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*

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LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Explain consequences of colonization with resistant organisms.
2. Describe the effect of bathing with chlorhexidine.
3. Use this information in a clinical setting.

Dr. Zuccotti has disclosed that her spouse received a financial honorarium from Merck. Dr. Fraser has disclosed that she was/is a recipient of grant/research funds from the CDC and NIH; was a consultant/advisor for Merck Quality Advisory Board 2007; and was/is a consultant/advisor for Chitopure and Ancora. Dr. Warren has disclosed that he was/is a recipient of grants/research funds from Sage Products, Inc.; was a consultant/advisor for Cardinal Health; and is a consultant/advisor for 3M Healthcare. Dr. Perl has disclosed that she was/is a recipient of grant/research funds from Sage and the CDC; is a recipient of grants/research funds from 3M; was a consultant/advisor for Cadence, 3M, Biomeneux, and IHI; is a consultant/advisor for Cadence, Theradoc, Biomeneux, and CMS; gave a talk for BD; and had a CME-supported symposium for Vivopharma (R. Michaels). The remaining authors have disclosed that they have no financial relationships with or interests in any commercial companies pertaining to this educational activity. The authors have disclosed that the U.S. Food and Drug Administration has not approved chlorhexidine for the treatment of methicillin-resistant *Staphylococcus aureus* and *Enterococcus* discussed in this article. Please consult the product's labeling information for approved indications and usage.

All faculty and staff in a position to control the content of this CME activity have disclosed that they have no financial relationship with, or financial interests in, any commercial companies pertaining to this educational activity.

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Objective: **Spread of multidrug-resistant organisms within the intensive care unit (ICU) results in substantial morbidity and mortality. Novel strategies are needed to reduce transmission. This study sought to determine if the use of daily chlorhexidine bathing would decrease the incidence of colonization and bloodstream infections (BSI) because of methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) among ICU patients.**

Design, Setting, and Patients: **Six ICUs at four academic centers measured the incidence of MRSA and VRE colonization and BSI during a period of bathing with routine soap for 6 months and then compared results with a 6-month period where all admitted patients received daily bathing with a chlorhexidine solution. Changes in incidence were evaluated by Poisson and segmented regression modeling.**

Interventions: **Daily bathing with a chlorhexidine-containing solution.**

Measurements and Main Results: **Acquisition of MRSA decreased 32% (5.04 vs. 3.44 cases/1000 patient days, $p = 0.046$) and acquisition of VREdecreased 50% (4.35 vs. 2.19 cases/1000 patient days, $p = 0.008$) following the introduction of daily chlorhexidine bathing. Segmented regression analysis demonstrated significant reductions in VRE bacteremia ($p = 0.02$) following the introduction of chlorhexidine bathing. VRE-colonized patients bathed with chlorhexidine had a lower risk of developing VRE bacteremia (relative risk 3.35; 95% confidence interval 1.13–9.87; $p = 0.035$), suggesting that reductions in the level of colonization led to the observed reductions in BSI.**

Conclusion: **We conclude that daily chlorhexidine bathing among ICU patients may reduce the acquisition of MRSA and VRE. The approach is simple to implement and inexpensive and may be an important adjunctive intervention to barrier precautions to reduce acquisition of VRE and MRSA and the subsequent development of healthcare-associated BSI. (Crit Care Med 2009; 37:1858–1865)**

KEY WORDS: *Staphylococcus aureus*; *Enterococcus*; methicillin resistance; vancomycin resistance; bacteremia; chlorhexidine

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Up to 20% of patients admitted to intensive care units (ICUs) develop a healthcare-associated infection during their stay (1). Many of these infections are caused by multidrug-resistant organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE), limiting the number of available antibiotics for treatment. These infections prolong lengths of stay and increase costs of care and patient morbidity and mortality. Many of these infections may be preventable, spurring interest in development of novel strategies to reduce incidence.

The leading cause of morbidity among ICU patients is hospital-acquired bloodstream infections (BSIs) most often associated with the use of indwelling central venous catheters. Previous studies have indicated that there are a number of modifiable risk factors to help prevent catheter-associated bloodstream infections (2). Most of these relate to proper sterile technique during the insertion and maintenance of central venous catheters (3), including proper site preparation with an effective skin disinfectant such as chlorhexidine. The use of chlorhexidine reduces residual skin organisms as well as inhibits their rebound growth and has been demonstrated to reduce catheter-associated BSIs more effectively in comparison with other skin disinfectant products such as povidone and iodine (4–7). Centers for Disease Control and Prevention guidelines now recommend that the preferential use of chlorhexidine-containing skin disinfectants can be used for site preparation before insertion (4).

Prevention of colonization and infection with multidrug-resistant organisms is recognized as key to protecting high-risk patients. Chlorhexidine gluconate has been used in several settings to control outbreaks and infections related to MRSA and VRE. In fact, many regimens used to eradicate skin carriage of MRSA include bathing with chlorhexidine (8–16). Chlorhexidine bathing has also been used in selective settings to reduce the incidence of MRSA acquisition within the ICU (8–11) and to control outbreaks of community-acquired MRSA outside of the hospital (12). Chlorhexidine-based solutions reduce the density of skin colonization with pathogens such as MRSA and VRE (skin asepsis), thus lowering the risk for horizontal transmission between healthcare workers and patients.

In two recent studies, chlorhexidine gluconate impregnated washcloths used to bathe ICU patients daily reduced VRE found on patient's skin and the rate of VRE acquisition by 65% (17, 18). Vernon et al theorized that reduced microbial density of VRE on a patient's skin (source control) led to decreased transmission to a healthcare worker's hands and thereby prevented subsequent transmission to additional patients. Because these studies were performed at single institutions, the generalizability of the findings is uncertain and requires verification. However, the results are intriguing and supported the hypothesis that daily bathing with a chlorhexidine-based product may help reduce healthcare-associated infection, particularly those caused by VRE.

We present data on the impact of daily chlorhexidine bathing on the rate of acquisition of MRSA and VRE and on the incidence of BSIs in several ICU settings.

MATERIALS AND METHODS

Study Design. This was a multicenter, before–after interventional design completed in six ICUs at four major tertiary care referral hospitals (The Johns Hopkins Hospital, Baltimore, MD; Memorial Sloan-Kettering Cancer Center, New York, NY; Barnes-Jewish Hospital, St. Louis, MO; and the Hunter Holmes McGuire Veteran Affairs Medical Center, Richmond, VA). The work was completed by participants in the Centers for Disease Control and Prevention Epicenters program, a collaborative research project funded by the Centers for Disease Control and Prevention to investigate new strategies to prevent healthcare-acquired infections. The study took place between December 2004 and January 2006. Study units were a mixture of medical intensive care units, coronary care units, surgical intensive care units, and cardiac surgery intensive care units. Descriptive characteristics of the involved ICUs are presented in Table 1.

Table 1. Characteristics of study units

	Unit 1	Unit 2	Unit 3	Unit 4	Unit 5	Unit 6
Type of unit	MICU	CSICU	MICU/CCU	SICU	MICU	SICU
Average monthly admissions (range)	83.75 (54–104)	58.58 (30–116)	58.75 (33–84)	54.33 (29–85)	52.83 (39–64)	135.58 (121–144)
Mean monthly patient days (range)	351.33 (199–480)	301.92 (206–567)	228.67 (138–297)	275.00 (155–416)	320.42 (277–359)	639.42 (476–695)
MRSA prevalence (% of admissions)	5.35%	1.64%	6.30%	5.58%	3.25%	1.71%
VRE prevalence (% of admissions)	6.91%	2.46%	0	0	3.09%	1.78%
Type of surveillance	MRSA/VRE	MRSA/VRE	MRSA	MRSA	MRSA/VRE	MRSA
Timing of surveillance	On admission and weekly	On admission and weekly	On admission and weekly	On admission and weekly	On admission and weekly	On admission and discharge
Initiation of active surveillance program	2004	2004	2003	2004	2004	2002
Compliance with active surveillance cultures						
All patients	91%	63%	72%	84%	100%	100%
Patients with stays >48 hours	98%	74%	85%	89%	100%	100%

MICU, medical intensive care unit; CSICU, cardiac surgery intensive care unit; MICU/CCU, combined medical intensive care unit and coronary care unit; SICU, surgical intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*.

All units had implemented active surveillance culturing (ASC) for MRSA and three of the six ICUs had implemented ASC programs for VRE before the initiation of the study. At each ICU, active surveillance cultures were obtained within 48 hours of admission and at least weekly thereafter with the exception of one ICU that obtained prevalence surveillance cultures at discharge. Surveillance cultures were obtained from the anterior nares for MRSA and from the perirectal area for VRE. All surveillance cultures were processed in the microbiology laboratory at each institution and all used standard culture-based identification of MRSA and VRE. All identified patients with MRSA and/or VRE were placed on contact precautions once culture results became available. Patients with a previous history of MRSA or VRE were placed on contact precautions at admission to all ICUs.

During the baseline period of 1–6 months, all patients admitted to the unit received routine daily bed baths with nonmedicated soap and water as dictated by local hospital or ICU policy. For the second 6 months of the study (intervention period), all patients admitted to the ICU underwent the same daily bed bath, except a chlorhexidine-containing solution was used instead of soap and water. Nurses at the bedside mixed the contents of a 4-oz bottle of 4% chlorhexidine gluconate with warm water in a six-quart basin. Patients were bathed from the neck down avoiding contact with the face and all mucous membranes and wounds, as recommended by the manufacturer.

Compliance with chlorhexidine bathing was assessed weekly by monitoring the inventory of chlorhexidine bottles supplied to the study units. Census figures were collected and used to calculate expected use of chlorhexidine. For the purposes of monitoring, use of one 4-oz bottle of chlorhexidine was considered to indicate receipt of one patient bath. If the expected usage of chlorhexidine was low for the given census (implying poor compliance with bathing), study coordinators met with unit personnel to urge better compliance. Direct observation of bathing was not performed. No other interventions aimed at reducing either BSIs or horizontal transmission of multiresistant bacteria took place during the study period for any of the involved units. Routine use of mupirocin to decolonize patients was not in place in any of the units during the time of the study. Local hospital policy did allow for its use on individuals identified as MRSA positive at the prerogative of physicians; however, a policy to routinely prescribe it was not in place at the time of the study. All of the study units had previously implemented the use of alcohol-based hand hygiene and had implemented and completed standard prevention efforts aimed at preventing central venous catheter-related infections (19, 20).

Definitions. A prevalent case was defined as any patient with: 1) an ASC or clinical culture showing growth of MRSA or VRE obtained within 48 hours of ICU admission, or 2) an ASC or clinical culture showing growth of MRSA or VRE obtained more than 48 hours after ICU admission in patients with a previous history of MRSA or VRE. An acquired or incident case of MRSA or VRE had to meet all the following requirements: no previous history of MRSA or VRE, a negative initial ASC for MRSA or VRE, and a follow-up culture showing growth of MRSA or VRE from either a surveillance or clinical specimen obtained more than 48 hours after admission to the ICU.

An incident case of MRSA or VRE bacteremia was defined as the first positive blood culture obtained more than 48 hours after ICU admission. Recurrent bacteremias or additional episodes of bacteremia in the same patient were excluded.

Rates for MRSA and VRE are presented as incidence density, the number of incident cases per 1000 at risk patient days. At-risk patient days were defined as the total patient days for the period minus patient days for those patients identified with prevalent cases of MRSA or VRE. The incidence density represents the true rate for newly acquired cases among eligible patients, i.e., who had not been previously diagnosed with MRSA or VRE. Rates of incident BSIs were calculated as the number of new cases per 1000 total patient days. We did not include data on the number of catheter days or the classification of bacteremias as primary vs. secondary as the intervention was intended to reduce all healthcare-associated bacteremias and not just those associated with intravascular catheter use.

Prevalence rates for MRSA and VRE were defined as the monthly prevalence rate or number of prevalent cases present in the unit each month per 1000 patient days. The percentage of MRSA or VRE prevalent days was defined as the total number of patient days occupied by patients with defined prevalent cases of MRSA or VRE divided by the total number of patient days; this represents the percentage of bed days that patients colonized with MRSA or VRE were present in the study unit.

Overall compliance with ASC was calculated as the percentage of admissions where ASC were obtained, i.e., had at least one ASC. To better define the population of patients eligible for healthcare-associated acquisition of MRSA or VRE (those with ICU stays longer than 48 hours), compliance is also presented for patients with stays longer than 48 hours.

Data Collection. Each institution entered data from its own cohort for each admission to the participating ICUs into a standardized Access database (Microsoft, Redmond, OR). Data included the results of all surveillance cultures, all positive clinical cultures for MRSA and VRE, and all positive blood cultures. Data on any previous history of MRSA and/or VRE for each patient were also collected. The studies were completed at each institution after obtaining approval of the local Investigational Review Board. Informed consent was waived at each institution because of the minimal risk nature of the study. Following completion of the studies, local approval to submit the data for aggregation and analysis was granted by all local Investigational Review Boards. At the completion of the study at each institution, data were sent to the coordinating center (McGuire) for aggregation and analysis.

Statistical Analysis. We evaluated changes in the mean incidence of MRSA and VRE colonization and bacteremia using a Poisson regression model that included consideration of the prevalence of MRSA and VRE as a confounder. We tested the null hypothesis that the incidence rate during the baseline period equals the incident rate during the intervention period using PROC GENMOD in SAS (version 8.2, Cary, NC) to fit a Poisson regression model. Modeling included considerations of the monthly prevalence of MRSA and VRE in the comparison to exclude the possibility that observed reductions in incidence were associated with clustering of MRSA and/or VRE. The monthly prevalence was calculated as the proportion of bed days occupied by patients with prevalent cases of MRSA or VRE compared with the total bed days and was included as covariates in the model.

An interrupted time series analysis was performed using the segmented regression procedure, evaluating the impact of the intervention on the level (abrupt change immediately following the intervention) and the secular trend of the series (changes in the slope of the incidence rate following the intervention) (21). We evaluated both the absolute change in the level of incidence and the trend following the introduction of chlorhexidine bathing as it was assumed that gradual decreases in the incidence of colonization might have a delayed effect on any observed reductions in VRE and MRSA bacteremias. The presence and significance of autocorrelation was tested by the Durbin–Watson statistic. To better characterize the absolute effect of the addition of chlorhexidine bathing on the incidence rates, we also calculated the absolute difference between the incidence rates at the end of the intervention and the value as determined by the time series model taking into account the level and trends before the introduction of chlorhexidine bathing.

The Cox proportional-hazards regression model was used to compare the differences in the acquisition of MRSA and VRE between the control group and the intervention group (chlorhexidine bathing). For the model, the survival time was calculated on eligible patients and was defined as: 1) the interval between admission and discharge from the study unit for those patients with no diagnosis of acquired MRSA or VRE and ICU stays >48 hours, and 2) the interval between admission and the first positive culture for acquired MRSA or VRE for those patients who acquired MRSA or VRE.

Table 2. Acquisition of VRE and MRSA among patients bathed with chlorhexidine

	Baseline Period	Intervention Period
Admissions	2670	2650
Total bed days of care	15,472	15,225
Total central venous catheter days[a]	10,062	9,633
Mean length of stay (days)	5.99	5.82
MRSA acquisition		
Number of cases	67	45
Number of eligible patient days	13,300	13,096
Incidence rate[b]	5.04	3.44 ($p = 0.046$)[c]
MRSA prevalence rate[b]	22.80	21.80
VRE acquisition		
Number of cases	61	30
Number of eligible patient days	13,412	13,610
Incidence rate[b]	4.35	2.19 ($p = 0.008$)[c]
VRE prevalence rate[d]	17.97	16.75

MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*.

[a]Total number of days in which a central venous catheter was in place among patients admitted to units; [b]number of new cases per 1000 eligible patient days; [c]determined by Poisson regression modeling; [d]number of cases colonized with VRE or MRSA on admission (prevalent cases) each month per 1000 patient days.

RESULTS

During the 12-month study period, there were a total of 5293 admissions to the six study units that included 5043 patients. Overall, 11,333 surveillance cultures were performed with compliance of 85% among all admissions. In most cases, active surveillance cultures were not obtained from those with short ICU stays, typically less than 48 hours in duration. Among those patients with ICU stays greater than 48 hours, representing patients eligible for nosocomial acquisition, overall compliance with ASC was 92%. For patients with ICU stays greater than 48 hours, compliance with ASC increased from 86% in the baseline period to 95% during the intervention period. Increased compliance with surveillance culturing was attributed to the recent introduction of active surveillance in three of the study units (units 1, 2, and 4).

Acquisition of MRSA. The overall rate of MRSA acquisition decreased 32% during the intervention period in comparison with the baseline period (Table 2; incidence density, 5.04 vs. 3.44 cases per 1000 eligible patient days; $p = 0.046$). Acquired MRSA cases were initially detected from nasal (71%), lower respiratory tract (20%), wound (5.5%), or blood cultures (1.8%). The risk of acquiring MRSA was significantly reduced among patients bathed with chlorhexidine in Cox proportional hazards survival regression analysis (Fig. 1; $p = 0.024$). Significant reductions in the acquisition of MRSA for patients with longer ICU stays were noted. Among patients with ICU length of stays longer than 10 days who were bathed with chlorhexidine, 11 of 252 (4.37%) acquired MRSA compared with 27 of 272 (9.93%) during the baseline period (relative risk 0.58; 95% confidence interval 0.351–0.968; $p = 0.02$).

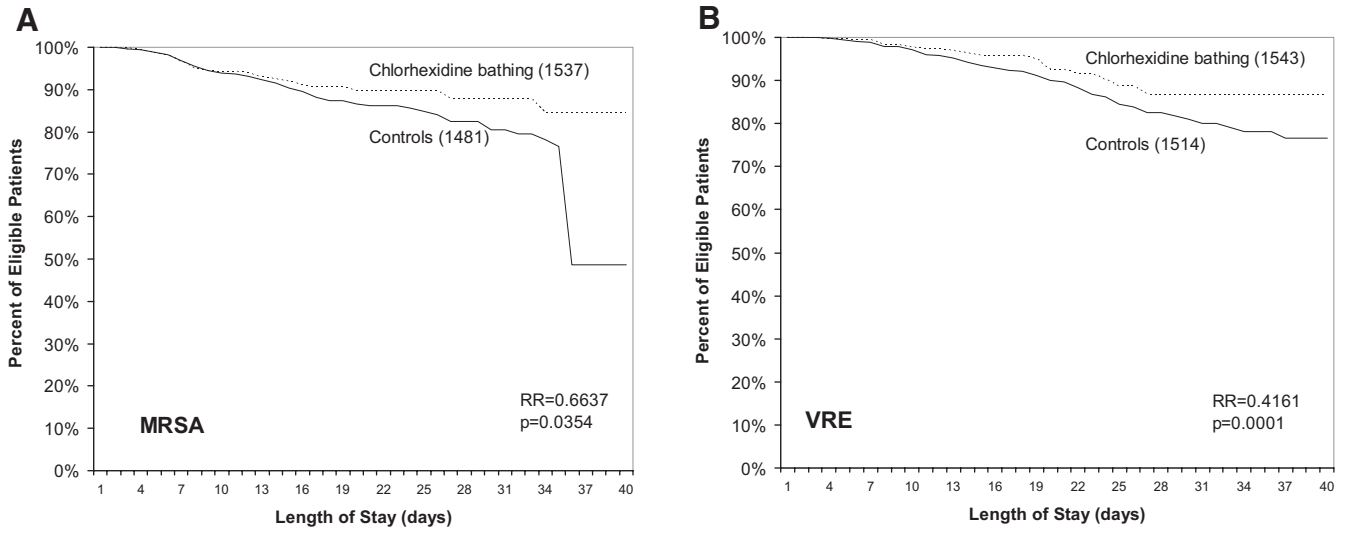
The observed reduction in the acquisition of MRSA was not related to changes in the overall prevalence of MRSA at admission. The average monthly prevalence rate of MRSA was similar between the baseline and intervention periods (22.80 vs. 21.80 cases per 1000 patient days). In addition, the percentage of patient days occupied by patients identified with prevalent MRSA was identical between the baseline and intervention period (14%). Finally, to exclude the possibility that differences in MRSA prevalence may have affected MRSA acquisition, we included monthly prevalence of MRSA within the study units in the Poisson regression model. When the proportion of bed days occupied by patients colonized with MRSA was included in the Poisson regression model as a covariate, the observed reduction in the acquisition of MRSA remained statistically significant.

Results of time series models are shown in Table 3. During the baseline period, there was a slight decrease in MRSA incidence as evidenced by a downward slope (−0.28). Following the introduction of chlorhexidine bathing there was a further reduction in the trend (−0.61, $p = 0.5$) resulting in an overall reduction in MRSA incidence during the intervention period. The time series did not show significant auto-correlation suggesting a lack of clustering (Durbin–Watson statistic = 1.39). Results of the time series model indicated that by the end of the intervention there was a 25% decrease in the incidence of MRSA attributable to the introduction of chlorhexidine bathing, representing a decrease of 0.66 cases per 1000 patient days (Table 3).

MRSA Bacteremia. Overall, there was a low rate of hospital-acquired MRSA bacteremias during the entire study period with eight cases detected in the baseline period compared with five cases in the intervention period.

Acquisition of VRE. The overall incidence of acquired VRE decreased 50% in the intervention period compared with the baseline period (Table 2; incidence density 4.35 vs. 2.19 cases per 1000 eligible patient days, $p = 0.008$). A statistically significant reduction in the risk of acquiring VRE was also seen among patients bathed with chlorhexidine in Cox proportional hazards survival regression analysis ($p = 0.0001$; Fig. 1). The average monthly prevalence rate for VRE among admissions was similar between the baseline and intervention period (17.97 vs. 16.75 cases per 1000 patient days) suggesting that changes in prevalence did not make a substantial impact on the observed reductions in incidence. In addition, the percentage of patient days occupied by patients identified with prevalent VRE was not statistically different between the baseline and intervention period (9.283% vs. 8.097%, $p = 0.3$). However, the possible effect of VRE prevalence as a covariate factor in the observed incidence was accounted for in the Poisson model and found not to be a significant factor in the observed reduction in VRE incidence.

Results of time series model indicated that there was a prompt reduction in the level of VRE incidence following the introduction of chlorhexidine bathing that represented an immediate decrease of 1.44 cases per 1000 patient days (Fig. 2; $p = 0.19$). During the baseline period, there was a decreasing trend for VRE incidence as evidenced by a downward slope (−0.14) that continued following the introduction of chlorhexidine bathing (−0.16). The time series did not show significant auto-correlation suggesting a lack of clustering (Durbin–Watson statistic = 2.71). Results of the time series model indicated that by the end of the intervention, there was a 45% decrease in the incidence of VRE attributable to the



Number of subjects at risk	Day 5	10	15	20	25	30	35	40
Control	778	317	168	100	65	43	28	16
Intervention	817	317	161	103	58	41	24	17

Number of subjects at risk	Day 5	10	15	20	25	30	35	40
Control	787	319	185	117	70	49	31	17
Intervention	828	332	175	111	60	40	25	18

Figure 1. Reduction in methicillin-resistant *Staphylococcus aureus* (*MRSA*) and vancomycin-resistant *Enterococcus* (*VRE*) acquisition among patients bathed with chlorhexidine. Comparison of the percentage of eligible patients free from MRSA (*A*) and VRE (*B*) following the completion of their intensive care unit admission during the baseline period (study months, 1–6); and during the intervention period (study months, 7–12). A statistically significant reduction in the time to detection of MRSA and VRE colonization among those patients at risk is seen among patients bathed with chlorhexidine. *RR*, relative risk. Controls, solid line; chlorhexidine bathing, dotted line.

Table 3. Time series analysis of the results of introduction of daily chlorhexidine bathing on the incidence of MRSA and VRE colonization and bacteremia

Outcome Measure	Incidence Rate as Modeled at End of Intervention in the Absence of Chlorhexidine Bathing[a]	Observed Incidence Rate at End of Intervention[b]	Change in Incidence Rate Attributable to Introduction of Chlorhexidine Bathing (% Change)[c]
MRSA incidence	2.59	1.93	−0.66 (25%)
MRSA bacteremia	<0.1	<0.1	0 (0)
VRE incidence	3.34	1.83	−1.51 (45%)
VRE bacteremia	3.38	0.74	−2.64 (78%)

MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*.

[a]Incidence rate (cases per 1000 patient days) as modeled in time series analysis at the end of the intervention period based on level and secular trends observed during the baseline period in the absence of chlorhexidine bathing. This represents the expected value that would be observed had chlorhexidine bathing not been introduced; [b]modeled incidence rate (cases per 1000 patient days) observed at the end of the intervention period; [c]difference between the time series' modeled value in the absence of chlorhexidine bathing and the observed model value at the end of the intervention period with the percentage change in parenthesis.

introduction of chlorhexidine bathing representing a decrease of 1.51 cases per 1000 patient days (Table 3).

VRE Bacteremia. Incident VRE bacteremias decreased 73% (2.13 vs. 0.59 cases per 1000 patient days, $p = 0.0006$). During the baseline period, there were 33 VRE bacteremias detected compared with nine VRE bacteremias in the study period. The observed reduction in bacteremias was closely correlated with reductions seen in acquisition of VRE within the study units (Fig. 2). Among patients identified with VRE colonization, there was a statistically significant reduction in the risk of progressing to VRE bacteremia among those patients bathed with chlorhexidine. In the baseline period, 16 of 270 colonized VRE patients developed VRE bacteremia compared with four of 226 VRE colonized patients bathed with chlorhexidine in the intervention period (16 of 270 [5.92%] vs. 4 of 226 [1.77%]; relative risk 3.35; 95% confidence interval 1.13–9.87; $p = 0.035$).

Results of the time series model indicated that during the baseline period there was an increasing rate of VRE bacteremia as evidenced by the upward slope of the trend (+0.15). Following the introduction of chlorhexidine bathing, there was a significant reduction in the overall level of bacteremias ($p = 0.02$) resulting in a decrease of 2.11 cases per 1000 patient days immediately following the introduction of chlorhexidine bathing (Fig.

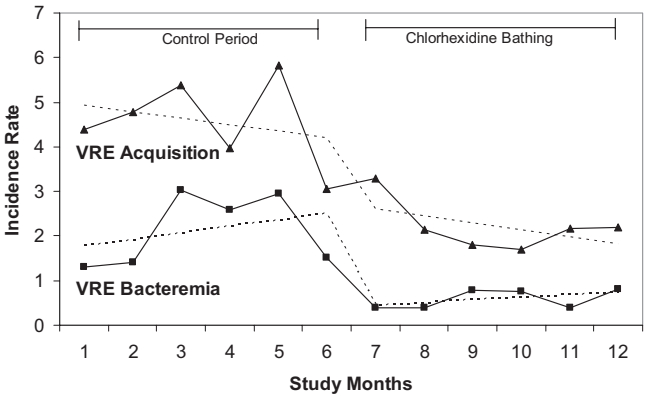


Figure 2. Reduction in the rate of vancomycin-resistant *Enterococcus* (*VRE*) acquisition and VRE bacteremia associated with chlorhexidine bathing. Comparison of rate of the acquisition of VRE (▲) with the rate of incident VRE bacteremias (■). The *dotted line* represents the modeled trend based on time series analysis. During the baseline period (study months, 1–6), all patients admitted to study units received regular bathing and during the intervention period (study months, 7–12), all patients admitted to the study units received daily bathing with chlorhexidine. The rate of acquisition of VRE is the number of new cases of VRE per 1000 eligible patient days. The rate of incident VRE bacteremias is the number of new cases of incident VRE bacteremias per 1000 total patient days.

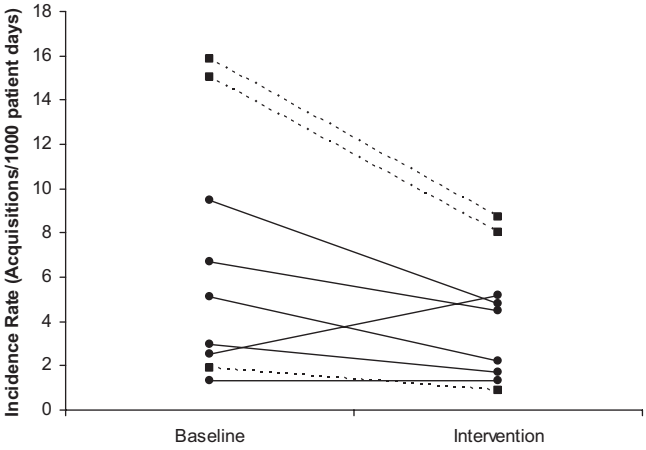


Figure 3. Reduction in the incidence of vancomycin-resistant *Enterococcus* (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) colonization associated with chlorhexidine bathing for all study units. The mean incidence rate of VRE (■) and MRSA (●) for each study unit is shown during the baseline period in comparison with the intervention period. The introduction of chlorhexidine bathing for all patients admitted to the intensive care units (ICUs) during the intervention was associated with a reduction in the mean incidence rate of MRSA in five of six ICUs. The mean incidence rate of VRE was decreased in all three ICUs following the introduction of chlorhexidine bathing.

2). The time series did not show significant auto-correlation suggesting a lack of clustering (Durbin–Watson statistic = 1.65). Results of the time series modeling indicated that by the end of intervention there was an overall reduction in the level of VRE bacteremias attributable to the introduction of chlorhexidine bathing of 78% or 2.64 cases per 1000 patient days (Table 3).

DISCUSSION

It is estimated that more than 125,000 patients are hospitalized with infections because of MRSA each year (22). The prevalence of infections because of VRE also continues to rise with up to 10% of enterococcal isolates showing resistance to vancomycin among hospitalized patients (23). Attempts to control MRSA, VRE, and other antimicrobial resistant bacteria during the past three decades have predominantly relied on the use of barrier precautions by hospital personnel to reduce horizontal transmission between patients. This strategy is predicated on the prompt identification of patients who are colonized with these resistant bacteria and initiation of contact (barrier) precautions. The efficacy of this strategy is dependent on high rates of compliance with the use of gloves and gowns and proper hand hygiene (handwashing). Despite long-standing recommendations for the use of barrier precautions for patients identified with MRSA and VRE, infections with these organisms continue to rise. Additional strategies to reduce the incidence of these multiresistant pathogens are needed.

We studied the universal use of chlorhexidine bathing as a means to reduce acquisition of MRSA, VRE, and healthcare-associated BSIs because of these organisms. The use of daily chlorhexidine bathing resulted in significant reductions in MRSA acquisition (32%), VRE acquisition (50%), and VRE bacteremias (73%). In addition, we found a reduction in the rate of VRE bacteremias among VRE colonized patients (44%). With the low number of overall MRSA BSIs observed (0.423 cases per 1000 patient days), we were unable to document a significant reduction following the introduction of chlorhexidine bathing. A longer study duration or a larger sample size would be needed to show an effect on the reduction in the level of MRSA bacteremia as colonized patients have a higher risk of developing bacteremia (24).

We applied this intervention in multiple study units that had an established active surveillance program in place (25, 26). In several of the units, active surveillance had been in place for years before the intervention. With the use of active surveillance, the issue of confounding might be raised since active surveillance by itself has been advocated as an infection control measure. Our data, during the baseline period when active surveillance was in place, showed that the rates of MRSA and VRE were in fact decreasing slightly, possibly as a result of the ongoing active surveillance programs in place. Despite the presence of ongoing ASC, there was actually an increasing rate of VRE bacteremias during the baseline period. The introduction of chlorhexidine bathing resulted in a significant decrease in VRE bacteremias of 2.64 cases per 1000 patient days. In an attempt to control for the decreasing trends seen within the study, we evaluated the change in incidence using time series modeling that removes the influence of the trend during the baseline period and allows for a more accurate description of the effects of the introduction of chlorhexidine bath-

ing. The incidence rate of MRSA decreased 25% (0.66 cases per 1000 patient days) and VRE incidence decreased 45% (1.51 cases per 1000 patient days) according to time series modeling following the introduction of chlorhexidine bathing. As such, the planned intervention was considered to be additive to any realized benefits that an active surveillance program had established. The stable prevalence throughout the study also argues strongly that the presented findings are not related to changes in culture technique, ascertainment, patient mix, or other potentially confounding variables.

The results extend observations by Vernon et al that chlorhexidine bathing reduces healthcare-associated acquisition of VRE (17). In their study of 1787 ICU patients, they demonstrated that the reduction of microbial density of VRE on patient's skin associated with the use of chlorhexidine leads to decreased transmission. In this study, we demonstrate that the reduction in VRE acquisition is associated with decreased development of VRE BSI as well. Patients colonized with VRE were three times less likely to develop VRE bacteremia when bathed with chlorhexidine compared with regular bathing. Although we did not document the microbial density of MRSA on patient's skin for those bathed with chlorhexidine, we theorize that a similar mechanism was responsible for our observed decrease in MRSA acquisition since chlorhexidine is highly active against MRSA. Reductions in Gram-positive bacteremias were also theorized to arise from reductions in bacterial burden on patient's skin that provided a safer environment for the proper aseptic insertion of central venous catheters and other indwelling devices.

The potential limitations of this study include its before–after design and the lack of randomization. In addition, we did not collect detailed patient level data that may have affected individuals' risk for nosocomial acquisition of MRSA or VRE including antimicrobial use or compliance with hand hygiene in the study units. We attempted to correct for these deficiencies by including a larger number of studied ICUs (six) at four different locations to minimize any localized effect. In addition, we evaluated the observed reductions in acquisition by several methods including Poisson regression modeling to account for the possible influence of varying prevalence of MRSA and VRE in the units on the results, time series analysis to examine for secular trends over time and Cox proportional regression analysis to compare the time with development of MRSA or VRE colonization among those at risk. The intervention was nearly universally active across all six units studied. VRE acquisition rates decreased in the intervention period for all three units studied (those with active surveillance in place for VRE) and MRSA acquisition decreased in five of the six units studied (Fig. 3). These reductions were demonstrated in the presence of stable prevalence rates of MRSA and VRE in the study units indicating that the observed reductions were not related to changing prevalence of MRSA or VRE during the two study periods and their attendant effect on any clustering of transmission.

The routine and frequent use of chlorhexidine bathing may raise concern about promoting the emergence of chlorhexidine resistance. In our study, we did not examine isolates for the presence or development of chlorhexidine resistance. However, Vernon et al examined this, but did not find any evidence of chlorhexidine resistance among VRE isolates in their study (17). Resistance to chlorhexidine is rare among both staphylococci and enterococci with reported minimum inhibitory concentrations (MICs) to chlorhexidine for staphylococci of 0.2–3 μg/mL [0.00002%–0.0003%] and for enterococci of 1–6 μg/mL [0.0001%–0.0006%] (29–32). Serial passage studies of both staphylococci and enterococci in the presence of chlorhexidine have shown only minimal changes in MIC values and no evidence of reported high-level resistance (32). Resistance to antiseptics and disinfectants among staphylococci is due to the presence of the *qacAB* and *qacCD* gene families that encode proton-dependent export proteins. Most prevalent is the *qacA* determinant found on the pSK1 family of conjugative plasmids that also typically encode resistance to a number of antimicrobials including β-lactamase (33). The presence of *qacA* results in substantial increases in MICs to quaternary ammonium compounds but only a 2.5-fold increase in MICs to chlorhexidine (0.8–2 μg/mL), corresponding to concentrations well below those seen in commercial preparations of chlorhexidine. Plasmid-mediated resistance to chlorhexidine has not been described among enterococci. High-level resistance to chlorhexidine among Gram-negative bacterial organisms particularly *Pseudomonas*, *Burkholderia*, and *Serratia* has been reported (34–36). In our study, we did not see significant increases in either Gram-negative organisms bacteremias or fungemias following the introduction of chlorhexidine bathing (data not shown). However, given this potential for resistance among Gram-negatives organisms, it will be prudent in future studies to screen isolates for the development of chlorhexidine resistance and determine whether selection of high-level chlorhexidine resistance among Gram negatives becomes a problem with more widespread use of chlorhexidine.

In summary, we demonstrate that the implementation of a relatively simple procedure, daily bathing with chlorhexidine, significantly reduced acquisition of VRE and MRSA and healthcare-associated bacteremias across several large university-affiliated ICUs. Universal bathing with chlorhexidine, a skin disinfectant with excellent activity against MRSA, VRE, and other staphylococci, also had the advantage that many patients who were colonized with these organisms could begin treatment to eradicate skin carriage before results of ASC being available. In addition, patients with longer ICU stays had reduced risk of acquiring MRSA with daily chlorhexidine bathing and as such this intervention could be seen as an enhancement of barrier precautions to prevent transmission from known colonized patients. Additional studies of the potential use of chlorhexidine in daily bathing are warranted to determine whether routine use can help reduce MRSA bacteremias within the ICU and should include enhanced surveillance for the development of resistance to chlorhexidine.

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