EDITORIAL

Screening Inpatients for MRSA — Case Closed

Michael B. Edmond, M.D., M.P.H., and Richard P. Wenzel, M.D.

One of the most controversial concepts in health care epidemiology during the past decade has been the active detection and isolation of patients with methicillin-resistant *Staphylococcus aureus* (MRSA) colonization. The basic strategy is to screen inpatients for MRSA, typically with a polymerase-chain-reaction–based technology, in order to rapidly identify patients colonized with the organism and then initiate contact precautions (place them in a private room and require gowns and gloves on room entry). This approach has been used for decades to control outbreaks caused by epidemiologically important pathogens. As MRSA became endemic in hospitals, studies began to appear suggesting that active detection and isolation reduced health care–associated infections. However, the vast majority of the studies were single-center, observational, nonrandomized, before-and-after evaluations, which yielded low-quality evidence and precluded the establishment of causality. Nonetheless, most hospitals adopted programs of active detection and isolation, and nine states mandated MRSA screening of inpatients.[1]

Active detection and isolation is an example of a vertical infection-prevention strategy. Vertical interventions are designed to reduce colonization or infection due to a specific pathogen, they often involve a microbiologic screening test, and they typically have high resource utilization, direct costs, and opportunity costs.[2] The philosophical underpinning is one of exceptionalism: some pathogens are more important than others and merit special control measures. Alternatively, a horizontal strategy is population-based, is applied universally, and uses interventions effective in controlling all pathogens transmitted by means of the same mechanism. The philosophical orientation is utilitarian, and the values favored are more consistent with those of the patient, who desires to avoid all infections, not just those due to MRSA. Horizontal interventions include hand hygiene, chlorhexidine bathing, and care bundles, and they often require modification of the behavior of health care workers.

In 2011, Jain et al. reported the results of a nationwide intervention at Veterans Affairs hospitals that included active detection and isolation along with efforts to improve compliance with hand-hygiene protocols and an institutional culture change to promote accountability for the prevention of infections.[3] The intervention was associated with a 62% decrease in health care–associated MRSA infections in intensive care units (ICUs) and a 45% decrease in wards. However, an independent analysis of the data with the use of mathematical modeling showed that only a very small fraction of the effect shown could be attributed to the interventions in the study.[4] Moreover, a federally funded, multicenter, cluster-randomized trial showed that active detection and isolation was not effective in the ICU setting.[5] Because the latter study had methodologic issues with regard to delays in obtaining the results of screening tests, the efficacy of active detection and isolation remained uncertain.

A study by Huang et al., now published in the *Journal*, formally assesses horizontal versus vertical strategies.[6] In a large, cluster-randomized, multicenter trial, 43 hospitals were randomly assigned to one of three intervention groups for all patients in adult ICUs. Group 1 used a strategy of active detection and isolation of MRSA — a vertical intervention. Group 2 used a strategy of targeted decolonization, with active detection and isolation plus intranasal mupirocin

and chlorhexidine bathing for 5 days — a mixed vertical and horizontal approach. Group 3 used a strategy of universal decolonization, with intranasal mupirocin for 5 days and daily chlorhexidine bathing for the entire ICU stay, but no active detection and isolation — a mostly horizontal strategy.

Active detection and isolation without decolonization was not effective in reducing rates of MRSA-positive clinical cultures, MRSA bloodstream infections, or bloodstream infections from any pathogen. In contrast, targeted and universal decolonization resulted in significant reductions in MRSA-positive clinical cultures and bloodstream infections from any pathogen but not MRSA bloodstream infections; however, the effect of universal decolonization was greater than the effect of targeted decolonization. Unfortunately, we are unable to ascribe the incremental contribution of each of the two decolonization components. However, a recent multicenter trial showed that daily chlorhexidine bathing of patients in the ICU without the use of mupirocin reduced the rate of bloodstream infections and the acquisition of multidrug-resistant pathogens.[7]

The strengths of the study by Huang et al. include its large size and rigorous design. Weaknesses include a lack of surveillance for infections other than bloodstream infections and a failure to assess for resistance to chlorhexidine or mupirocin. In vitro resistance to chlorhexidine has been described, although its clinical relevance remains uncertain.[8] However, mupirocin resistance is well documented, is associated with decolonization failure, and occurs commonly when mupirocin is used in a widespread fashion.[9] Thus, we would urge caution in implementing the universal use of mupirocin in patients in the ICU.

The implications of this study are highly important. The lack of effectiveness of active detection and isolation should prompt hospitals to discontinue the practice for control of endemic MRSA. A benefit will be a reduced proportion of patients requiring contact precautions, which is a patient-unfriendly practice that interferes with care.[10] In addition, the folly of pursuing legislative mandates when evidence is lacking has been shown, and laws mandating MRSA screening should be repealed.

Lastly, this study has implications beyond MRSA. New resistance mechanisms continue to emerge in nosocomial pathogens. The recent dissemination of carbapenem-resistant Enterobacteriaceae has stimulated calls to implement active detection and isolation for these organisms. We hope that the results of this study will redirect that discussion and reinforce the utility of horizontal interventions to control not only the pathogens of today but those of tomorrow as well.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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ORIGINAL ARTICLE

Targeted versus Universal Decolonization to Prevent ICU Infection

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ABSTRACT

BACKGROUND

Both targeted decolonization and universal decolonization of patients in intensive care units (ICUs) are candidate strategies to prevent health care–associated infections, particularly those caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

METHODS

We conducted a pragmatic, cluster-randomized trial. Hospitals were randomly assigned to one of three strategies, with all adult ICUs in a given hospital assigned to the same strategy. Group 1 implemented MRSA screening and isolation; group 2, targeted decolonization (i.e., screening, isolation, and decolonization of MRSA carriers); and group 3, universal decolonization (i.e., no screening, and decolonization of all patients). Proportional-hazards models were used to assess differences in infection reductions across the study groups, with clustering according to hospital.

RESULTS

A total of 43 hospitals (including 74 ICUs and 74,256 patients during the intervention period) underwent randomization. In the intervention period versus the baseline period, modeled hazard ratios for MRSA clinical isolates were 0.92 for screening and isolation (crude rate, 3.2 vs. 3.4 isolates per 1000 days), 0.75 for targeted decolonization (3.2 vs. 4.3 isolates per 1000 days), and 0.63 for universal decolonization (2.1 vs. 3.4 isolates per 1000 days) ($P=0.01$ for test of all groups being equal). In the intervention versus baseline periods, hazard ratios for bloodstream infection with any pathogen in the three groups were 0.99 (crude rate, 4.1 vs. 4.2 infections per 1000 days), 0.78 (3.7 vs. 4.8 infections per 1000 days), and 0.56 (3.6 vs. 6.1 infections per 1000 days), respectively ($P<0.001$ for test of all groups being equal). Universal decolonization resulted in a significantly greater reduction in the rate of all bloodstream infections than either targeted decolonization or screening and isolation. One bloodstream infection was prevented per 54 patients who underwent decolonization. The reductions in rates of MRSA bloodstream infection were similar to those of all bloodstream infections, but the difference was not significant. Adverse events, which occurred in 7 patients, were mild and related to chlorhexidine.

CONCLUSIONS

In routine ICU practice, universal decolonization was more effective than targeted decolonization or screening and isolation in reducing rates of MRSA clinical isolates and bloodstream infection from any pathogen. (Funded by the Agency for Healthcare Research and the Centers for Disease Control and Prevention; REDUCE MRSA ClinicalTrials.gov number, NCT00980980.)

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Health care–associated infection is a leading cause of preventable illness and death and often results from colonizing bacteria that overcome body defenses.[1-5] Among the pathogens causing health care–associated infection, methicillin-resistant *Staphylococcus aureus* (MRSA) has been given priority as a target of reduction efforts because of its virulence and disease spectrum, multidrug-resistant profile, and increasing prevalence in health care settings, particularly among patients in the intensive care unit (ICU). Hospitals commonly screen patients in the ICU for nasal carriage of MRSA and use contact precautions with carriers.[2-6] Nine states mandate such screening.[7]

Decolonization has been used to reduce transmission and prevent disease in *S. aureus* carriers, primarily carriers of methicillin-resistant strains but also carriers of methicillin-sensitive ones.[8,9] *S. aureus*, including both methicillin-resistant and methicillin-susceptible strains, accounts for more health care–associated infections than any other pathogen.[4] It is the most common cause of ventilator-associated pneumonia and surgical-site infection and the second most common cause of central-catheter–associated bloodstream infection.[4] Decolonization commonly involves a multiday regimen of intranasal mupirocin and chlorhexidine bathing.

There is debate about whether decolonization should be used and, if so, whether to target high-risk pathogens or patient populations that are susceptible to infection from many pathogens.[10] In particular, the broad antimicrobial activity of chlorhexidine makes it attractive for preventing health care–associated infection from many pathogens.[11-14] Several studies have shown that daily chlorhexidine bathing of all patients in the ICU can reduce MRSA acquisition, the concentration of bacteria on the body surface, and bloodstream infection from all pathogens.[11-14] A comparative-effectiveness trial is needed to determine what type of decolonization strategy works best to reduce MRSA and other pathogens in ICUs.[15] In addition, it is important to know whether decolonization can be effective in routine ICU care. We conducted a cluster-randomized, pragmatic, comparative-effectiveness trial in adult ICUs to compare targeted and universal decolonization with one another and with MRSA screening and contact precautions alone.

Methods

Study Design

We designed the Randomized Evaluation of Decolonization versus Universal Clearance to Eliminate MRSA (REDUCE MRSA) trial, a three-group, cluster-randomized trial, to compare strategies for preventing MRSA clinical isolates and infections in adult ICUs in Hospital Corporation of America (HCA) hospitals. The trial design has been described previously,[15] and the protocols are available with the full text of this article at NEJM.org. The training materials are provided in the Supplementary Appendix, available at NEJM.org. All the authors vouch for the accuracy of the reported data and the fidelity of the study to the protocol. There was a 12-month baseline period from January 1 through December 31, 2009; a phase-in period from January 1 through April 7, 2010; and an 18-month intervention period from April 8, 2010, through September 30, 2011.

The three strategy groups were defined as follows. In group 1 (screening and isolation), bilateral screening of the nares for MRSA was performed on ICU admission, and contact precautions were implemented for patients with a history of MRSA colonization or infection and for those who had any positive MRSA test. This was the previous standard of care in all hospitals. The MRSA screening program for patients in the ICU, who are a group at high risk for infection, began in 2007 at HCA hospitals.[16] More than 90% of the patients admitted to the ICU underwent screening, and contact precautions were implemented for carriers of MRSA and other multidrug-resistant pathogens.

In group 2 (targeted decolonization), MRSA screening and contact precautions were similar to those in group 1. Patients known to have MRSA colonization or infection underwent a 5-day decolonization regimen consisting of twice-daily intranasal mupirocin and daily bathing with chlorhexidine-impregnated cloths.

In group 3 (universal decolonization), there was no screening for MRSA on admission to the ICU. Contact precautions were similar to those in group 1. All patients received twice-daily intranasal mupirocin for 5 days, plus daily bathing with chlorhexidine-impregnated cloths for the entire ICU stay.

All adult ICUs in a participating hospital were

assigned to the same study group. Contact-precaution policies, which were based on long-standing guidance from the Centers for Disease Control and Prevention (CDC), were identical and unchanged for all hospitals. Precautions were initiated on the basis of current or historical MRSA cultures or other standard indications.[6] Results of cultures obtained on admission became available the next day.

STUDY OUTCOMES

The primary outcome was ICU-attributable, MRSA-positive clinical cultures. Screening tests were excluded from all analyses because hospitals implementing universal decolonization discontinued such cultures. Secondary outcomes included ICU-attributable bloodstream infection caused by MRSA and ICU-attributable bloodstream infection caused by any pathogen. Clinical cultures were obtained at the clinician's discretion.

RECRUITMENT AND ELIGIBILITY CRITERIA

Recruitment occurred among the 160 HCA hospitals. Most were community hospitals with single-occupancy ICU rooms. Eligibility criteria included commitment by the hospital administration to have the hospital undergo randomization for the trial, less than 30% of patients in participating adult ICUs receiving either chlorhexidine bathing or intranasal mupirocin at baseline, stable use of infection-prevention initiatives and products during the baseline period, and agreement to refrain from adopting new initiatives that would conflict with the trial. Throughout the study, corporate-wide campaigns were used to ensure compliance with national practice guidelines.[16-18]

Each hospital obtained approval from an institutional review board, with more than 90% of the hospitals delegating review to the Harvard Pilgrim Health Care institutional review board. Patient notices about group-specific protocols were posted in each ICU room. The requirement for written informed consent was waived.[19]

RANDOMIZATION

Randomization was stratified to optimize balance in patient volume and baseline prevalence of MRSA carriage on the basis of clinical cultures and screening tests from July 2008 through June 2009. Hospitals were ranked according to ICU volume and were grouped into sets of six. Within each set, we ordered the hospitals according to the prevalence of MRSA carriage in the ICU. Each group of three consecutive hospitals was randomly assigned, one to each strategy group, with the use of block randomization. Hospitals in states with legislative mandates for MRSA screening in the ICU were similarly and separately randomly assigned to group 1 or 2.

IMPLEMENTATION

On-site activities were implemented by hospital personnel responsible for quality-improvement initiatives, including ICU directors, infection preventionists, and nurse educators. Standard communication channels were used, including group-specific, computer-based training modules and daily electronic documentation by nursing staff for all groups. On-site training in bathing with chlorhexidine-impregnated cloths was provided to hospitals assigned to a decolonization regimen (i.e., group 2 or 3). Nursing directors performed at least three quarterly observations of bathing, including questioning staff about protocol details.

Investigators hosted group-specific coaching teleconferences at least monthly to discuss implementation, compliance, and any new, potentially conflicting initiatives. Compliance assessment involved verification on 1 day per week for each ICU. HCA leadership evaluated trial processes during routine hospital visits. Additional site visits were made at the request of the hospital or if compliance was found to be low.

Intranasal mupirocin ointment 2% (Bactroban, GlaxoSmithKline) and 2% chlorhexidine–impregnated cloths (Sage Products) were used for decolonization. All mupirocin and chlorhexidine-impregnated cloths were purchased at their usual cost by the participating hospitals. In groups 2 and 3, bathing products and products used for wound prophylaxis that were incompatible with chlorhexidine were replaced with compatible products. Adverse events were managed by treating physicians.

DATA COLLECTION AND OUTCOME ASSIGNMENT

Census (i.e., the unit location of each patient for every hospitalization day), microbiologic, pharmacy, supply-chain, nursing-query, and administrative data were obtained from corporate data warehouses, which undergo line-item validation until 99% accuracy is achieved. CDC criteria were used for microbiologic outcomes (first outcome per patient). Pathogens were attributed to an ICU

if the collection date occurred during the period from the third day after ICU admission through the second day after ICU discharge. For bloodstream infections to be attributed to skin-commensal organisms, the same organism had to be isolated from two or more blood cultures obtained within 2 calendar days of one another.[20]

STATISTICAL ANALYSIS

We powered the trial on the basis of the rarest outcome, MRSA bloodstream infection. The study was designed to have 80% power to detect a 40% relative reduction in the rate of MRSA bloodstream infection in group 2, and a 60% relative reduction in the rate in group 3, as compared with group 1. The primary analyses were conducted according to the intention-to-treat principle (as-assigned analyses) and were unadjusted. Proportional-hazards models with shared frailties accounted for clustering within hospitals (see the Supplementary Appendix).[21,22] The intervention effect was assessed on the basis of the interaction between group and study period, reflecting the difference in hazard between the baseline and intervention periods among the groups. Data from the phase-in period were excluded from all analyses. When the null hypothesis of equal changes across the groups was rejected, we examined pairwise comparisons.

Sensitivity analyses included multivariable covariate-adjusted models, as-treated models, models that excluded hospitals in states mandating MRSA screening in the ICU, models that accounted for assigned randomization strata, and models that excluded the small numbers of medical-only and surgical-only ICUs. Adjusted models accounted for age, sex, race, insurance type, coexisting conditions (defined with the use of codes from the *International Classification of Diseases, 9th Revision*), and surgery during the hospital stay. Analyses were performed with the use of SAS software, version 9.3 (SAS Institute).

RESULTS

STUDY PARTICIPANTS

A total of 45 hospitals in 16 states underwent randomization (Fig. 1). A total of 43 (comprising 74 ICUs) implemented the assigned intervention; 2 hospitals that underwent randomization were excluded from all analyses because preexisting exclusion criteria were discovered before the intervention started. One hospital in group 2 (assigned to targeted decolonization) withdrew after the intervention started and was included in the as-assigned analyses but not in the as-treated analyses.

Patient characteristics were similar across groups and between the baseline and intervention periods (Table 1). There was excellent separation of interventions across groups. In group 1, less than 1.0% of patients (range for hospitals in group, 0 to 2.1%) received mupirocin or chlorhexidine. In group 2, a total of 90.8% of MRSA carriers (range for hospitals in group, 56.5 to 100%) received mupirocin and 88.8% (range for hospitals in group, 54.2 to 98.4%) received chlorhexidine. In group 3, a total of 86.1% of patients (range for hospitals in group, 41.0 to 99.1%) received mupirocin and 80.8% (range for hospitals in group, 53.1 to 98.6%) received chlorhexidine.

Reasons for noncompliance included discharge before scheduled bathing or mupirocin administration, discharge before MRSA-positive results were obtained, moribund state of the patient, length of ICU stay of less than 1 day, and patient's decision to decline the intervention. MRSA screening occurred in 97.5% of patients (hospital range, 90.6 to 100%) in group 1, in 98.6% (hospital range, 95.6 to 100%) in group 2, and in 0.7% (hospital range, 0 to 4.7%) in group 3. Of the 69 proposed practice changes that occurred at various hospitals during the trial, 36 conflicted with the trial protocol and were not implemented.

OUTCOMES

For the primary outcome of ICU-attributable, MRSA-positive clinical cultures in the as-assigned analysis, the relative hazards differed significantly among the groups in a comparison of the intervention period with the baseline period ($P=0.01$) (Fig. 2). Pairwise analyses showed that universal decolonization resulted in a significantly greater reduction in the hazard of MRSA-positive clinical cultures than did screening and isolation (hazard ratio in group 3, 0.63; 95% confidence interval [CI], 0.52 to 0.75; hazard ratio in group 1, 0.92; 95% CI, 0.77 to 1.10; $P=0.003$ for test of all groups being equal).

The effects of the strategies on ICU-attributable MRSA bloodstream infection were not significantly different across the study groups ($P=0.11$ for test of all groups being equal), although the hazard reduction with universal decolonization was greater than the reductions with the other strategies (hazard ratio, 0.72 [95% CI,

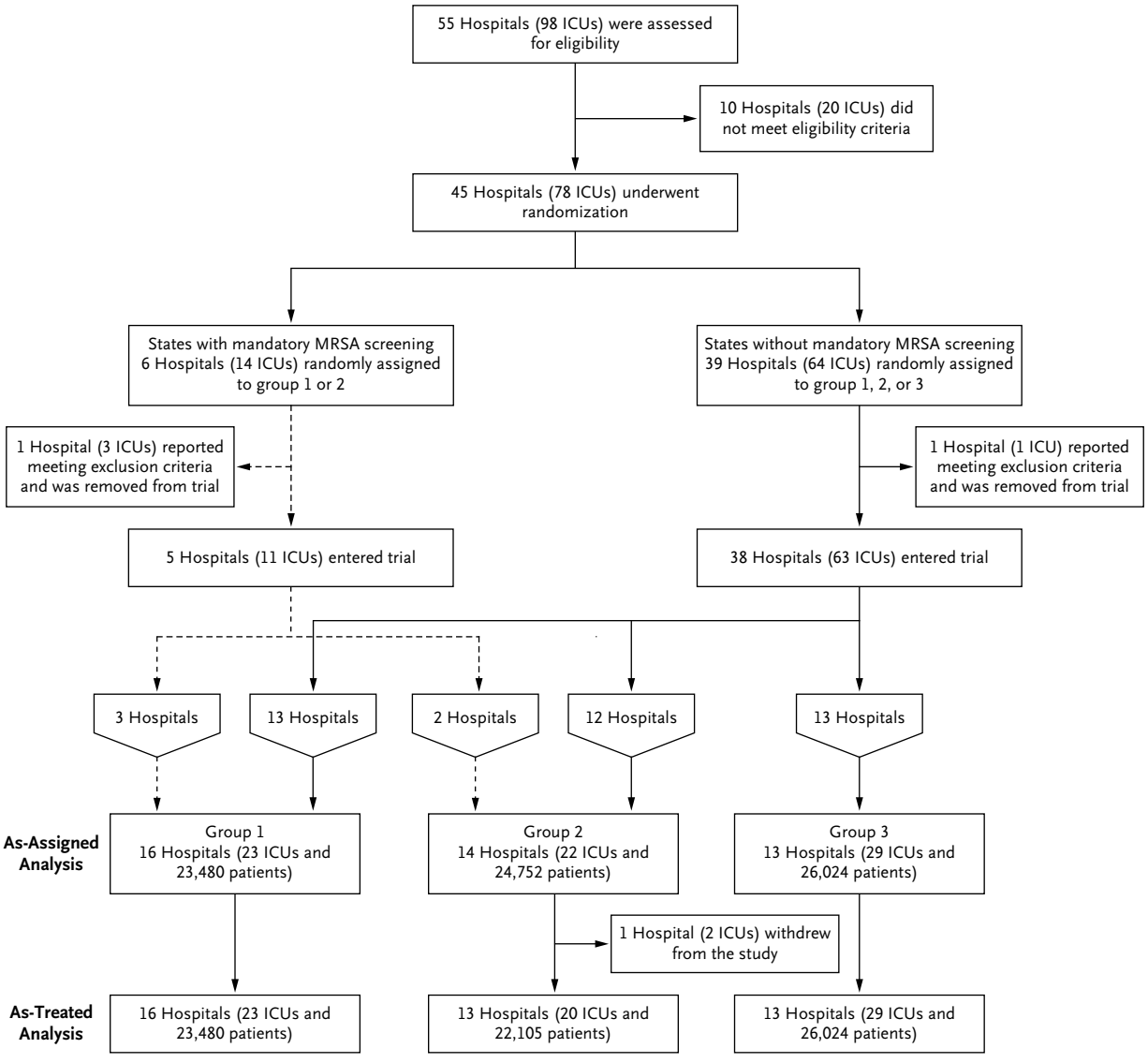

Figure 1. Recruitment, Randomization, and Inclusion in As-Assigned and As-Treated Analyses.

A total of 45 hospitals in 16 states were randomly assigned to a study group, with 43 (comprising 74 ICUs) beginning the assigned intervention; 2 hospitals were excluded from all analyses because preexisting exclusion criteria were discovered before the intervention started. One hospital in group 2 (assigned to targeted decolonization) withdrew after the intervention started and was included in the as-assigned analyses but not the as-treated analyses. The numbers of patients shown in each group are the numbers from the intervention period.

0.48 to 1.08] vs. 1.23 [95% CI, 0.82 to 1.85] for screening and isolation and 1.23 [95% CI, 0.82 to 1.85] for targeted decolonization). For ICU-attributable bloodstream infection from any pathogen, differences among the groups were significant ($P<0.001$ for test of all groups being equal). In pairwise comparisons, universal decolonization resulted in a significantly greater reduction in the hazard of infection (hazard ratio, 0.56; 95% CI, 0.49 to 0.65) than either screening and isolation (hazard ratio, 0.99; 95% CI, 0.84 to 1.16; $P<0.001$) or targeted decolonization (hazard ratio, 0.78; 95% CI, 0.66 to 0.91; $P=0.04$). We found no significant difference in mortality across the groups, although the trial was inadequately powered to observe even relatively large effects on death.

The effect of targeted decolonization was intermediate between the effects of usual care (i.e., screening and isolation) and universal decolonization for ICU-attributable MRSA cultures

Table 1. Characteristics of the Intensive Care Unit (ICU) Population, According to Study Period and Group.*

Variable	12-Mo Baseline Period (N=48,390)			18-Mo Intervention Period (N=74,256)		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
Admission with ICU stay (no.)	15,816	15,218	17,356	23,480	24,752	26,024
Attributable ICU patient-days (no.)	63,135	57,418	69,668	88,222	92,978	101,603
ICU type (no.)†						
Medical	3	5	5	3	5	5
Surgical	1	2	6	1	2	6
Mixed medical and surgical	19	14	18	19	15	17
Hospital stay (days)						
Median	7	7	8	7	7	7
Interquartile range	5–12	5–12	5–12	5–12	5–12	5–12
ICU stay (days)						
Median	3	3	3	3	3	3
Interquartile range	2–5	2–5	2–5	1–5	2–5	2–5
Age (yr)						
Median	65	66	65	65	66	65
Interquartile range	52–77	53–77	51–77	52–77	53–77	52–77
Female sex (%)‡	47.2	47.2	47.9	47.6	47.2	47.5
Nonwhite race (%)§	25.9	22.1	30.8	25.9	23.5	31.7
Coexisting condition (%)						
Diabetes	31.3	33.0	30.7	31.8	32.7	31.5
Renal failure	20.0	20.4	19.0	20.3	22.2	19.7
Cancer	10.4	10.8	14.1	9.9	10.8	13.0
Liver failure	3.4	4.4	3.9	4.0	4.1	4.2
History of MRSA infection (%)¶	10.2	11.5	10.6	9.7	11.1	3.9
Surgery during hospitalization (%)	40.5	38.6	47.5	38.7	37.7	46.2

* Group 1 implemented methicillin-resistant *Staphylococcus aureus* (MRSA) screening and isolation; group 2, targeted decolonization (i.e., screening, isolation, and decolonization of MRSA carriers with chlorhexidine and mupirocin); and group 3, universal decolonization (i.e., no screening and all patients underwent decolonization). At baseline, there were no significant between-group differences. For additional details, see the Supplementary Appendix.

† Differences in the number of ICUs in the groups between the baseline and intervention periods reflect the fact that one ICU in group 2 opened during the trial and one in group 3 closed.

‡ Data were missing for eight patients.

§ Race was determined from electronic administrative data at each hospital.

¶ A history of MRSA infection was identified with the use of all available screening and clinical cultures, with the history defined as MRSA carriage documented by the Hospital Corporation of America during the period from 1 year before admission to day 2 of the ICU stay. Data from group 3 during the intervention period are not comparable to data from the other groups because universal decolonization, without screening, was performed for all patients in this group. As the intervention progressed, patients who were readmitted to the ICU were less likely to be identified as MRSA-positive.

and bloodstream infection from any pathogen. Targeted decolonization resulted in significantly lower rates of bloodstream infection from any pathogen than did screening and isolation; other outcomes did not differ significantly between these two groups. Findings in all sensitivity analyses were similar to those in the as-assigned analysis (Table 2).

Outcome events and their associated rates are shown in Table 3 and in the Supplementary Appendix. There were no significant between-group differences at baseline (P≥0.30 for all outcomes). The baseline rate of MRSA-positive clinical cultures was higher in group 2 (4.3 per 1000 attributable days) than in the other strategy groups (3.4 per 1000 attributable days in each), but the difference was not significant. At baseline, the rate of bloodstream infections from any pathogen was higher in group 3 (6.1 infections per 1000 attributable days) than in groups 2 and 3

(4.2 and 4.8 infections per 1000 attributable days, respectively), but the difference was not significant (P=0.87).

By chance, group 3 contained three of the four hospitals that performed bone marrow and solid-organ transplantations. These three hospitals accounted for much of the excess risk in this group, including 72% of the baseline coagulase-negative staphylococcal bloodstream infections (baseline risk of 0.01 events per patient in these three hospitals). The baseline risk per patient in all other hospitals in group 3 (0.004 events) was similar to the baseline risks in all hospitals in groups 1 and 2 (0.003 events in each group). During the intervention period, the risk declined in the three hospitals (0.002) and in all other hospitals implementing universal decolonization (0.0004), as compared with the baseline risks and as compared with the intervention risk for groups 1 and 2 (0.002 in each group). Analyses with adjustment for coexisting conditions such as cancer supported the findings of the as-assigned analyses (Table 2).

ADVERSE EVENTS

There were seven adverse events (two in group 2 and five in group 3) (see the Supplementary Appendix). All involved mild pruritus or rash after chlorhexidine bathing and resolved on discontinuation of the use of chlorhexidine-impregnated cloths.

DISCUSSION

Universal decolonization of patients in the ICU was the most effective strategy, significantly reducing MRSA-positive clinical cultures by 37% and bloodstream infections from any pathogen by 44%. This effect was observed under usual practice conditions in a wide array of hospitals, including community hospitals, that had already implemented national, evidence-based recommendations for preventing health care–associated MRSA infection. A total of 181 patients would need to undergo decolonization to prevent one MRSA-positive clinical culture, and 54 patients would need to undergo decolonization to prevent one bloodstream infection from any pathogen.

Several factors may account for our observation that universal decolonization had a greater preventive effect than the two other strategies. First, chlorhexidine reduces skin colonization by many pathogens, thus protecting patients in the

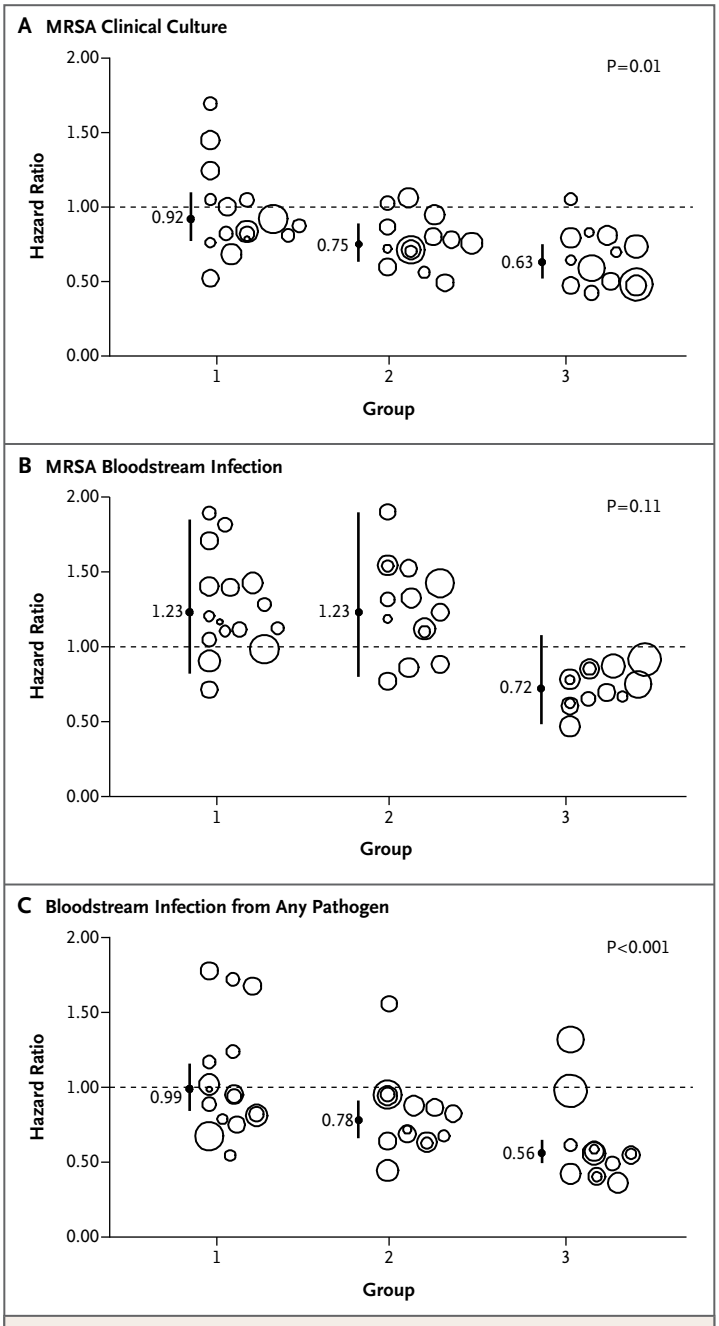

Figure 2. Effect of Trial Interventions on Outcomes.

Shown are group-specific hazard ratios and 95% confidence intervals (indicated by vertical lines) for outcomes attributable to the intensive care unit. Results are based on unadjusted proportional-hazards models that accounted for clustering within hospitals. Analyses were based on the as-assigned status of hospitals. Panel A shows hazard ratios for clinical cultures that were positive for methicillin-resistant *Staphylococcus aureus* (MRSA) infection, Panel B hazard ratios for MRSA bloodstream infection, and Panel C hazard ratios for bloodstream infection from any pathogen. Bubble plots of hazard ratios (predicted random effects or exponentiated frailties) from individual hospitals relative to their group effects are shown. The size of the bubble indicates the relative number of patients contributing data to the trial.

Table 2. Hazard Ratios for Primary and Secondary Trial Outcomes.

Variable	Hazard Ratio (95% CI)			Overall P Value
	Group 1	Group 2	Group 3	
MRSA				
Clinical culture				
As-assigned analysis				
Unadjusted*	0.92 (0.77–1.10)	0.75 (0.63–0.89)	0.63 (0.52–0.75)	0.01
Adjusted	0.92 (0.77–1.10)	0.74 (0.62–0.88)	0.64 (0.53–0.77)	0.02
As-treated analysis, unadjusted	0.93 (0.78–1.11)	0.78 (0.65–0.94)	0.63 (0.52–0.75)	0.01
Randomization to all three groups, unadjusted analysis†	0.93 (0.76–1.13)	0.74 (0.62–0.89)	0.63 (0.52–0.75)	0.02
Randomization strata accounted for, unadjusted analysis	0.93 (0.78–1.11)	0.75 (0.63–0.89)	0.63 (0.52–0.75)	0.01
Mixed medical and surgical ICUs only, unadjusted analysis	0.93 (0.76–1.12)	0.71 (0.59–0.86)	0.57 (0.46–0.71)	0.004
Bloodstream infection				
As-assigned analysis				
Unadjusted	1.23 (0.82–1.85)	1.23 (0.80–1.90)	0.72 (0.48–1.08)	0.11
Adjusted	1.20 (0.80–1.81)	1.19 (0.77–1.84)	0.74 (0.49–1.12)	0.18
As-treated analysis, unadjusted	1.24 (0.82–1.86)	1.34 (0.84–2.15)	0.72 (0.48–1.08)	0.08
Randomization to all three groups, unadjusted analysis†	1.15 (0.74–1.79)	1.18 (0.74–1.89)	0.72 (0.48–1.08)	0.19
Randomization strata accounted for, unadjusted analysis	1.24 (0.83–1.86)	1.22 (0.79–1.88)	0.73 (0.48–1.09)	0.12
Mixed medical and surgical ICUs only, unadjusted analysis	1.15 (0.75–1.77)	1.20 (0.75–1.93)	0.72 (0.44–1.20)	0.28
Bloodstream infection from any pathogen				
As-assigned analysis				
Unadjusted‡	0.99 (0.84–1.16)	0.78 (0.66–0.91)	0.56 (0.49–0.65)	<0.001
Adjusted	0.98 (0.84–1.15)	0.77 (0.65–0.90)	0.55 (0.48–0.64)	<0.001
As-treated analysis, unadjusted	0.99 (0.84–1.16)	0.78 (0.66–0.92)	0.56 (0.49–0.65)	<0.001
Randomization to all three groups, unadjusted analysis†	0.93 (0.78–1.10)	0.77 (0.65–0.91)	0.56 (0.49–0.65)	<0.001
Randomization strata accounted for, unadjusted analysis	0.99 (0.84–1.16)	0.78 (0.66–0.91)	0.56 (0.49–0.65)	<0.001
Mixed medical and surgical ICUs only, unadjusted analysis	0.96 (0.81–1.13)	0.80 (0.67–0.96)	0.59 (0.50–0.69)	<0.001

* P values in the pairwise analysis were as follows: P=0.09 for the comparison of group 2 with group 1, P=0.003 for the comparison of group 3 with group 1, and P=0.16 for the comparison of group 3 with group 2.
† This analysis excluded the five hospitals in states with laws requiring MRSA screening in the ICU.
‡ P values in the pairwise analysis were as follows: P=0.04 for the comparison of group 2 with group 1, P<0.001 for the comparison of group 3 with group 1, and P=0.003 for the comparison of group 3 with group 2.

ICU from their own microbiota during a period of heightened vulnerability to infection.[11-14] Second, universal decolonization reduces the environmental microbial burden, reducing opportunities for patient-to-patient transmission.[14,23] Third, universal decolonization began on the first ICU day, thus avoiding the delay in decolonization pending the results of screening tests.

Another potential benefit of universal decolonization is the elimination of MRSA surveillance tests and the associated reduction in contact precautions, which can interfere with care.[24] These findings have implications for legislative mandates requiring MRSA screening in the ICU.[25] Nevertheless, there may be occasions when screening is warranted, such as periodic monitor-

Table 3. Frequency and Rates of Outcomes during the Baseline and Intervention Periods, According to Study Group.*

Outcome	Group 1		Group 2		Group 3	
	Baseline	Intervention	Baseline	Intervention	Baseline	Intervention
	no. of events (crude rate per 1000 patient-days)					
MRSA clinical cultures	216 (3.4)	279 (3.2)	245 (4.3)	301 (3.2)	240 (3.4)	217 (2.1)
Bloodstream infection						
MRSA	37 (0.6)	63 (0.7)	31 (0.5)	61 (0.6)	46 (0.6)	48 (0.5)
Any pathogen†	265 (4.2)	360 (4.1)	273 (4.8)	341 (3.7)	412 (6.1)	356 (3.6)
Gram-positive organism	165 (2.6)	228 (2.6)	159 (2.8)	203 (2.2)	253 (3.7)	187 (1.9)
Skin commensal organism	50 (0.8)	55 (0.6)	49 (0.9)	46 (0.5)	120 (1.8)	38 (0.4)
Noncommensal organism	115 (1.8)	173 (2.0)	110 (1.9)	157 (1.7)	133 (2.0)	149 (1.5)
Gram-negative organism	62 (1.0)	83 (0.9)	58 (1.0)	75 (0.8)	100 (1.5)	107 (1.1)
Candida species	38 (0.6)	49 (0.6)	56 (1.0)	63 (0.7)	59 (0.9)	62 (0.6)

* Provided rates are crude rates, defined as the number of events per 1000 ICU-attributable patient-days at risk for the event. Patient-days after each event were excluded from the analysis; thus, denominators are different for each cell and are not included.

† The distribution of all bloodstream events is based on the first eligible event from any pathogen per patient. For example, a patient with a first ICU-associated bloodstream infection (due to a gram-positive organism) followed by a second ICU-associated bloodstream infection (due to a gram-negative organism) would be counted only in the listing for gram-positive organisms.

ing of resistance. Formal cost-effectiveness analysis is needed to understand whether the observed cessation of screening, reduced contact precautions, and reduced infections offset the product costs and the potential emergence of resistance. It remains to be seen whether universal decolonization can obviate the need for all contact precautions for carriers of MRSA or other multidrug-resistant organisms.

The benefits attributable to universal decolonization are notable for several reasons. First, the large reductions in infections that we observed were achieved over and above the substantial reductions in bloodstream infections due to MRSA and other pathogens that have occurred at HCA hospitals and other hospitals nationally within the past decade.[3,26,27] Our study included a direct comparison with high-compliance active surveillance and accompanying contact precautions, which have been associated with decreased rates of MRSA transmission and MRSA bloodstream infection.[9,16,25,27,28] Hospitals that have not fully implemented a strategy of screening and isolation may derive additional benefit from this intervention. Second, universal decolonization was implemented as part of routine practice with the use of the usual infrastructure of the hospital for practice change, without the need for on-site study personnel. These results are thus likely to be generally achievable as part of regular practice. Third, the intervention was effective in community hospitals, which make up the majority of U.S. hospitals.

The reduction in bloodstream infections from any pathogen occurred in the context of the relatively higher baseline rates of infection for all pathogen types (gram-positive, gram-negative, and fungal) in group 3, as compared with the other groups. One explanation for these high rates is that this group included three of the four hospitals providing bone marrow and solid-organ transplantations. Such differences across groups are largely accounted for by comparing the outcome rate in each hospital with that hospital's baseline rate, providing reassurance that the benefit is attributable to decolonization rather than to baseline variation in case mix or clinical practices across groups. In addition, group 3 did not have higher baseline rates of MRSA-positive clinical cultures than the other groups did, so regression to the mean would not explain the beneficial effect on that outcome.

It is unknown whether a threshold level of compliance with universal decolonization is required to achieve the observed benefit or whether a compliance rate higher than the rate in our study (85%) would yield further improvement. Although hospital staff members were aware of the assigned strategy, which could have resulted in unmeasured behavior that affected trial outcomes,[29] it is unclear what unmeasured behavior could effect a 44% improvement.

This trial provides no information on the attributable benefit of mupirocin, either alone or

in combination with chlorhexidine. On the basis of microbiologic activity, any reduction in non–*S. aureus* bloodstream infections should be attributed to chlorhexidine. However, for *S. aureus*, the most common cause of health care–associated infection,[4] clearance of the nasal reservoir in combination with body decolonization may be superior to either method alone.[30]

Widespread use of chlorhexidine and mupirocin could possibly engender resistance.[9,31,32] Mupirocin resistance has been reported in some studies of MRSA decolonization,[9,30] but not all such studies.[8,32-35] MRSA resistance to chlorhexidine lacks a standard definition, but recent reports suggest that resistant strains are rare in the United States.[36,37] A gene encoding a multidrug efflux pump that is active against chlorhexidine has been reported in MRSA,[38] but its clinical significance is not understood. Reduced susceptibility to chlorhexidine has also been reported in gram-negative bacteria.[39] It will therefore be important for surveillance programs to monitor mupirocin and chlorhexidine resistance.[3,8]

This trial was designed as a pragmatic, comparative-effectiveness trial implemented primarily through usual hospital processes.[15,19] We chose this design to obtain results that could be generalized to the broadest set of hospitals, to use processes potentially adoptable by many hospitals, and to conduct a study of sufficient size — all ICUs in dozens of hospitals — with the available resources. Randomization of entire hospitals allowed us to recruit a broad array of hospitals, including community hospitals with no prior experience in clinical research. Finally, the efficient design meant that the total cost of the trial, including the decolonizing product and contributed personnel effort, was less than $3 million, or approximately $40 per patient.

Opportunities to integrate comparative-effectiveness research into routine clinical settings with the use of methods such as those used in the current study will increase as more hospitals adopt electronic health data systems and as multicenter care-improvement collaboratives develop. This trial also highlights the importance of performing rigorous evaluation of quality-improvement initiatives and controlling the introduction of new processes and products. Harnessing such initiatives to identify best practices is an important tenet of the advocacy by the Institute of Medicine for a learning health system.[40]

In conclusion, we found that universal decolonization prevented infection, obviated the need for surveillance testing, and reduced contact isolation. If this practice is widely implemented, vigilance for emerging resistance will be required.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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CORRESPONDENCE

Targeted Decolonization to Prevent ICU Infections

TO THE EDITOR: Huang and colleagues (June 13 issue)[1] report that universal decolonization was more effective than targeted decolonization or screening and isolation in reducing rates of methicillin-resistant *Staphylococcus aureus* (MRSA) clinical isolates. However, the study protocol indicates that patients with a history of MRSA infection who underwent universal decolonization were still isolated; of the patients undergoing universal decolonization, 10.6% had a MRSA history during the observation period and 3.7% had such a history during the intervention period. This suggests that one third of patients with positive tests for MRSA in this group may have been isolated and that universal decolonization meant more than simply decolonization. The protocol describes extensive training and regular input in hospitals that were randomly assigned to targeted or universal decolonization, but the facilities that were assigned to screening and isolation (standard of care) did not appear to receive this training and input. It is conceivable that training led to improved infection control and reduced infection rates that were independent of the study-specific interventions. The protocol indicates that resistance to mupirocin or chlorhexidine was a secondary outcome. These data are not reported but are required to weigh the gains from universal decolonization against the emergence of resistance.

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TO THE EDITOR: Huang et al. state that "universal decolonization . . . obviated the need for surveillance testing," a conclusion that seems to be based on a lack of change in the culture rate for MRSA in the screening-and-isolation group. However, the lack of change may have been because interventions were applied to intensive care units (ICUs) in which a screening-and-isolation program had been in place for more than 30 months. This program resulted in a 39% decline in central-catheter–associated bloodstream infections and a 54% decrease in ventilator-associated pneumonias.[1] The Department of Veterans Affairs observed a similar effect. After an initial 62% decline in health care–associated MRSA infections during the first 33 months of the Veterans Affairs MRSA Prevention Initiative,[2] rates continued to decline in the ICUs during the next 24 months. However, the difference was not significant, suggesting the effect was becoming asymptotic.[3] The effect of screening and isolation in the study by Huang et al. may have been better assessed in

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ICUs in which the intervention was novel. We agree with the authors that "hospitals that have not fully implemented a strategy of screening and isolation may derive additional benefit from this intervention."

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DOI: 10.1056/NEJMc1309704

TO THE EDITOR: Several clarifications would be useful in the study by Huang et al. with respect to targeted versus universal decolonization of patients in the ICU. Why would one expect that hospitals already using MRSA screening and isolation (Hospital Corporation of America and Illinois hospitals) would have decreased MRSA culture rates when there was no new or additional intervention implemented at these hospitals?[1,2] MRSA culture rather than polymerase-chain-reaction (PCR) assay resulted in MRSA-positive patients remaining out of isolation in the ICU, often until discharge. Why did the intervention not reduce MRSA bloodstream infections? The rate of "MRSA-positive clinical cultures," the primary outcome, is never defined; distribution of MRSA cultures according to site would be useful. The intervention reduced the rate of bloodstream infections caused by "skin commensal organisms" (probably mostly coagulase-negative staphylococci, although the data are not shown). Subtracting the bloodstream infections caused by skin commensal organisms from those caused by "any pathogen" appears to result in a nonsignificant reduction in bloodstream infections caused by the remaining pathogens. The investigators should have evaluated resistance to mupirocin and chlorhexidine, and such resistance should remain an important concern and caution for those contemplating universal decolonization of patients in the ICU.[3,4]

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TO THE EDITOR: Huang et al. state that universal decolonization with the use of chlorhexidine is more effective than other strategies for MRSA decolonization, screening, and isolation in reducing rates of MRSA clinical isolates and bloodstream infections from any pathogen. The latter was mainly caused by a reduction in the rate of bloodstream infections caused by coagulase-negative staphylococcus, but the rate of MRSA bloodstream infections did not change significantly. Even though the investigators used the criteria of the Centers for Disease Control and Prevention for skin commensal organisms causing bacteremia, it is not clear which specimen collection technique was used (e.g., central vs. peripheral-blood cultures).[1] Therefore, a reduction in the contamination rate for coagulase-negative staphylococcus blood cultures rather than in the rate of true bacteremia cannot be ruled out. The authors do not provide data on the minimum inhibitory concentrations for chlorhexidine in cultures of organisms obtained from patients before

and after bathing with chlorhexidine-impregnated cloths. This is of particular importance, since in one study, the continuous use of chlorhexidine increased the rate of chlorhexidine-resistant MRSA isolates by up to 47%.[2] We conclude that on the basis of the vague collection techniques for blood cultures, the absent effect on MRSA bloodstream infections, and the threat of chlorhexidine resistance, great caution should be exercised in transferring the study's results into clinical practice.

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TO THE EDITOR: In their editorial discussing inpatient MRSA screening and decolonization, Edmond and Wenzel[1] question the wisdom of targeted detection and isolation of carbapenem-resistant Enterobacteriaceae (CRE). We disagree. The decision to pursue "vertical" or "horizontal" interventions versus multidrug-resistant organisms (MDROs) should be made while considering the pathogens, their prevalence, and the resources available to implement control measures. Unlike MRSA, CRE has no established decolonization protocol; the effect of selective digestive decontamination on antimicrobial resistance has been understudied. A horizontal intervention in a population in which CRE must be considered would therefore require placing every patient in contact isolation, a costly proposition unlikely to be met with high compliance. Moreover, targeted interventions to prevent the spread of a sporadic MDRO have been shown to be effective.[2] In the Israeli CRE outbreak, a vertical national intervention, which was aimed at detecting and isolating carriers, was necessary to contain spread.[3] The Israeli approach has since been incorporated into international guidelines.[4,5] Horizontal and vertical approaches are not mutually exclusive. A comprehensive strategy of MDRO prevention should use both approaches, with periodic evaluation of target attainment.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Cartwright et al. inquire whether training and routine input produced unanticipated changes that reduced infection. This is unlikely. First, training was limited to intervention implementation (e.g., how to warm and apply cloths). Second, we monitored and restricted new practices that would conflict with the trial. Third, all study groups received routine input through monthly coaching calls. Fourth, Hospital Corporation of America continued its usual campaigns in all hospitals, emphasizing adherence to best-practice guidelines.

We agree with Evans et al. and Jarvis that our study provides no information about the absolute effect of screening and isolation. We published evidence suggesting that a strategy of screening and isolation reduces infection.[1] Regardless of whether such a strategy produces benefit, the finding that universal decolonization produced sizable and significant incremental reductions in the MRSA burden and in rates of all-cause bloodstream infections suggests that

universal decolonization is the more effective strategy. Furthermore, the use of PCR would be unlikely to change the study's findings. The use of chromogenic agar provided next-day results in our trial. Recent evidence suggests that the additional isolation time gained by PCR is insufficient to reduce transmission or infection.[2]

With regard to the comments by Jarvis and Krause et al.: our study had the power to determine a relative reduction of 60% in the rate of MRSA bloodstream infections with universal decolonization. Thus, it is not surprising that the observed 28% reduction was not statistically significant. However, the direction of this reduction is similar to the statistically significant change in MRSA clinical cultures (our primary outcome) and all-cause bloodstream infections. Therefore, our finding is consistent with a positive effect on MRSA bloodstream infections. Certainly, the lack of a significant difference in this trial is not evidence against an effect.

Furthermore, the larger proportion of bloodstream infections caused by coagulase-negative staphylococcus and *Staphylococcus aureus* is consistent with the usual distribution of bloodstream pathogens. We did not test the effect on gram-positive, gram-negative, and fungal pathogens, since such testing was not prespecified in our analysis plan. However, the reduction in these types of pathogens in the group receiving universal decolonization appears to be proportional to their prevalence.

As we state in our article and as many of the correspondents note, it will be important to monitor the effect of universal decolonization on the emergence of resistance to chlorhexidine and mupirocin.

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Since publication of their article, the authors report no further potential conflict of interest.

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THE EDITORIALISTS REPLY: We agree with Schwaber et al. that vertical infection-control interventions, such as active detection and isolation, are useful in outbreak settings. However, for control of endemic pathogens, we conclude that horizontal interventions should be the cornerstone of prevention. Given the high direct and opportunity costs associated with vertical strategies, basic horizontal practices, such as hand hygiene, may not be sufficiently emphasized. Lastly, we agree that horizontal and vertical interventions are not mutually exclusive. However, the key question remains: given an optimally functioning horizontal program (i.e., near perfect compliance with hand hygiene and chlorhexidine bathing), what is the incremental benefit of a superimposed vertical strategy?

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Treatment of Acute Promyelocytic Leukemia

TO THE EDITOR: Lo-Coco et al. (July 11 issue)[1] report that a combination of all-*trans* retinoic acid (ATRA) and arsenic trioxide as an induction and consolidation therapy was not inferior and was possibly superior to ATRA plus chemotherapy in patients with low-to-intermediate-risk acute promyelocytic leukemia (APL).[1] It is notable that the advantage of ATRA plus arsenic trioxide therapy was mainly its lower mortality from toxicity. We assume that the advantage of the less