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Nasal Iodophor Antiseptic vs Nasal Mupirocin Antibiotic in the Setting of Chlorhexidine Bathing to Prevent Infections in Adult ICUs
A Randomized Clinical Trial

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IMPORTANCE Universal nasal mupirocin plus chlorhexidine gluconate (CHG) bathing in intensive care units (ICUs) prevents methicillin-resistant *Staphylococcus aureus* (MRSA) infections and all-cause bloodstream infections. Antibiotic resistance to mupirocin has raised questions about whether an antiseptic could be advantageous for ICU decolonization.

OBJECTIVE To compare the effectiveness of iodophor vs mupirocin for universal ICU nasal decolonization in combination with CHG bathing.

DESIGN, SETTING, AND PARTICIPANTS Two-group noninferiority, pragmatic, cluster-randomized trial conducted in US community hospitals, all of which used mupirocin-CHG for universal decolonization in ICUs at baseline. Adult ICU patients in 137 randomized hospitals during baseline (May 1, 2015-April 30, 2017) and intervention (November 1, 2017-April 30, 2019) were included.

INTERVENTION Universal decolonization involving switching to iodophor-CHG (intervention) or continuing mupirocin-CHG (baseline).

MAIN OUTCOMES AND MEASURES ICU-attributable *S aureus* clinical cultures (primary outcome), MRSA clinical cultures, and all-cause bloodstream infections were evaluated using proportional hazard models to assess differences from baseline to intervention periods between the strategies. Results were also compared with a 2009-2011 trial of mupirocin-CHG vs no decolonization in the same hospital network. The prespecified noninferiority margin for the primary outcome was 10%.

RESULTS Among the 801 668 admissions in 233 ICUs, the participants' mean (SD) age was 63.4 (17.2) years, 46.3% were female, and the mean (SD) ICU length of stay was 4.8 (4.7) days. Hazard ratios (HRs) for *S aureus* clinical isolates in the intervention vs baseline periods were 1.17 for iodophor-CHG (raw rate: 5.0 vs 4.3/1000 ICU-attributable days) and 0.99 for mupirocin-CHG (raw rate: 4.1 vs 4.0/1000 ICU-attributable days) (HR difference in differences significantly lower by 18.4% [95% CI, 10.7%-26.6%] for mupirocin-CHG, $P < .001$). For MRSA clinical cultures, HRs were 1.13 for iodophor-CHG (raw rate: 2.3 vs 2.1/1000 ICU-attributable days) and 0.99 for mupirocin-CHG (raw rate: 2.0 vs 2.0/1000 ICU-attributable days) (HR difference in differences significantly lower by 14.1% [95% CI, 3.7%-25.5%] for mupirocin-CHG, $P = .007$). For all-pathogen bloodstream infections, HRs were 1.00 (2.7 vs 2.7/1000) for iodophor-CHG and 1.01 (2.6 vs 2.6/1000) for mupirocin-CHG (nonsignificant HR difference in differences, −0.9% [95% CI, −9.0% to 8.0%]; $P = .84$). Compared with the 2009-2011 trial, the 30-day relative reduction in hazards in the mupirocin-CHG group relative to no decolonization (2009-2011 trial) were as follows: *S aureus* clinical cultures (current trial: 48.1% [95% CI, 35.6%-60.1%]; 2009-2011 trial: 58.8% [95% CI, 47.5%-70.7%]) and bloodstream infection rates (current trial: 70.4% [95% CI, 62.9%-77.8%]; 2009-2011 trial: 60.1% [95% CI, 49.1%-70.7%]).

CONCLUSIONS AND RELEVANCE Nasal iodophor antiseptic did not meet criteria to be considered noninferior to nasal mupirocin antibiotic for the outcome of *S aureus* clinical cultures in adult ICU patients in the context of daily CHG bathing. In addition, the results were consistent with nasal iodophor being inferior to nasal mupirocin.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03140423

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Visual Abstract

Multimedia

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Staphylococcus aureus has remained a common pathogen in intensive care units (ICUs), with estimates in North American hospitals that *S aureus* has caused 23% of ICU infections.[1] Both methicillin-susceptible *S aureus* and methicillin-resistant *S aureus* (MRSA) have produced a wide spectrum of ICU-associated infections, including ventilator-associated pneumonia, bloodstream infections, and surgical site infections.[2,3]

Universal ICU decolonization involving nasal mupirocin and daily chlorhexidine gluconate (CHG) bathing reduced MRSA clinical cultures by 37% and all-cause bloodstream infections by 44% in the 43-hospital cluster-randomized REDUCE MRSA Trial (2009-2011).[4] Universal ICU decolonization was superior to universal screening followed by either contact precautions alone or contact precautions plus targeted decolonization for MRSA carriers.

While universal CHG antiseptic bathing has been broadly adopted in ICUs,[5-7] adoption of mupirocin as a universal topical antibiotic has been slowed by concerns for engendering mupirocin resistance.[8-10] A 2021 survey of 5000 US hospitals found that 63% of US hospitals have adopted universal ICU CHG bathing, but only 59% of those hospitals (37% overall) have adopted universal ICU nasal decolonization.[6] This cluster-randomized, pragmatic, comparative effectiveness trial in adult ICUs was conducted to assess whether universal nasal antiseptic povidone-iodine (iodophor), to which minimal *S aureus* resistance is expected,[11] was an acceptable alternative to universal nasal mupirocin for reducing *S aureus* and MRSA clinical cultures as well as all-cause bloodstream infection in the setting of daily CHG bathing.

Key Points

Question Does nasal iodophor antiseptic work as well as nasal mupirocin antibiotic for preventing *Staphylococcus aureus* clinical cultures in intensive care unit (ICU) patients receiving daily chlorhexidine bathing?

Findings In this noninferiority, cluster-randomized trial of 801 668 admissions at 137 hospitals, exposure to nasal mupirocin significantly reduced *S aureus* clinical cultures by 18.4% compared with iodophor in adult ICUs in the context of daily chlorhexidine bathing.

Meaning Nasal iodophor antiseptic did not meet criteria to be considered noninferior to nasal mupirocin antibiotic for the outcome of *S aureus* clinical cultures in adult ICU patients in the context of daily CHG bathing. In addition, the results were consistent with nasal iodophor being inferior to nasal mupirocin.

Methods

Study Design

The Mupirocin-Iodophor ICU Decolonization Swap Out Trial was a 2-group, pragmatic, noninferiority, cluster-randomized trial comparing 2 universal decolonization strategies in adult ICUs in HCA Healthcare (HCA) hospitals. The trial protocol and statistical analysis plan are in Supplement 1. The trial consisted of a 24-month baseline period from May 1, 2015, to April 30, 2017; a phase-in period from May 1 to October 31, 2017; and an 18-month intervention period from November 1, 2017, to April 30, 2019. All adult ICUs in a participating hospital were assigned to the same strategy. Intervention period strategies included universal iodophor-CHG decolonization. All ICU patients in this group received twice-daily intranasal 10% povidone-iodine swabs for 5 days plus daily 2% no-rinse CHG cloth baths for the entire ICU stay. In the universal mupirocin-CHG decolonization (routine care group), all ICU patients received twice-daily intranasal 2% mupirocin ointment for 5 days plus daily 2% no-rinse CHG cloth baths for the entire ICU stay.

During the baseline period, all HCA hospitals were using mupirocin-CHG for universal ICU decolonization. HCA adopted this practice systemwide in 2013. Contact precaution policies for MRSA were required to be stable during the baseline, phase-in, and intervention periods for participating hospitals. This trial was registered at ClinicalTrials.gov (NCT03140423).

Harvard Pilgrim Health Care provided centralized institutional review board oversight. As a minimal-risk evaluation of quality improvement protocols, written informed consent from individual patients was not required.

Study Outcomes

The primary outcome was *S aureus* clinical cultures attributed to the ICU (occurring from ICU day 3 through 2 days after ICU discharge). Surveillance tests were excluded from all analyses. Secondary outcomes included MRSA clinical cultures and all-cause bloodstream infection attributed to the ICU stay.

Recruitment and Eligibility Criteria

Recruitment of hospitals occurred within HCA's community hospital system. Eligibility criteria included having at least 1 adult ICU, stable infection prevention initiatives and products during the baseline period, and agreement to refrain from new initiatives conflicting with the trial. Exclusion criteria included an ICU mean length of stay of less than 2 days and having an electronic health record (EHR) other than MEDITECH.

Randomization

Hospitals were randomized in a 1:1 ratio. Aggregated baseline hospital data were used to establish similar hospital pairs based on key variables. These variables included mean monthly ICU-attributable patient-days; rates (per 1000 ICU-attributable patient-days) of *S aureus* clinical cultures, MRSA clinical cultures, and all-cause bloodstream infections; the proportion of mupirocin-resistant MRSA strains from a baseline sampling; ICU mupirocin and CHG adherence; median ICU length of stay; mean Elixhauser comorbidity count score[12]; ICU proportion of patients with surgery; ICU proportion of patients with a history of MRSA; and whether the hospital had dedicated services for immunocompromised hosts (oncology, transplant). Pairing was done using a web-based Shiny application (Posit Software) calculating the Mahalanobis distance between facilities across baseline values of weighted variables and choosing pairings with the minimum mean within-pair distance (Goldilocks approach).[13,14]

Implementation

On-site activities were implemented by hospital personnel responsible for quality improvement initiatives, including ICU directors, infection preventionists, physician leaders, and nurse educators. Usual training and documentation processes were used, including group-specific computer-based training modules and nursing EHR documentation each shift. At least 3 bathing observations per month were performed using a standardized skills assessment form, which included questions about protocol details.

Study investigators held monthly group-specific coaching calls to discuss implementation, review adherence reports, and solicit reports of any adverse events or new potentially conflicting initiatives. In addition, ICU-specific decolonization adherence reports were available on-demand and emailed monthly to local champions and unit directors. Low performance was addressed through the usual quality improvement process involving discussions between hospital, division, and corporate HCA leadership to identify opportunities for improvement. Adverse events were managed by the patient's clinical team.

Data Collection and Outcome Assignment

Demographic, census, microbiology, pharmacy, supply chain, nursing queries, and administrative data were obtained from HCA data warehouses. Race and ethnicity were included as collected in the HCA EHR to address population diversity and generalizability. Microbiologic outcomes represented the first per patient within the ICU-attributable period. Pathogens were attributed to an ICU if the collection date occurred more than 2 days after ICU admission through 2 days after ICU discharge; 2 or more positive blood cultures within 2 calendar-days were required for skin commensals to be classified as bloodstream infections.[15,16]

Statistical Analysis

The trial sample size was chosen to achieve more than 80% power to detect noninferiority of iodophor-CHG compared with mupirocin-CHG within a hazard ratio (HR) of 1.1 for the primary outcome of *S aureus* clinical cultures. The main results reflected as-randomized, unadjusted analyses based on proportional hazard models for time to *S aureus* clinical culture with shared frailties accounting for clustering by hospital and person across admissions (details in Supplement 1). The intervention effect was estimated by the group-by-treatment period interaction, which assesses the difference from baseline to intervention periods between the strategies. Phase-in period data were excluded from all analyses.

Additional analyses included (1) multivariable covariate-adjusted as-randomized models and (2) as-treated models. Covariates were age, sex, race and ethnicity, Medicaid insurance, Elixhauser comorbidity count score,[12] discharge to nursing home within 90 days prior to admission, surgery during admission, history of MRSA, history of other multidrug-resistant organisms (ie, vancomycin-resistant *Enterococcus*, extended-spectrum beta-lactamase producers, carbapenem-resistant Enterobacterales, multidrug-resistant *Acinetobacter*, multidrug-resistant *Pseudomonas*, *Pseudomonas* sp, carbapenem-resistant *Acinetobacter*), ICU type, and presence of transplant services at the participating hospital. As-treated models were conducted by limiting the population to patients who received at least 2 doses of study product, excluding those who had both mupirocin and iodophor exposure, and removing data after hospitals dropped from the trial.

To assess whether the effectiveness of mupirocin-CHG had diminished since the original demonstration of efficacy, presumably due to the emergence of resistance following nearly a decade of sustained use in the same health system, the cumulative hazards of trial outcomes were used to compare the intervention period of the current trial (November 2017-April 2019) to the baseline (January-December 2009) and intervention (April 2010-September 2011) periods of a prior cluster-randomized trial in the same health system (REDUCE MRSA Trial) in a post hoc analysis.[4] The number of ICU-attributable days until the occurrence of trial outcomes were compared between mupirocin-CHG in 2017-2019 (routine care, current trial) and mupirocin-CHG in the 2010-2011 trial using the log-rank test. The iodophor-CHG strategy in 2017-2019 (current trial) was compared with the no-decolonization baseline strategy in 2009 to assess the strategy impact against a historical control. Of the 13 hospitals in the mupirocin-CHG group of the REDUCE MRSA Trial, 12 (92.3%) participated in the current trial.

Significance was 2-sided at $\alpha = .05$ for the primary outcome, with a prespecified noninferiority margin of 10%.

All analyses used SAS software (version 9.4, SAS Institute Inc) or R Statistical Software (version 4.2.0, R Core Team 2021).

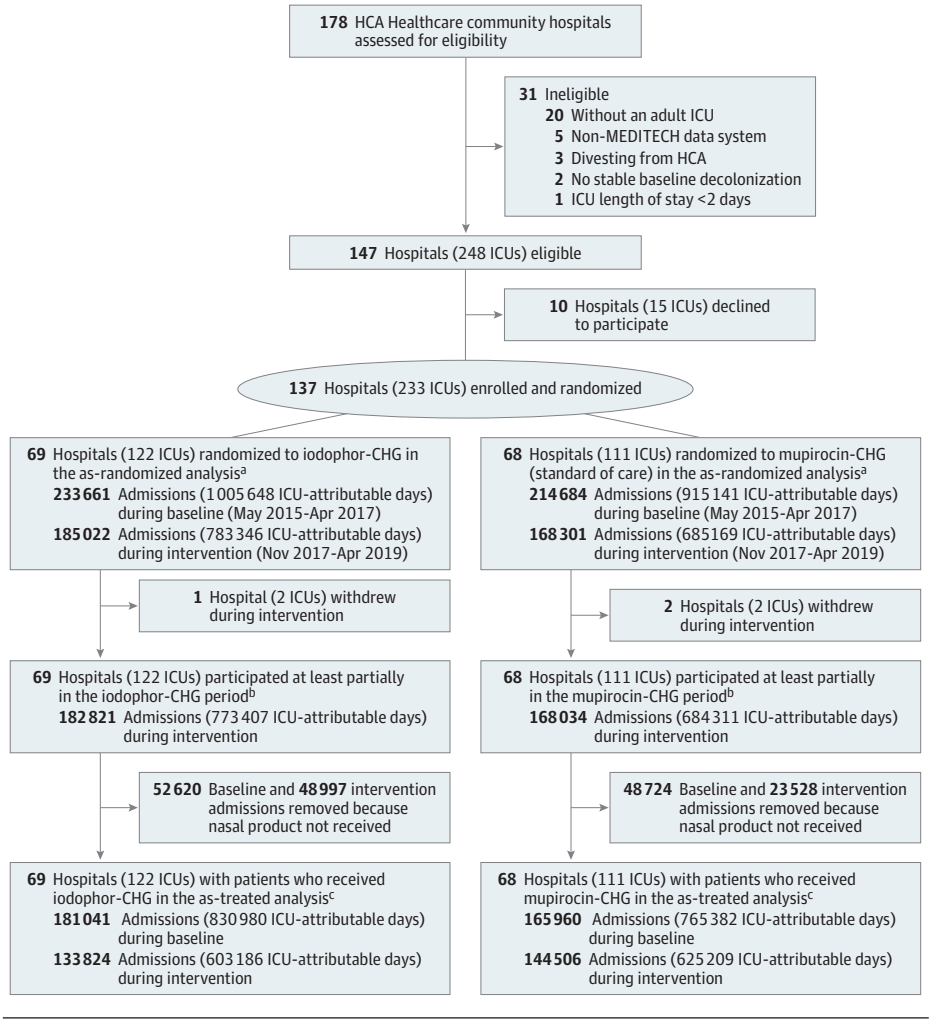
Results

Of 178 HCA hospitals, 31 were ineligible due to not having an adult ICU (n = 20), having an EHR other than MEDITECH (n = 5), having planned divestment from HCA (n = 3), being new to HCA without accessible data or adoption of ICU decolonization at baseline (n = 2), and ICU length of stay of less than 2 days (n = 1). Of the 147 eligible HCA hospitals, 137 hospitals from 18 states enrolled and were randomized (**Figure 1**).

The 137 hospitals had 233 adult ICUs, which included mixed medical-surgical (n = 130 [56%]), cardiac (n = 36 [16%]), surgical (n = 25 [11%]), medical (n = 22 [9%]), and neurosurgical (n = 20 [9%]) ICUs. Three hospitals withdrew after the intervention started and were included in the as-randomized but not the as-treated analyses. The reasons for withdrawal included loss of dedicated adult ICU (mupirocin-CHG group: 2 hospitals, 2 ICUs) and adoption of a competing intervention (MRSA contact precautions were discontinued; iodophor-CHG group: 1 hospital, 2 ICUs). Of the 37 quality improvement interventions proposed by participating hospitals during the trial, 8 conflicted with the trial (7 were not pursued and 1 resulted in the mentioned trial drop out).

A total of 353 323 admissions contributed 1 468 515 ICU-attributable patient-days during the 18-month intervention period. An additional 448 345 admissions contributed 1 920 789 ICU-attributable patient-days during the 24-month baseline

Figure 1. Mupirocin-Iodophor Swap Out Trial Flow Diagram



Aggregated baseline hospital data were used to establish similar hospital pairs based on key variables using the Goldilocks approach.[14] Members of each pair were randomly assigned, 1 to each group. ICU indicates intensive care unit.

[a] As-randomized analyses used health system data from hospitals regardless of withdrawal.

[b] Patients were included in the analysis until the time of withdrawal for all 3 hospitals that withdrew during the intervention period. The 1 hospital (2 ICUs) that withdrew from the iodophor-chlorhexidine group midintervention contributed 3737 admissions and 18 062 ICU-attributable days during baseline and 786 admissions and 3679 ICU-attributable days during intervention. The 2 hospitals (2 ICUs) that withdrew from the mupirocin-chlorhexidine group shortly after the intervention period began contributed 3010 admissions and 11 976 ICU-attributable days during baseline and 141 admissions and 480 ICU-attributable days during intervention.

[c] As-treated analyses used data up until the time of withdrawal. The as-treated analysis also removed admissions where the patient did not receive at least 2 doses of the assigned nasal product.

period. Patient characteristics were similar across groups and between baseline and intervention periods (**Table 1**; eTable 1 in Supplement 2). Adoption of the assigned intervention differed between the groups (eFigure 1 in Supplement 2). The iodophor-CHG group switched from mupirocin to iodophor during the phase-in period and experienced an increase in iodophor adherence across the intervention period (first month: median, 75% [IQR, 65%-81%]; last month: median, 79% [IQR, 69%-85%]). The mupirocin-CHG group continued the same universal decolonization regimen in the phase-in and intervention periods as in the baseline period, and mupirocin adherence, defined as at least 2 doses, increased from the first month of the intervention period (median, 86% [IQR, 75%-92%]) to the last month (91% [IQR, 86%-94%]). In both groups, CHG bathing adherence increased from 78% to 90% across the intervention period.

As-Randomized Analysis

Iodophor-CHG was inferior to mupirocin-CHG for the primary outcome of *S aureus* clinical cultures and the secondary outcome of MRSA clinical cultures (**Table 2**, **Figure 2**). When comparing the intervention vs baseline periods, the relative hazard of *S aureus* clinical cultures was significantly higher by 18.4% (95% CI, 10.7%-26.6%) for the iodophor-CHG group (HR, 1.17 [95% CI, 1.12-1.23]) compared with the mupirocin-CHG group (HR, 0.99 [95% CI, 0.94-1.04]) ($P < .001$). Similarly, MRSA clinical cultures, a secondary outcome, was significantly higher by 14.1% (95% CI, 3.7%-25.5%) for the iodophor-CHG group (HR, 1.13 [95% CI, 1.06-1.20]) compared with the mupirocin-CHG group (HR, 0.99 [95% CI, 0.92-1.06]) ($P = .007$). For the secondary outcome of all-cause bloodstream infection, iodophor-CHG (HR, 1.00 [95% CI, 0.94-1.06]) was not inferior to mupirocin-CHG (HR, 1.01 [95% CI, 0.95-1.07]) ($P = .84$). The distribution of bloodstream pathogens is shown in eTable 2 in Supplement 2. Analyses adjusting for demographic and comorbidity data showed similar, but larger, increases in *S aureus* and MRSA clinical culture outcomes for iodophor-CHG (eTable 3 in Supplement 2).

As-Treated Analysis

Effects were similar, but with even greater point estimate reductions, when restricting data to ICU patients who received

Table 1. Hospital ICU and Population Characteristics During the Baseline and Intervention Periods[a]

	24-mo Baseline period (5/1/2015-4/30/2017)		18-mo Intervention period (11/1/2017-4/30/2019)	
	Iodophor	Mupirocin	Iodophor	Mupirocin
Hospital-level ICU characteristics				
Hospitals, No.	69	68	69	68
Oncology/transplant hospital, No. (%)[b]	5 (7.2)	5 (7.4)	5 (7.2)	5 (7.4)
ICUs, No. (%)	122	111	122	111
Mixed medical/surgical	63 (51.6)	67 (60.4)	63 (51.6)	67 (60.4)
Cardiac	21 (17.2)	15 (13.5)	21 (17.2)	15 (13.5)
Surgical	15 (12.3)	10 (9.0)	15 (12.3)	10 (9.0)
Medical	12 (9.8)	10 (9.0)	12 (9.8)	10 (9.0)
Neurosurgical	11 (9.0)	9 (8.1)	11 (9.0)	9 (8.1)
Monthly ICU-attributable patient-days, mean (SD)[b]	607.3 (458.3)	560.7 (358.3)	630.7 (484.3)	568.1 (372.4)
ICU length of stay, median (IQR), d[b]	4.5 (4.1-5.3)	4.7 (4.4-4.9)	4.6 (4.2-5.0)	4.6 (4.2-4.8)
Elixhauser comorbidity count score, median (IQR)[b,c]	3.7 (3.4-4.0)	3.8 (3.6-4.2)	3.8 (3.6-4.1)	4.0 (3.8-4.3)
ICU nasal product (mupirocin or iodophor) adherence, median (IQR), %[b]	83.4 (74.1-91.2)	85.2 (73.8-91.0)	79.0 (70.6-84.2)	89.0 (84.5-94.0)
ICU chlorhexidine adherence, median (IQR), %[b]	80 (70-89)	79 (68-90)	86 (79-93)	88 (79-94)
ICU history of MRSA, median (IQR), %[b]	5.0 (3.7-7.6)	5.9 (4.2-7.6)	6.2 (4.6-8.5)	5.9 (4.7-8.6)
ICU surgery, median (IQR), %[b]	22.1 (15.3-28.3)	22.7 (13.4-27.8)	15.8 (10.1-21.1)	16.0 (9.9-22.0)
Mupirocin-resistant MRSA, mean (SD), %[b]	12.9 (10.6)	13.1 (10.9)	Not available	Not available
ICU population characteristics				
Admissions with ICU stay, No.	233 661	214 684	185 022	168 301
Attributable ICU patient-days, No.	1 005 648	915 141	783 346	685 169
ICU stay, median (IQR), d	3.0 (2.0-5.0)	3.0 (2.0-5.0)	3.0 (2.0-5.0)	3.0 (2.0-5.0)
Age, median (IQR), y	65.0 (53.0-76.0)	65.0 (53.0-76.0)	66.0 (54.0-76.0)	66.0 (54.0-76.0)
Sex, No. (%)	n = 233 578	n = 214 634	n = 184 950	n = 168 219
Male	125 796 (53.9)	115 097 (53.6)	99 756 (53.9)	90 145 (53.6)
Female	107 782 (46.1)	99 537 (46.4)	85 194 (46.1)	78 074 (46.4)
Race, No. (%)	n = 219 773	n = 200 857	n = 171 982	n = 155 666
Black/African American	34 296 (15.9)	27 932 (14.1)	27 776 (16.5)	21 901 (14.3)
White	172 946 (80.4)	162 723 (82.0)	135 060 (80.2)	126 749 (82.5)
Other[d]	12 531 (5.7)	10 202 (5.1)	9152 (5.3)	7018 (4.5)
Ethnicity, No. (%)	n = 224 084	n = 207 796	n = 176 794	n = 161 375
Non-Hispanic	196 618 (87.7)	174 731 (84.1)	154 370 (87.3)	134 092 (83.1)
Hispanic	27 466 (12.3)	33 065 (15.9)	22 424 (12.7)	27 285 (16.9)
Comorbidities, No. (%)				
Diabetes	81 134 (34.7)	76 754 (35.8)	65 689 (35.5)	61 517 (36.6)
With chronic complications	31 500 (13.5)	31 208 (14.5)	40 490 (21.9)	39 443 (23.4)
Without chronic complications	49 634 (21.2)	45 546 (21.2)	25 199 (13.6)	22 074 (13.1)
Chronic pulmonary disease	62 604 (26.8)	60 162 (28.0)	50 393 (27.2)	48 343 (28.7)
Kidney insufficiency	49 289 (21.1)	48 327 (22.5)	41 991 (22.7)	40 840 (24.3)
Obesity	38 423 (16.4)	37 461 (17.4)	37 082 (20.0)	36 143 (21.5)
Congestive heart failure	35 010 (15.0)	32 595 (15.2)	31 865 (17.2)	29 641 (17.6)
Cancer	16 010 (6.9)	14 294 (6.7)	13 495 (7.3)	12 133 (7.2)
Elixhauser comorbidity count score, median (IQR)[c]	3.0 (2.0-5.0)	4.0 (2.0-5.0)	4.0 (2.0-5.0)	4.0 (2.0-5.0)
History of MRSA, No. (%)[e]	15 940 (6.8)	13 437 (6.3)	11 704 (7.0)	13 809 (7.5)
Nasal product doses, median (IQR)	4.0 (2.0-8.0)	4.0 (2.0-8.0)	4.0 (2.0-7.0)	5.0 (3.0-8.0)
Died, No. (%)	16 903 (7.2)	14 398 (6.7)	10 305 (6.1)	12 331 (6.7)

Abbreviations: ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*.

[a] See eTable 1 in Supplement 2 for complete population characteristics. All data in this table were collected from HCA Healthcare's centralized electronic data warehouse for medical records with the exception of mupirocin-resistant MRSA. The percentages of mupirocin-resistant MRSA were obtained from a sample of 3121 isolates from 53 HCA hospitals and proportional resistance was assigned regionally to hospitals participating in the study for an estimate of 2015-2016 baseline mupirocin resistance.

[b] Each hospital's baseline value of this variable was used to help form matched pairs prior to randomization. In addition, baseline values for trial outcomes (Table 2) were also used to help form matched pairs prior to randomization.

[c] Elixhauser comorbidity count score[12] is based on the summed count of comorbidities based on diagnostic codes. Higher number indicates greater illness.

[d] "Other" was a category used by the health system.

[e] History of MRSA was defined using all available relevant screening and clinical cultures in the electronic health record for the year prior to admission until day 2 of the ICU stay.

Table 2. Group Comparisons for As-Randomized Outcomes of the Mupirocin-Iodophor Swap Out Trial[a]

	Iodophor-chlorhexidine, 69 hospitals			Mupirocin-chlorhexidine, 68 hospitals			Hazard ratio difference-in-differences	
	Raw events/1000 ICU-attributable days (No. of events/ No. of ICU-attributable days)			Raw events/1000 ICU-attributable days (No. of events/ No. of ICU-attributable days)				
	24-mo Baseline period	18-mo Intervention period	Clustered hazard ratio (95% CI)[b]	24-mo Baseline period	18-mo Intervention period	Clustered hazard ratio, (95% CI)[b]	Trial result main analysis[c]	*P* value
Primary outcome								
ICU-attributable *Staphylococcus aureus* clinical cultures	4.3 (4133/968 280)	5.0 (3563/710 051)	1.17 (1.12 to 1.23)	4.0 (3569/885 660)	4.1 (2708/663 439)	0.99 (0.94 to 1.04)	Mupirocin-CHG: 18.4% (95% CI, 10.7% to 26.6%) significant decrease over iodophor-CHG	<.001
Secondary outcomes								
ICU-attributable MRSA clinical cultures	2.1 (2036/987 177)	2.3 (1682/727 397)	1.13 (1.06 to 1.20)	2.0 (1829/899 953)	2.0 (1377/674 161)	0.99 (0.92 to 1.06)	Mupirocin-CHG: 14.1% (95% CI, 3.7% to 25.5%) significant decrease over iodophor-CHG	.007
ICU-attributable bloodstream infections	2.7 (2668/982 886)	2.7 (1956/727 346)	1.00 (0.94 to 1.06)	2.6 (2330/895 263)	2.6 (1766/672 092)	1.01 (0.95 to 1.07)	0.86% (95% CI, −8.95% to 7.96%) no difference between groups	.84

Abbreviations: CHG, chlorhexidine gluconate; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*.

[a] See eTables 3 and 4 in Supplement 2 for adjusted outcomes and as-treated analyses.

[b] Hazard ratio is not equal to the ratio of raw event rates due to the effect of clustering within hospital and patient. Clustered hazard ratio obtained from unadjusted proportional hazard model analyses.

[c] The prespecified main analysis of the trial was based on an as-randomized unadjusted proportional hazard model. Model terms included group, period (baseline vs intervention), and a group-by-period interaction term to assess whether the difference in relative hazard between the baseline and intervention periods differed significantly between the two groups (difference in differences) when accounting for clustering within hospital and patient. The study was powered to detect 10% noninferiority (difference in differences) of iodophor-CHG to mupirocin-CHG.

at least 2 doses of nasal decolonization product (eTable 4 in Supplement 2). The as-treated hazard of *S aureus* clinical cultures was significantly higher by 27.4% (95% CI, 18.4%-37.5%) for the iodophor-CHG group (HR, 1.27 [95% CI, 1.21-1.33]) compared with the mupirocin-CHG group (HR, 1.00 [95% CI, 0.94-1.05]) when comparing the intervention vs baseline periods. The as-treated hazard of MRSA clinical cultures also was significantly higher by 21.5% (95% CI, 9.5%-35.4%) for the iodophor-CHG group (HR, 1.22 [95% CI, 1.13-1.31]) compared with the mupirocin-CHG group (HR, 1.00 [95% CI, 0.93-1.08]). All-cause bloodstream infection as-treated outcomes remained similar between the groups.

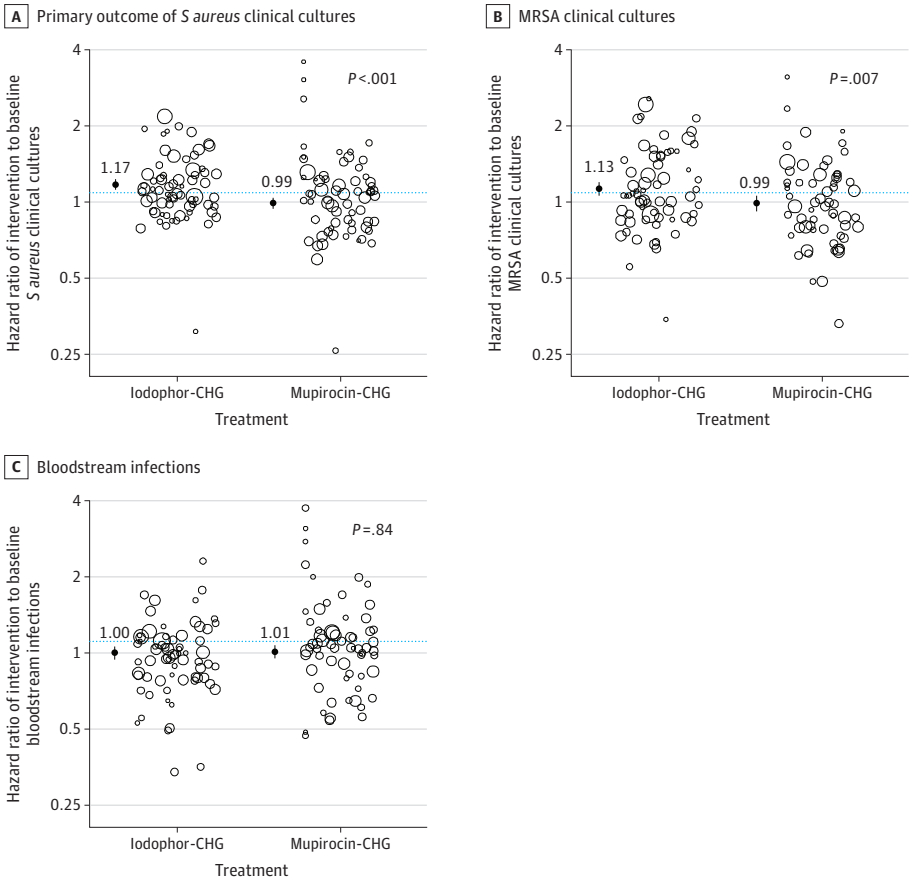
Durability of Clinical Effect

Figure 3 shows the cumulative hazard of ICU-attributable *S aureus* clinical cultures by accrued time in the ICU for the current trial (2017-2019) and a prior trial in the same hospital system (2009-2011) in a post hoc analysis. Comparisons showed similar protective effects of the mupirocin-CHG regimen for all 3 outcomes after more than 7 years of continuous universal ICU decolonization (Figure 3; eFigure 2 and eTable 5 in Supplement 2).

For the hazard of *S aureus* clinical cultures by ICU-attributable day 30, mupirocin-CHG (2010-2011) was associated with a statistically significant 58.8% reduction (95% CI, 47.5%-70.7%) and mupirocin-CHG (2017-2019) was associated with a statistically significant 48.1% reduction (95% CI, 35.6%-60.1%) relative to no decolonization (baseline period of the 2009-2011 trial). There was no difference in the overall cumulative hazard of *S aureus* clinical cultures between the 2 mupirocin-CHG periods (χ^2 = 0.45, *P* = .50). Similarly, for the hazard of MRSA clinical cultures by ICU-attributable day 30, there was a statistically significant 67.0% reduction (95% CI, 56.4%-78.6%) in 2010-2011 and a statistically significant 55.2% reduction (95% CI, 42.4%-68.0%) in the current trial relative to no decolonization (baseline period of the 2009-2011 trial). There was no difference in the overall cumulative hazard of MRSA clinical cultures between the 2 mupirocin-CHG periods (χ^2 = 2.86, *P* = .09). For the hazard of bloodstream infection by ICU-attributable day 30, there was a statistically significant 60.1% reduction (95% CI, 49.1%-70.7%) in 2010-2011 and a statistically significant 70.4% reduction (95% CI, 62.9%-77.8%) in 2017-2019, relative to no-decolonization (baseline period of the 2009-2011 trial). There was no difference in the overall cumulative hazard of bloodstream infection between the two Mupirocin-CHG time periods (χ^2 = 0.68; *P* = .41).

The overall cumulative hazards of all 3 outcomes with iodophor-CHG (2017-2019) in the current trial were superior to those in the prior trial during the baseline period with no decolonization (2009): *S aureus* clinical cultures (χ^2 = 10.14, *P* = .001; 19.5% reduction [95% CI, 3.3%-35.9%] in 30-day ICU-attributable cumulative hazard), MRSA clinical cultures (χ^2 = 15.48; *P* < .001; 36.6% reduction [95% CI, 21.4%-53.5%] in 30-day ICU-attributable cumulative hazard), and all-cause bloodstream infection (χ^2 = 158.02; *P* < .001; 70.6% reduction [95% CI, 63.6%-77.2%] in 30-day ICU-attributable cumulative hazard).

Figure 2. As-Randomized Unadjusted Clustered Comparison of Iodophor-Chlorhexidine Gluconate (CHG) vs Mupirocin-CHG Comparing Differences in Hazard Ratios of Trial Outcomes in the Intervention to Baseline Period



Graphic shows impact of trial interventions on trial outcomes attributable to participating intensive care units (ICUs). Group-specific hazard ratios (and their 95% confidence limits) comparing outcomes in the intervention and baseline periods are derived from proportional hazard models (as-randomized, unadjusted) accounting for clustering by hospital and person using parameter estimates and their variance matrix. These are shown for *Staphylococcus aureus* clinical cultures (A), methicillin-resistant *S aureus* (MRSA) clinical cultures (B), and all-cause bloodstream infections (C) based on 7696, 3718, and 4624 respective events in the iodophor-CHG group; 6277, 3206, and 4096 respective events in the mupirocin-CHG group; 1 678 331, 1 714 574, and 1 710 232 respective attributable ICU days in the iodophor-CHG group; and 1 549 099, 1 574 114, and 1 567 355 respective attributable ICU days in the mupirocin-CHG group. *P* values for the difference in within-group hazard ratios are derived from these same models. Bubble plots of the hospital-specific hazard ratios (accounting for clustering by patient) are shown adjacent to group-specific hazard ratios and confidence intervals. The size of the bubble shows the relative number of admissions contributing data to the trial. For readability, hazard ratios greater than 4 or less than 0.25 are not depicted: 2 mupirocin-CHG (5.7 and 10.6) and 1 iodophor-CHG (5.7) for MRSA and 2 mupirocin-CHG (0.24 and 11.4) for all-cause bloodstream infections. For each outcome, the panel displays a horizontal dotted line indicating the 10% absolute noninferiority margin from the overall hazard ratio of the mupirocin-CHG group.

Adverse Events

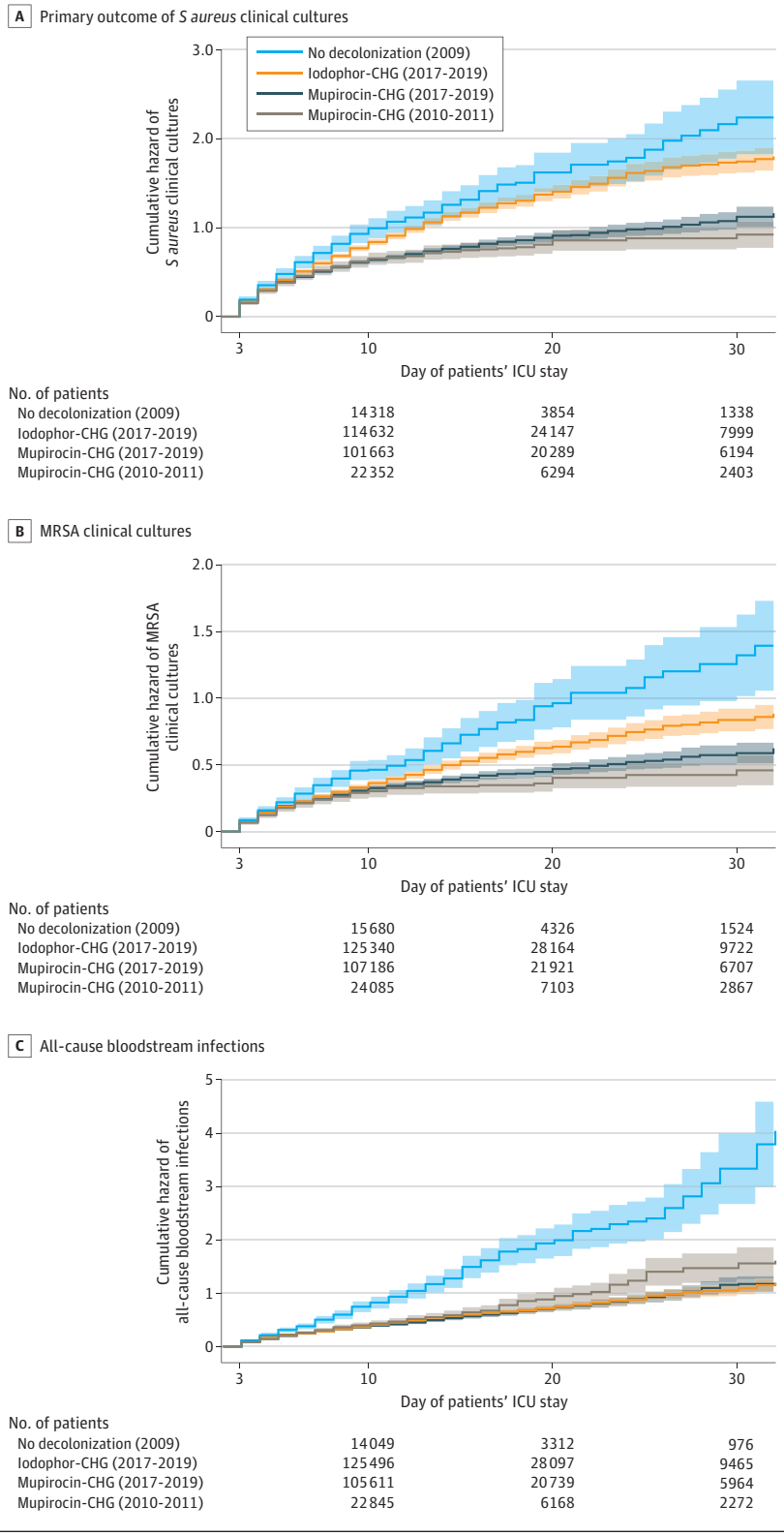
There were 2 adverse events, both in the iodophor-CHG group. One involved mild nasal pruritus, and one involved total body hives requiring treatment. Both resolved on discontinuation of decolonization.

Discussion

This large-scale, pragmatic trial found universal mupirocin-CHG to be superior to universal iodophor-CHG for reducing *S aureus* and MRSA clinical cultures in critically ill patients. This finding is important for 2 reasons. First, it demonstrated that addition of a nasal decolonization product to chlorhexidine bathing reduces *S aureus* and MRSA clinical cultures in ICUs. This trial and guidance from the Centers for Disease Control and Prevention support the combined strategy of mupirocin-CHG given that *S aureus* is implicated as the causal agent in nearly one-quarter of US ICU infections.[1,17] In addition, US hospital-onset bloodstream infections due to MRSA had plateaued after years of successful decline,[3] and then markedly rose during the COVID-19 pandemic, presumably spurred by extensive necessary and unnecessary antibiotic use as well as infection prevention staffing and practice challenges.[18-20]

Second, this trial showed that mupirocin nasal decolonization was significantly superior to iodophor for *S aureus* and MRSA outcomes, thus providing important information about the comparative effectiveness of existing nasal decolonization

Figure 3. Cumulative Hazard of Trial Outcomes by Day of Patient's Intensive Care Unit (ICU) Stay



Graphic showing the durability of clinical effects for trial outcomes due to universal ICU decolonization over a span of more than 7 years in the same hospital system (post hoc analysis). Group-specific cumulative hazards for the first 30 days of ICU-attributable events are shown for ICU-attributable *Staphylococcus aureus* clinical cultures (A), methicillin-resistant *S aureus* (MRSA) clinical cultures (B), and all-cause bloodstream infections (C). Day 3 is noted on the x-axis because cases attributed to the ICU are defined by the Centers for Diseases Control and Prevention as occurring from ICU day 3 through 2 days after ICU discharge. Thus, the first 30 days of ICU-attributable events occur between ICU day 3 through 33. At that point, the x-axis is truncated because data after that period are sparse. Full figure is found in eFigure 2 in Supplement 2 with associated at-risk days in eTable 5 in Supplement 2. Note the different y-axis scales across the panels. Comparisons are made between the mupirocin-CHG group of the current trial (2017-2019) to data from the mupirocin-CHG group of a prior trial in the same hospital system (2010-2011). Effect of mupirocin-CHG (2017-2019) vs mupirocin-CHG (2010-2011) was unchanged for *S aureus* clinical cultures ($P = .50$), MRSA clinical cultures ($P = .09$), and all-cause bloodstream infections ($P = .41$). The cumulative hazard of all 3 outcomes with iodophor-CHG (2017-2019) in the current trial was superior to the hazard in the prior trial during the baseline period with no decolonization (2009): *S aureus* clinical cultures ($P = .001$), MRSA clinical cultures ($P < .001$), and all-cause bloodstream infections ($P < .001$).

products. Not only was iodophor inferior to mupirocin in reducing *S aureus* and MRSA clinical cultures, but it was also less well adopted (79% vs 89%). It is possible that mupirocin's higher adoption was achieved over many years, although its adoption in the previous REDUCE MRSA Trial (86%) was higher than achieved by the iodophor group in this trial.[4] Regardless,

adherence with both nasal products increased steadily across this trial, suggesting that adherence could be improved. Nevertheless, the as-treated analysis limited to those who received at least 2 doses of nasal product found the same superiority for mupirocin.

The superiority of mupirocin was not anticipated. While mupirocin has been repeatedly shown to reduce *S aureus* disease among *S aureus* carriers,[21-25] reports of widely ranging regional mupirocin resistance among *S aureus* isolates drove the desire to identify an equivalently effective antiseptic to which minimal *S aureus* resistance is expected.[8-10,26-28] The superiority of mupirocin despite expectations of some degree of mupirocin resistance may suggest that current breakpoints underestimate mupirocin's effect and benefit.[29] Alternatively, iodophor's effect may simply be inferior, possibly due to its suppressive (vs cidal) activity.[30] Another possibility is that an ointment may more effectively coat the nasal mucosa compared with a water-based swab. Despite iodophor's inferiority to mupirocin, it is a viable alternative in settings or situations where filling prescriptions or cost concerns (including co-pays) are factors.

The inferiority of iodophor-CHG was not attributable to lesser adoption or a simpler regimen. First, as-treated analyses recapitulated as-randomized findings. Second, the documented occurrence of high-level *S aureus* mupirocin resistance (7.5% in the REDUCE MRSA Trial), if also present in this population, should have counteracted the lesser adoption of iodophor.[26] Third, the nasal regimens were identical, with both products given twice daily for 5 days, in contrast to iodophor's single-dose use for preoperative *S aureus* suppression.[31]

The existence of 2 universal ICU decolonization trials conducted 7 years apart in the same health system enabled us to assess the durability of the mupirocin-CHG benefit.[4] This opportunity was afforded because HCA implemented universal ICU mupirocin-CHG enterprise-wide after the findings of the first trial.[7] If continuous use had either engendered or selected for additional resistance, a diminished effect would have been expected. Instead, the benefit of mupirocin-CHG in reducing *S aureus* and MRSA clinical cultures was preserved, possibly due to the brevity of exposure limited to the ICU setting. The lack of decrement in clinical benefit over 7 years of continuous use in a large health system provides reassurance to hospital infection prevention or critical care programs that have held off adopting universal ICU nasal decolonization that the more effective mupirocin-CHG regimen may not engender clinically meaningful resistance.

Importantly, the type of nasal product was not associated with a difference in the risk of bloodstream infections. This may be because *S aureus* accounted for only a minority of that outcome.

Limitations

This large-scale, pragmatic trial was conducted using existing quality improvement infrastructure at participating community hospitals, a fact that should support adoption. Limitations to generalizability first include the trial's conduct in a health system familiar with universal ICU decolonization in community settings. Second, no data on mupirocin or iodophor resistance among *S aureus* strains from participating hospitals were provided because these tests were not routinely performed. Findings of this trial may differ depending on local mupirocin resistance. Third, the role of CHG alone cannot be elucidated in this trial. Other publications support CHG's ability to reduce person-to-person spread of MRSA, although CHG alone does not appear to decrease disease risk among those already known to be MRSA carriers.[32-34]

Conclusions

Nasal iodophor antiseptic did not meet criteria to be considered noninferior to nasal mupirocin antibiotic for the outcome of *S aureus* clinical cultures in adult ICU patients in the context of daily CHG bathing. In addition, the results were consistent with nasal iodophor being inferior to nasal mupirocin.

ARTICLE INFORMATION

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Other–laboratory work: Khan.

Conflict of Interest Disclosures: Dr Huang reported conducting studies for which participating nursing homes and hospital patients received contributed antiseptic (Xttrium, Medline) and cleaning (Medline) products outside of the submitted work. Dr Kleinman reported conducting studies for which participating nursing homes and hospital patients received contributed antiseptic (Xttrium, Medline) and cleaning (Medline) products outside of the submitted work. Dr Poland reported receiving nonfinancial support from HCA Healthcare. Dr Coady reported Harvard Pilgrim Health Care Institute receiving research funding from Clorox for collection/processing of bacterial strains during the conduct of the study. Dr Lee

reported receiving personal fees from Harvard Pilgrim Health Care Inc (consulting) during the conduct of the study. Dr Blanchard reported serving in 2020 as a member for the Medline Hand Hygiene Advisory Board (no financial relationship). Dr Hayden reported receiving grants from Clorox to test MRSA strains from this study for susceptibility to mupirocin and iodophor during the conduct of the study and receiving grants from the Centers for Disease Control and Prevention (CDC) and nonfinancial support from Stryker Sage outside the submitted work. Dr Weinstein reported serving as a subject matter expert for selected infection control content for UpToDate. No other disclosures were reported.

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