria,[7] has been used to bathe hospitalized patients to reduce the bacterial density on the skin, especially in intensive care units (ICUs). Chlorhexidine gluconate is a positively charged molecule that binds to the negatively charged sites on the cell wall of bacteria to destabilize the cell wall and interfere with osmosis regulation, resulting in bacterial cell death.[8] Moreover, chlorhexidine gluconate can be applied directly as a solution (at a 2% concentration) or as an ingredient in soaps and gels (at a 4% concentration). Several experimental studies have reported the impact of skin cleansing with chlorhexidine gluconate at both concentrations on reducing the incidence of central line–associated bloodstream infections (CLABSI) and colonization. The results of cleansing the patient's skin with chlorhexidine gluconate revealed 23% to 50% reduction in skin colonization, particularly from VRE and MRSA. The rate of CLABSI was decreased to 0.69-4.1 cases per 1,000 catheter-days.[9–14] However, the benefit of chlorhexidine gluconate for preventing gram-negative colonization and infections has not been well documented.[15] Currently in hospitals, 2% chlorhexidine gluconate–impregnated washcloths for cleansing the patient's

Affiliation: Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

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body surface are widely available. Siriraj Hospital (Bangkok, Thailand) produced 2% chlorhexidine gluconate–impregnated washcloths in the pharmacy department to be used for hospitalized patients at risk of VRE during a VRE outbreak in 2012. Chlorhexidine gluconate–impregnated washcloths have also been used since at the hospital for cleansing patients with any documented MDR organisms. A previous prospective study at Siriraj Hospital observed that newly hospitalized patients had rates of colonization of 45.1% for ESBL-producing bacteria, 18.4% for MDR *A. baumannii*, 14.1% for MDR *P. aeruginosa*, and 9.4% for MRSA.[16] These data indicated that colonization with MDR gram-negative bacteria in hospitalized patients at Siriraj Hospital was more common than with MDR gram-positive bacteria.

The objective of this study was to determine the effectiveness of cleansing the patient's body surface with chlorhexidine gluconate–impregnated washcloths for the prevention of MDR bacterial colonization, especially gram-negative bacteria, and hospital-acquired infections in adult patients in the ICU at Siriraj Hospital.

METHODS

The study protocol was approved by the Siriraj Institutional Review Board and written informed consent was obtained from all study patients or their legal representatives.

Study Design and Participants

A randomized, open-label trial was conducted with hospitalized patients in 4 medical ICUs from December 2013 to January 2015. Adult patients aged 18 years or older who were expected to stay in the ICU longer than 48 hours and who had swab samples collected from the target sites within 48 hours were included. The patients who were allergic to chlorhexidine, had extensive skin lesions, or were unable to receive routine bathing were excluded. The eligible patients were randomly assigned to the control group or the chlorhexidine group by block randomization (1:1) for each ICU. A random sequence was generated by a computer using a block size of 4 and was concealed in sequentially numbered, sealed, opaque envelopes.

Study Procedure

The patients in the control group received routine bathing with non-antimicrobial soap and water twice daily and were allowed to use skin-care products such as moisturizer. The patients in the chlorhexidine group received 2% chlorhexidine–impregnated washcloths to wipe their body surfaces once daily in the morning and were not allowed to use other skin-care products. All baths were performed by nurses. In brief, 6 chlorhexidine-impregnated cloths were used in sequential order to wipe the body surfaces from neck to toe to avoid exposure of chlorhexidine to the mucous membranes of the eyes, ears and mouth. If the patient received any procedure that might remove chlorhexidine from the body surfaces, such as a tepid sponge, the same procedures for wiping the body with chlorhexidine-impregnated cloths were repeated. The chlorhexidine-impregnated washcloths were made by the pharmacy department of Siriraj Hospital. Our chlorhexidine-impregnated washcloths were analyzed for chlorhexidine gluconate concentration by high-performance liquid chromatography method. We performed in vitro microbiologic activity tests of locally produced chlorhexidine-impregnated washcloths every few weeks up to 6 months and we found that they still contained similar in vitro microbiologic activity up to 6 months.[17–19] Hand hygiene adherence of healthcare personnel in all ICUs was greater than 70% throughout the study period. There were no other interventions introduced during the study. The adherence to the intervention was more than 95% during the study period. The swab samples were collected from nares, axilla, antecubital, groin, and perianal areas from each enrolled patient within 48 hours of admission to the ICU and on days 3, 5, 7, and 14, or until the patient left the ICU. The swabs were sent to the infectious diseases laboratory for determination of target MDR bacteria—that is, MRSA, VRE, ESBL-producing *Klebsiella pneumoniae*, ESBL-producing *Escherichia coli*, MDR *A. baumannii*, and MDR *P. aeruginosa*. Preliminary isolation of ESBL-producing gram-negative bacteria was performed using ceftriaxone (4 μg/mL)–supplemented MacConkey agar. Confirmation of ESBL-producing gram-negative isolates was obtained by the double disk diffusion method. Preliminary isolation of MRSA was performed using mannitol salt agar. Preliminary isolation of VRE was performed using vancomycin (6 μg/mL)–supplemented enterococcal agar. Antibiotic susceptibility of the isolated MDR bacteria was determined by a disc diffusion assay. MDR *A. baumannii* and MDR *P. aeruginosa* were defined as the isolates that were resistant to at least 3 of 5 classes of systemic antibiotics—that is, cephalosporins, beta-lactam/beta-lactamase inhibitors, carbapenems, aminoglycosides, and fluoroquinolones.

Outcome Assessment

The study outcomes were a favorable event; target MDR bacteria colonization-free time; hospital-acquired infections—that is, ventilator-associated pneumonia (VAP), CLABSI, and catheter-associated urinary tract infection (CAUTI); length of ICU stay and length of hospital stay; and adverse skin reactions. A favorable event was defined as (1) the swab samples collected from all the aforementioned sites were persistently negative for target MDR throughout ICU admission, or (2) the initial swab samples showed the presence of any target MDR bacteria but the samples collected thereafter were negative for target MDR bacteria. The target MDR bacteria colonization-free time was defined as the time for which a favorable event was maintained. Hospital-acquired infections were determined by trained infection control personnel in accordance with criteria defined by the Centers for Disease Control and Prevention National Healthcare Safety Network. The length of ICU stay and hospital stay were recorded.

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Each patient was monitored for skin reactions to the study intervention by the ward nurses. Skin reactions were graded as (1) faint erythematous macule or dry skin, (2) erythematous papule, (3) skin blisters, or (4) skin ulceration. Isolation and identification of the target MDR bacteria was performed by the personnel in the infectious disease laboratory who were unaware of the patient groupings.

Sample Size Estimation and Statistical Analyses

A previous prospective study at Siriraj Hospital found that 58% of newly hospitalized patients were colonized with MDR bacteria within 48 hours of admission. To detect a 25% reduction in target MDR bacterial colonization in the ICU patients who received chlorhexidine wipes over 14 days, 236 patients per group were needed with a power of 80% and a 2-sided type I error of 5%. All analyses were based on a modified intention-to-treat analysis. The χ^2 test or Fisher exact test was used to compare the proportions of categorical variables between the groups. The unpaired *t* test or Mann-Whitney test, as appropriate, was used to compare continuous variables. Survival analysis was used to compare favorable events between the 2 groups. $P < .05$ was considered significant. The PASW statistical software, version 18.0 (IBM), was used for data analyses.

RESULTS

In total, 997 patients who were admitted to 4 ICUs were screened for eligibility to the study as shown in Figure 1. Of these, 516 patients were not eligible; 327 of them had stayed in the ICU less than 48 hours. The remaining 481 patients were randomized and followed up throughout their ICU admissions. Nineteen patients died suddenly, 35 patients were transferred to general medical wards after admission, and microbiologic data were not available for 39 patients. Therefore, 388 patients were suitable for outcome analysis. The baseline characteristics of the patients in both groups are shown in Table 1. The MDR bacterial colonization at enrollment, preexisting conditions, and causes of ICU admission were similar in both groups.

The prevalence of target MDR bacteria colonization at each site of the patients at enrollment is shown in Table 2. ESBL-producing *E. coli*, ESBL-producing *K. pneumoniae*, MDR *P. aeruginosa*, and MDR *A. baumannii* were mainly isolated from perianal swabs from 35.2% to 38.6% of the patients in both groups. MRSA colonization was detected in 2.1% of the nasal swabs taken from the patients in the chlorhexidine group. VRE was isolated in only approximately 1% of the samples collected from the groin and perianal areas. The prevalence of target MDR bacterial colonization at each site of the patients at enrollment did not differ between the 2 groups.

The prevalence of target MDR bacteria colonization by site and time after enrollment were determined. MDR *A. baumannii* and ESBL-producing *K. pneumoniae* colonizing the nares, axilla, and cubital areas increased after ICU admission. Groin and perianal areas were initially colonized with ESBL-producing *E. coli* but the colonizing organisms after

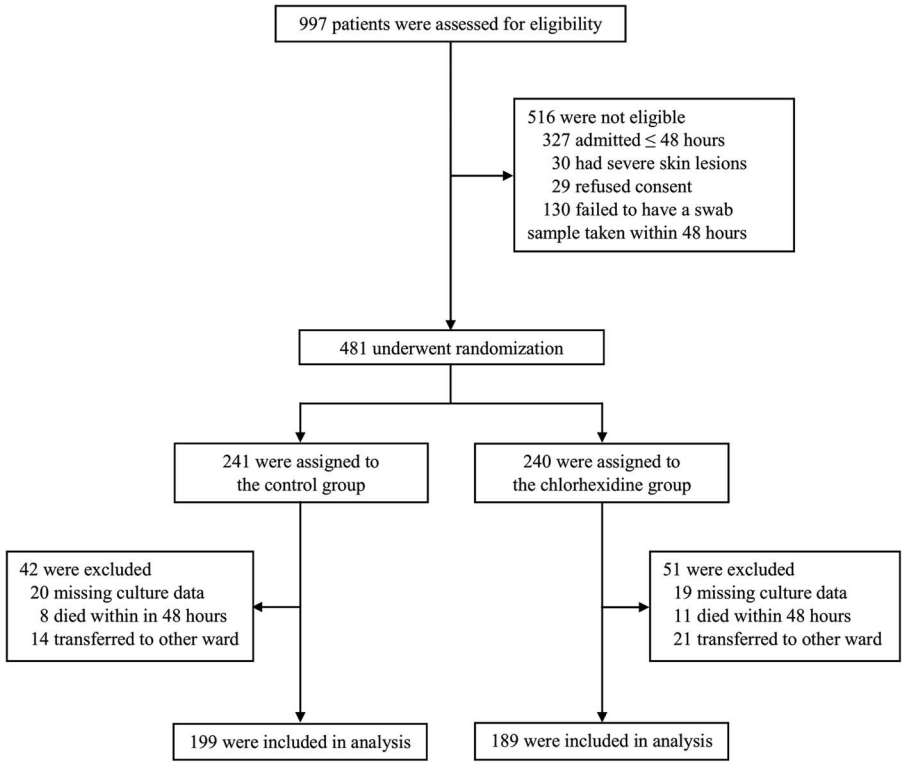

FIGURE 1. Flow chart of the patients in study of effectiveness of chlorhexidine wipes.

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TABLE 1. Baseline Characteristics of the Patients in Study of Effectiveness of Chlorhexidine Wipes

Characteristic	Control group (n = 199)	Chlorhexidine group (n = 189)	*P* value
Age, years			.97
Mean ± SD	64.0 ± 17.2	63.6 ±17.9	
Median (range)	67 (23-97)	65 (19-96)	
Male sex, no. (%)	92 (46.2)	84 (44.4)	.80
Ward, no. (%)			.64
Medical ICU 1	50 (25.1)	56 (29.6)	
Medical ICU 2	50 (25.1)	48 (25.4)	
Respiratory care unit	47 (23.6)	36 (19.0)	
Cardiac care unit	52 (26.1)	49 (25.9)	
Preexisting conditions, no. (%)			
Diabetes mellitus	65 (32.7)	52 (27.5)	.32
Hypertension	109 (54.8)	104 (55.0)	>.99
Dyslipidemia	63 (31.7)	52 (27.5)	.43
Chronic kidney disease	42 (21.1)	39 (20.6)	>.99
Chronic kidney disease requiring long-term dialysis	17 (8.5)	14 (7.4)	.82
Chronic obstructive pulmonary disease	17 (8.5)	9 (4.8)	.20
Ischemic heart disease	31 (15.6)	39 (20.6)	.24
Cancer	31 (15.6)	28 (14.8)	.95
Cause of ICU admission, no. (%)			
Pneumonia	61 (30.7)	71 (37.6)	.18
Acute coronary syndrome	25 (12.6)	20 (10.6)	.65
Congestive heart failure	14 (7.0)	17 (9.0)	.60
Urinary tract infection	13 (6.5)	10 (5.3)	.76
Primary bacteremia	11 (5.5)	4 (2.1)	.14

NOTE. ICU, intensive care unit.

TABLE 2. Prevalence of Target MDR Bacterial Colonization at Enrollment

	Control group (N = 199)					Chlorhexidine group (N = 189)				
Target MDR bacteria	Nares (N = 199)	Axilla (N = 199)	Cubital (N = 199)	Groin (N = 199)	Perianal (N = 199)	Nares (N = 189)	Axilla (N = 189)	Cubital (N = 189)	Groin (N = 189)	Perianal (N = 189)
ESBL-producing *E. coli*	3 (1.5%)	6 (3.0%)	2 (1.0%)	33 (16.6%)	70 (35.2%)	6 (3.2%)	6 (3.2%)	4 (2.1%)	37 (19.6%)	73 (38.6%)
ESBL-producing *K. pneumoniae*	4 (2.0%)	7 (3.5%)	1 (0.5%)	15 (7.5%)	26 (13.1%)	6 (3.2%)	1 (0.5%)	2 (1.1%)	15 (7.9%)	17 (9.0%)
MDR *P. aeruginosa*	4 (2.0%)	5 (2.5%)	5 (2.5%)	8 (4.0%)	9 (4.5%)	4 (2.1%)	4 (2.1%)	0	6 (3.2%)	3 (1.6%)
MDR *A. baumannii*	15 (7.5%)	17 (8.5%)	9 (4.5%)	20 (10.1%)	25 (12.6%)	13 (6.9%)	12 (6.3%)	2 (1.1%)	14 (7.4%)	13 (6.9%)
MRSA	0	0	0	4 (2.0%)	4 (2.0%)	4 (2.1%)	2 (1.1%)	0	4 (2.1%)	3 (1.6%)
VRE	0	0	1 (0.5%)	2 (1.0%)	2 (1.0%)	2 (1.1%)	0	0	0	2 (1.1%)

NOTE. *A. baumannii, Acinetobacter baumannii*; *E. coli, Escherichia coli*; ESBL, extended-spectrum beta-lactamase; *K. pneumoniae, Klebsiella pneumoniae*; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; *P. aeruginosa, Pseudomonas aeruginosa*; VRE, vancomycin-resistant enterococci.

ICU admission were predominantly MDR *A. baumannii*. The overall prevalence of ESBL-producing *E. coli* colonization tended to decrease over time whereas the prevalence of MDR *A. baumannii* colonization tended to increase over time during ICU admission as shown in Figure 2. The overall prevalence of carbapenem-resistant Enterobacteriaceae at any site or time after enrollment did not differ significantly between the control and chlorhexidine groups (4.0% and 4.8%, respectively).

The number of favorable events observed on day 14 in the control group (34.8%) did not differ significantly from the chlorhexidine group (28.6%), and the incidence rates of VAP, CLABSI, and CAUTI were similar in both groups as shown in Table 3. The subgroup analyses between no-MDR and MDR bacterial colonization at enrollment resulted in higher favorable events in the no-MDR bacterial colonization group, as shown in Table 3. MDR bacterial colonization at enrollment was the risk factor of unfavorable outcome in Table 4. The CLABSI rate was the highest among hospital-acquired infections at 7.7 and 9.9 per 1,000 catheter-days in the control and chlorhexidine groups, respectively. The median lengths of

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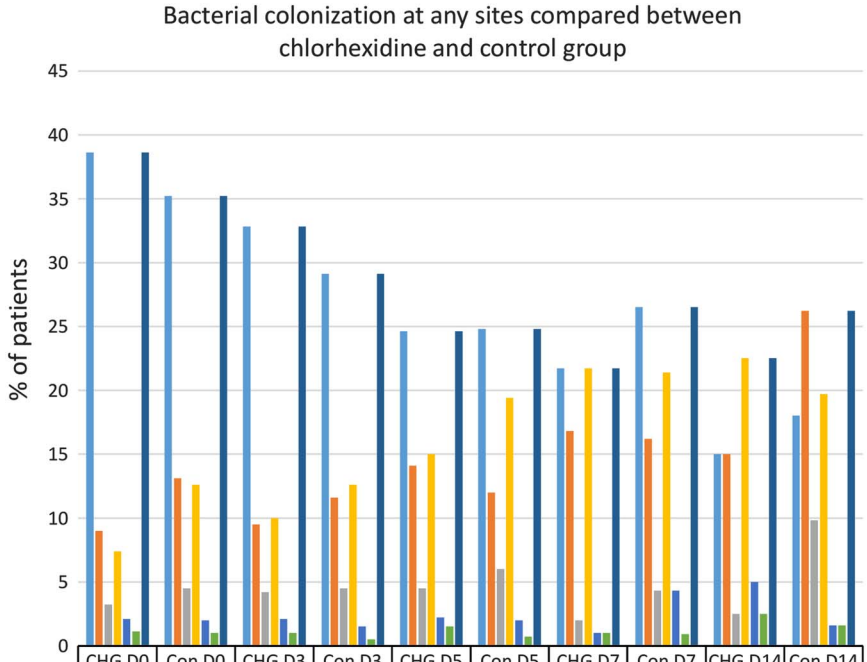

	CHG D0 (n=189)	Con D0 (n=199)	CHG D3 (n=189)	Con D3 (n=199)	CHG D5 (n=134)	Con D5 (n=149)	CHG D7 (n=101)	Con D7 (n=117)	CHG D14 (n=40)	Con D14 (n=61)
ESBL-E.coli (n%)	38.6	35.2	32.8	29.1	24.6	24.8	21.7	26.5	15	18
ESBL-K.pneumoniae (n%)	9	13.1	9.5	11.6	14.1	12	16.8	16.2	15	26.2
MDR P.aeruginosa (n%)	3.2	4.5	4.2	4.5	4.5	6	2	4.3	2.5	9.8
MDR A.baumannii (n%)	7.4	12.6	10	12.6	15	19.4	21.7	21.4	22.5	19.7
MRSA (n%)	2.1	2	2.1	1.5	2.2	2	1	4.3	5	1.6
VRE (n%)	1.1	1	1	0.5	1.5	0.7	1	0.9	2.5	1.6
Any Bacteria (n%)	38.6	35.2	32.8	29.1	24.6	24.8	21.7	26.5	22.5	26.2

FIGURE 2. The numbers of patients for which target multidrug-resistant (MDR) bacterial colonization was detected at any site in the chlorhexidine and control groups. *A. baumannii, Acinetobacter baumannii*; CHG, chlorhexidine gluconate; Con, control; D0, day 0; D3, day 3; D5, day 5; D7, day 7; D14, day 14; *E. coli, Escherichia coli*; ESBL, extended-spectrum beta-lactamase; *K. pneumoniae, Klebsiella pneumoniae*; MRSA, methicillin-resistant *Staphylococcus aureus*; *P. aeruginosa, Pseudomonas aeruginosa*; VRE, vancomycin-resistant enterococci.

stay in the ICUs and in the hospital did not differ significantly between the control and chlorhexidine groups, 10 vs 9 days and 23 vs 21 days, respectively, as shown in Table 3. The etiologic agents of hospital-acquired infections are shown in Table 5. Most of the infections were caused by gram-negative bacteria—that is, 64% in the control group and 69% in the chlorhexidine group.

The overall incidence of adverse skin reactions in the patients who received chlorhexidine-gluconate wipes was 2.5%. All skin reactions were mild (grade 1 and 2) and all of the patients who had skin reactions received routine bathing with non-antimicrobial soap instead.

DISCUSSION

This randomized controlled trial showed that once-daily cleansing of ICU patients with no-rinse 2% chlorhexidine–impregnated washcloths did not prevent or delay MDR gram-negative bacteria colonization compared with routine twice-daily cleansing with non-antimicrobial soap. Our findings differed from the results of 4 previous observational and experimental studies that revealed the benefit of 2% chlorhexidine–impregnated washcloths in reducing MDR bacteria colonization, particularly for VRE and MRSA.[14,20–23] The discrepancy could be due to differences in ICU structure, facilities, and the types of colonizing bacteria. The major colonizing organisms in ICU patients in the present study were gram-negative bacteria including ESBL-producing *E. coli*, ESBL-producing *K. pneumoniae*, MDR *P. aeruginosa*, and MDR *A. baumannii*, whereas the major colonizing organisms in the previous studies were MRSA and VRE, with no data reported on gram-negative bacteria. However, several previous studies on using chlorhexidine bathing in ICU patients did not observe any reduction in the colonization of patients with *Acinetobacter* spp. and Enterobacteriaceae.[22,24] Previous studies on the in vitro activity of chlorhexidine against various bacteria found that the minimum inhibitory concentration of chlorhexidine for *P. aeruginosa* (5–60 μg/mL)

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TABLE 3. Outcomes in Study of Effectiveness of Chlorhexidine Wipes

Characteristic	Control group (n = 199)	Chlorhexidine group (n = 189)	*P* value
Day 0 (Baseline at enrollment)			.10
No MDR bacterial colonization	84/199 (42.2)	64/189 (33.9)	
MDR bacterial colonization	115/199 (57.8)	125/189 (66.1)	
Favorable events, no. (%)			
Day 3	72/165 (43.6)	60/166 (36.1)	.20
No MDR bacterial colonization at enrollment	45/65 (69.2)	41/55 (74.5)	.66
MDR bacterial colonization at enrollment	27/100 (27.0)	19/111 (17.1)	.12
Day 5	46/121 (38.0)	46/119 (38.7)	>.99
No MDR bacterial colonization at enrollment	28/48 (58.3)	25/41 (61.0)	.97
MDR bacterial colonization at enrollment	18/73 (24.7)	21/78 (26.9)	.90
Day 7	35/86 (4.7)	33/95 (34.7)	.50
No MDR bacterial colonization at enrollment	21/34 (61.8)	17/33 (51.5)	.55
MDR bacterial colonization at enrollment	14/52 (26.9)	16/62 (25.8)	>.99
Day 14	16/46 (34.8)	10/35 (28.6)	.72
No MDR bacterial colonization at enrollment	9/20 (45.0)	7/12 (58.3)	.72
MDR bacterial colonization at enrollment	7/26 (26.9)	3/23 (13.0)	.40
Ventilator-associated pneumonia			.69
No. of infections (%)	10 (5.0)	11 (5.8)	
Incidence rate (no. per 1,000 ventilator-days)	6.5	6.1	
Central line–associated blood stream infection			.74
No. of infections (%)	4 (2.0)	2 (1.1)	
Incidence rate (no. per 1,000 catheter-days)	7.8	9.9	
Catheter-associated urinary tract infection			.17
No. of infections (%)	14 (7.0)	16 (8.5)	
Incidence rate (no. per 1,000 catheter-days)	5.7	6.0	
Length of stay in ICU, days			.42
Mean	16.5	14.6	
Median (range)	10 (3-136)	9 (3-212)	
Length of stay in hospital, days			
Mean	35.9	31.8	
Median (range)	23 (4-307)	21 (4-335)	

NOTE. ICU, intensive care unit; MDR, multidrug-resistant.

TABLE 4. Factors Associated With Outcomes in Study of Effectiveness of Chlorhexidine Wipes

Outcome measurement	Variable	Crude odds ratio (95% CI)	*P* value	Adjusted odds ratio[a] (95% CI)	*P* value
Day 3	CHG	1.21 (0.82-1.79)[b]	.35	1.22 (0.77-1.93)	.40
	MDR	10.36 (6.51-16.49)[c]	<.001	10.37 (6.51-16.51)	<.001
Day 5	CHG	1.13 (0.71-1.81)[b]	.60	1.11 (0.67-1.83)	.68
	MDR	4.27 (2.59-7.06)[c]	<.001	4.27 (2.58-7.05)	<.001
Day 7	CHG	1.38 (0.80-2.37)[b]	.25	1.42 (0.81-2.50)	.22
	MDR	3.25 (1.85-5.73)[c]	<.001	3.29 (1.86-5.81)	<.001
Day 14	CHG	1.24 (0.52-2.94)[b]	.63	1.21 (0.49-2.98)	.68
	MDR	3.72 (1.52-9.06)[c]	.004	3.70 (1.52-9.04)	.004

NOTE. CHG, chlorhexidine gluconate; MDR, multidrug-resistant.
[a]Adjusted for CHG and MDR.
[b]Compared with soap groups.
[c]Compared with no MDR at enrollment.

was higher than that for *S. aureus* (0.5–1 μg/mL) and chlorhexidine-resistant *A. baumannii* and *E. coli* owing to a drug efflux pump.[25,26] In subgroup analyses, MDR bacterial colonization at enrollment had significantly fewer favorable events compared with no-MDR bacterial colonization at enrollment, and the MDR bacterial colonization was the major risk factor of unfavorable outcomes. The reason might be that MDR gram-negative bacteria isolated from the ICU patients in this study were resistant to chlorhexidine. However, this postulation was not certain because the susceptibility

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TABLE 5. Etiologic Agents of Hospital-Acquired Infections in Study of Effectiveness of Chlorhexidine Wipes

Characteristic	Control group (n = 199)	Chlorhexidine group (n = 189)	*P* value
Ventilator-associated pneumonia, no. (%)			
E. coli	1 (0.5)	1 (0.5)	> .99
K. pneumoniae	1 (0.5)	0 (0)	> .99
P. aeruginosa	1 (0.5)	1 (0.5)	> .99
A. baumannii	6 (3.0)	8 (4.2)	.71
S. maltophilia	0 (0)	1 (0.5)	.49
C. albicans	1 (0.5)	0 (0)	> .99
Total of ventilator-associated pneumonia, no. (%)	10 (5.0)	11 (5.8)	.82
Central line–associated bloodstream infection, no. (%)			
K. pneumoniae	1 (0.5)	1 (0.5)	> .99
P. aeruginosa	1 (0.5)	0 (0)	> .99
A. baumannii	1 (0.5)	0 (0)	> .99
MRSA	0 (0)	1 (0.5)	.49
C. albicans	1 (0.5)	0 (0)	> .99
Total of central line–associated bloodstream infection, no. (%)	4 (2.0)	2 (1.1)	.69
Catheter-associated urinary tract infection, no. (%)			
E. coli	1 (0.5)	4 (2.1)	.21
K. pneumoniae	4 (2.0)	0 (0)	.12
Enterobacter spp.	1 (0.5)	0 (0)	> .99
P. aeruginosa	0 (0)	2 (1.1)	.24
A. baumannii	0 (0)	2 (1.1)	.24
MRSA	0 (0)	1 (0.5)	.49
MRCNS	1 (0.5)	0 (0)	> .99
Enterococcus spp.	6 (3.0)	4 (2.1)	.75
C. albicans	1 (0.5)	3 (1.6)	.36
Total of catheter-associated urinary tract infection, no. (%)	14 (7.0)	16 (8.5)	.71

NOTE. *A. baumannii*, *Acinetobacter baumannii*; *C. albicans*, *Candida albicans*; *E. coli*, *Escherichia coli*; *K. pneumoniae*, *Klebsiella pneumoniae*; MRCNS, methicillin-resistant coagulase-negative staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*; *S. maltophilia*, *Stenotrophomonas maltophilia*; *P. aeruginosa*, *Pseudomonas aeruginosa*.

to chlorhexidine of these MDR gram-negative bacterial isolates was not determined. Other possible reasons for the failure of 2% chlorhexidine–impregnated washcloths in reducing MDR bacteria colonization in the present study may be (1) the concentration of chlorhexidine was too low, (2) once-daily cleansing of ICU patients with no-rinse 2% chlorhexidine–impregnated washcloths was insufficient, (3) additional infection control practices were inadequate, or (4) most of the MDR gram-negative bacteria colonization was found in the swab samples collected from the perianal area, which should be related to gastrointestinal colonization with MDR bacteria that was not affected by chlorhexidine bathing. Several studies have demonstrated that once-daily bathing and 4-times-daily oral care with 2% chlorhexidine aqueous solution, environmental cleaning, contact precautions, cohorting of patients, and antibiotic stewardship collectively could limit colonization and infection with extremely drug-resistant *A. baumannii* and carbapenemase-producing *K. pneumoniae* in medical ICUs and in long-term acute care hospitals.[27,28] Therefore, no-rinse 2% chlorhexidine–impregnated washcloths alone may be inadequate to control MDR gram-negative bacteria colonization in ICU patients.

The present study also revealed that the incidence rate of hospital-acquired infections, especially VAP and CAUTI, did not differ significantly between the 2 groups. This observation was similar to previous studies.[9,13,22,27,29,30] However, Martinez-Resendez et al[31] reported the benefit of daily use of 2% chlorhexidine–impregnated wipes and hair washing with no-rinse 0.12% chlorhexidine foam shampoo for the prevention of VAP and CAUTI but provided no data on the etiologic agents of such infections. Recently, there was a meta-analysis that found daily bathing with chlorhexidine would decrease the incidence risk of VAP. The authors of the meta-analysis hypothesized that daily chlorhexidine bathing plays a great role in decreasing the colonization pressure, which is a momentous risk factor for hospital-acquired infections and in reducing the risk of subsequent infection from manipulation of devices associated with the patient.[32] The effect of chlorhexidine on the incidence rate of CLABSI varied. Five studies demonstrated that chlorhexidine bathing reduced the incidence of CLABSI mainly caused by gram-positive bacteria[9,11–13,22] whereas the present study did not show such a benefit. A recent randomized controlled trial also revealed that hospital-acquired infections including CLABSI, VAP, CAUTI, and *Clostridium difficile* infection did not significantly differ

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between the chlorhexidine group and the control group; however, there was no microbiologic data for hospital-acquired infections.[30] The incidence of adverse skin reactions in this study was low and skin reactions that did occur were mild, similar to a previous study.[11]

There were several limitations to the current study. Many patients stayed in the ICU less than 48 hours and many patients were discharged from the ICU before 14 days. Therefore, the number of the subjects with outcomes on day 14 was limited. Moreover, we did not determine whether the MDR gram-negative organisms were resistant to chlorhexidine. The strengths of the current study, however, were the large number of enrolled patients, the modified intention-to-treat analysis, and the inclusion of a control non-antimicrobial soap group. In addition, the prevalence of ESBL-producing *E. coli* colonization at the time of admission was high in this population because many patients were transferred from general wards and from other hospitals after hospitalizations for a while. Generalizability of study results to populations with lower prevalence may be limited. Furthermore, this study was likely underpowered to detect a difference in rates of hospital-acquired infections. Although the present randomized controlled trial does not show any benefit of once-daily cleansing of ICU patients with no-rinse 2% chlorhexidine–impregnated washcloths in preventing or delaying MDR bacterial colonization compared with routine twice-daily cleansing with non-antimicrobial soap, the time spent using the washcloths was much less than with the soap. Besides, the cost of washcloths was low. Most of the healthcare personnel who used no-rinse 2% chlorhexidine–impregnated washcloths and the patients who received this treatment were satisfied with this cleansing method. Therefore, no-rinse 2% chlorhexidine–impregnated washcloths can be considered an alternative method of cleansing the body surface of ICU patients.

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Address correspondence to Adhiratha Boonyasiri, MD, Faculty of Medicine Siriraj Hospital, Mahidol University Bangkok, 10700 Thailand (nonghor@yahoo.com).

REFERENCES

1. Pumart P, Phodha T, Thamlikitkul V, Riewpaiboon A, Prakongsai P, Limwattananon S. Health and economic impacts of antimicrobial resistant infections in Thailand: a preliminary study. *J Health Syst Res* 2012;6:352–360.
2. Chavers LS, Moser SA, Benjamin WH, et al. Vancomycin-resistant enterococci: 15 years and counting. *J Hosp Infect* 2003;53:159–171.
3. Safdar N, Bradley EA. The risk of infection after nasal colonization with *Staphylococcus aureus*. *Am J Med* 2008;121:310–315.
4. Ren Y, Ma G, Peng L, Ren Y, Zhang F. Active screening of multidrug resistant bacteria effectively prevent and control the potential infections. *Cell Biochem Biophys* 2015;71:1235–1238.
5. Latibeaudiere R, Rosa R, Laowansiri P, Arheart K, Namias N, Munoz-Price LS. Surveillance cultures growing carbapenem-resistant *Acinetobacter baumannii* predict the development of clinical infections: a retrospective cohort study. *Clin Infect Dis* 2015;60:415–422.
6. Kassakian SZ, Mermel LA, Jefferson JA, Parenteau SL, Machan JT. Impact of chlorhexidine bathing on hospital-acquired infections among general medical patients. *Infect Control Hosp Epidemiol* 2011;32:238–243.
7. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. *Am J Infect Control* 1999;27:97–132.
8. Puig Silla M, Montiel Company JM, Almerich Silla JM. Use of chlorhexidine varnishes in preventing and treating periodontal disease: a review of the literature. *Med Oral Patol Oral Cir Bucal* 2008;13:E257–E260.
9. Bleasdale SC, Trick WE, Gonzalez IM, Lyles RD, Hayden MK, Weinstein RA. Effectiveness of chlorhexidine bathing to reduce catheter-associated bloodstream infections in medical intensive care unit patients. *Arch Intern Med* 2007;167:2073–2079.
10. Climo MW, Sepkowitz KA, Zuccotti G, et al. The effect of daily bathing with chlorhexidine on the acquisition of methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, and healthcare-associated bloodstream infections: results of a quasi-experimental multicenter trial. *Crit Care Med* 2009;37:1858–1865.
11. Climo MW, Yokoe DS, Warren DK, et al. Effect of daily chlorhexidine bathing on hospital-acquired infection. *N Engl J Med* 2013;368:533–542.
12. Munoz-Price LS, Hota B, Stemer A, Weinstein RA. Prevention of bloodstream infections by use of daily chlorhexidine baths for patients at a long-term acute care hospital. *Infect Control Hosp Epidemiol* 2009;30:1031–1035.
13. Popovich KJ, Hota B, Hayes R, Weinstein RA, Hayden MK. Effectiveness of routine patient cleansing with chlorhexidine gluconate for infection prevention in the medical intensive care unit. *Infect Control Hosp Epidemiol* 2009;30:959–963.
14. Vernon MO, Hayden MK, Trick WE, Hayes RA, Blom DW, Weinstein RA. Chlorhexidine gluconate to cleanse patients in a medical intensive care unit: the effectiveness of source control to reduce the bioburden of vancomycin-resistant enterococci. *Arch Intern Med* 2006;166:306–312.
15. Derde LP, Dautzenberg MJ, Bonten MJ. Chlorhexidine body washing to control antimicrobial-resistant bacteria in intensive care units: a systematic review. *Intensive Care Med* 2012;38:931–939.
16. Choorat C, Rattanaumpawan P, Thamlikitkul V. *Epidemiology of Multidrug-Resistance Bacteria Colonization Among Hospitalized General Medical Patients at Siriraj Hospital [dissertation]*. Bangkok: Mahidol University, 2014.

17. Block SS. *Disinfection, Sterilization, and Preservation*, 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2001:321–336.
18. Chlorhexidine gluconate 2% w/v impregnated pads PL27821/0004: UK Public Assessment Report. Medicines and Healthcare Products Regulatory Agency website. http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con091190.pdf. Updated July 7, 2010. Accessed October 15, 2015.
19. Clinical and Laboratory Standards Institute (CLSI). *Performance standards for antimicrobial susceptibility testing; 23rd informational supplement*. Wayne, PA: CLSI, 2013:M100–S23.
20. Bass P, Karki S, Rhodes D, et al. Impact of chlorhexidine-impregnated washcloths on reducing incidence of vancomycin-resistant enterococci colonization in hematology-oncology patients. *Am J Infect Control* 2013;41:345–348.
21. Karki S, Cheng AC. Impact of non-rinse skin cleansing with chlorhexidine gluconate on prevention of healthcare-associated infections and colonization with multi-resistant organisms: a systematic review. *J Hosp Infect* 2012;82:71–84.
22. Evans HL, Dellit TH, Chan J, Nathens AB, Maier RV, Cuschieri J. Effect of chlorhexidine whole-body bathing on hospital-acquired infections among trauma patients. *Arch Surg* 2010;145:240–246.
23. Ridenour G, Lampen R, Federspiel J, Kritchevsky S, Wong E, Climo M. Selective use of intranasal mupirocin and chlorhexidine bathing and the incidence of methicillin-resistant *Staphylococcus aureus* colonization and infection among intensive care unit patients. *Infect Control Hosp Epidemiol* 2007;28:1155–1161.
24. Cassir N, Papazian L, Fournier PE, Raoult D, La Scola B. Insights into bacterial colonization of intensive care patients' skin: the effect of chlorhexidine daily bathing. *Eur J Clin Microbiol Infect Dis* 2015;34:999–1004.
25. McDonnell G, Russell AD. Antiseptics and disinfectants: activity, action, and resistance. *Clin Microbiol Rev* 1999;12:147–179.
26. Hassan KA, Jackson SM, Penesyan A, et al. Transcriptomic and biochemical analyses identify a family of chlorhexidine efflux proteins. *Pro Natl Acad Sci U S A* 2013;110:20254–20259.
27. Apisarnthanarak A, Pinitchai U, Warachan B, Warren DK, Khawcharoenporn T, Hayden MK. Effectiveness of infection prevention measures featuring advanced source control and environmental cleaning to limit transmission of extremely-drug resistant *Acinetobacter baumannii* in a Thai intensive care unit: an analysis before and after extensive flooding. *Am J Infect Control* 2014;42:116–121.
28. Munoz-Price LS, Hayden MK, Lolans K, et al. Successful control of an outbreak of *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* at a long-term acute care hospital. *Infect Control Hosp Epidemiol* 2010;31:341–347.
29. Popovich KJ, Hota B, Hayes R, Weinstein RA, Hayden MK. Daily skin cleansing with chlorhexidine did not reduce the rate of central-line associated bloodstream infection in a surgical intensive care unit. *Intensive Care Med* 2010;36:854–858.
30. Noto MJ, Domenico HJ, Byrne DW, et al. Chlorhexidine bathing and health care-associated infections: a randomized clinical trial. *JAMA* 2015;313:369–378.
31. Martinez-Resendez MF, Garza-Gonzalez E, Mendoza-Olazaran S, et al. Impact of daily chlorhexidine baths and hand hygiene compliance on nosocomial infection rates in critically ill patients. *Am J Infect Control* 2014;42:713–717.
32. Chen W, Cao Q, Li S, et al. Impact of daily bathing with chlorhexidine gluconate on ventilator associated pneumonia in intensive care units: a meta-analysis. *J Thorac Dis* 2015;7:746–753.