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Effect of body surface decolonisation on bacteriuria and candiduria in intensive care units: an analysis of a cluster-randomised trial

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Background

Urinary tract infections (UTIs) are common health-care-associated infections. Bacteriuria commonly precedes UTI and is often treated with antibiotics, particularly in hospital intensive care units (ICUs). In 2013, a cluster-randomised trial (REDUCE MRSA Trial [Randomized Evaluation of Decolonization vs Universal Clearance to Eradicate MRSA]) showed that body surface decolonisation reduced all-pathogen bloodstream infections. We aim to further assess the effect of decolonisation on bacteriuria and candiduria in patients admitted to ICUs.

Methods

We did a secondary analysis of a three-group, cluster-randomised trial of 43 hospitals (clusters) with patients in 74 adult ICUs. The three groups included were either meticillin-resistant *Staphylococcus aureus* (MRSA) screening and isolation, targeted decolonisation (screening, isolation, and decolonisation of MRSA carriers) with chlorhexidine and mupirocin, and universal decolonisation (no screening, all patients decolonised) with chlorhexidine and mupirocin. Protocol included chlorhexidine cleansing of the perineum and proximal 6 inches

(1 × 24 cm) of urinary catheters. ICUs within the same hospital were assigned the same strategy. Outcomes included high-level bacteriuria ($\geq 50\,000$ colony forming units [CFU]/mL) with any uropathogen, high-level candiduria ($\geq 50\,000$ CFU/mL), and any bacteriuria with uropathogens. Sex-specific analyses were specified a priori. Proportional hazards models assessed differences in outcome reductions across groups, comparing an 18 month intervention period to a 12-month baseline period.

Findings

122 646 patients (48 390 baseline, 74 256 intervention) were enrolled. Intervention versus baseline hazard ratios (HRs) for high-level bacteriuria were 1.02 (95% CI 0.88–1.18) for screening or isolation, 0.88 (0.76–1.02) for targeted decolonisation, and 0.87 (0.77–1.00) for universal decolonisation (no difference between groups, $p=0.26$), with no sex-specific reductions (HRs for men: 1.09 [95% CI 0.85–1.40] for screening or isolation, 1.01 [0.79–1.29] for targeted decolonisation, and 0.78 [0.63–0.98] for universal decolonisation, $p=0.12$; HRs for women: 0.97 [0.80–1.17] for screening and isolation, 0.83 [0.70–1.00] for targeted decolonisation, and 0.93 [0.79–1.09] for universal decolonisation, $p=0.49$). HRs for high-level candiduria were 1.14 (0.95–1.37) for screening and isolation, 0.99 (0.83–1.18) for targeted decolonisation, and 0.83 (0.70–0.99) for universal decolonisation ($p=0.05$). Differences between sexes were due to reductions in men in the universal decolonisation group (HRs: 1.21 [95% CI 0.88–1.68] for screening or isolation, 1.01 [0.73–1.39] for targeted decolonisation, and 0.63 [0.45–0.89] for universal decolonisation, $p=0.02$). Bacteriuria with any CFU/mL was also reduced in men in the universal decolonisation group (HRs 1.01 [0.81–1.25] for screening or isolation, 1.04 [0.83–1.30] for targeted decolonisation, and 0.74 [0.61–0.90] for universal decolonisation, $p=0.04$).

Interpretation

Universal decolonisation of patients in the ICU with once a day chlorhexidine baths and short-course nasal mupirocin could be a potential preventive strategy in male patients because it significantly decreases candiduria and any bacteriuria, but not for women.

Funding

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Introduction

Urinary tract infections (UTIs) are one of the most common hospital-associated infections with 93 000 annual cases reported in the USA, incurring an excess cost of US\$900 per episode.^{1, 2} 38% of these occur in the intensive care unit (ICU) where urinary catheters are commonly used.¹

Risk factors for UTIs include female sex, aged 65 years or older, compromised immune system, and urinary catheters. Although prevention is needed for all-cause UTIs, prevention strategies have focused on catheter-associated UTIs that account for 80% of hospital-associated UTIs.³ Guidelines emphasise appropriate catheter indications, aseptic insertion, maintenance of a closed unobstructed drainage system, and timely removal.⁴ Body decolonisation, which could affect catheter-related and non-catheter related UTIs, has not been explored in large-scale studies.

UTIs in the ICU setting are difficult to diagnose because patients are often sedated and unable to verbalise symptoms such as dysuria, urinary frequency, or urgency. Thus, these symptoms are poor predictors of UTI in the ICU setting.⁵ Because of this difficulty, many studies have used colony count thresholds in urinary cultures to suggest UTI for known uropathogens.^{6–8} Even though this measure probably shows a mixture of UTIs and asymptomatic bacteriuria, this approach allows a pragmatic and objective definition that correlates with antibiotic treatment by clinicians.⁹

In 2013, a large cluster-randomised trial of hospitals (REDUCE MRSA Trial [Randomized Evaluation of Decolonization vs Universal Clearance to Eradicate MRSA]) reported that universal decolonisation of adult ICU patients with a chlorhexidine bath every day and a short course of mupirocin nasal ointment resulted in a reduction in both meticillin-resistant *Staphylococcus aureus* (MRSA) clinical cultures and all pathogen bloodstream infections.¹⁰ We aim to assess the effect of the three REDUCE MRSA Trial interventions on bacteriuria and candiduria in patients in hospital ICUs.

Methods

Study design and participants

We did a secondary analysis of the REDUCE MRSA trial, a cluster-randomised trial of 43 hospitals (clusters; 74 adult ICUs) in the USA assigned to three MRSA prevention strategies. Patients admitted to participating hospital ICUs during baseline and intervention periods were included in the REDUCE MRSA study; we used these patient data. The trial included a 12-month baseline period from Jan 1, 2009, to Dec 31, 2009, a phase-in period from Jan 1, 2010, to April 7, 2010, and an 18-month intervention period from April 8, 2010, to Sept 30, 2011. This trial and protocol have been described elsewhere.¹⁰ This study obtained ethics approval from the Harvard Pilgrim Health Care Institutional Review Board, the central institutional review board for the trial (reference number 367981). Patient notices about group-specific protocols and use of their data were posted in each ICU room of participating hospitals; written informed consent was not needed.¹⁰

Intervention and randomization

43 hospitals (74 adult ICUs) were randomly assigned, using block randomisation to one of three strategies: screening and isolation, where all patients underwent nasal screening for MRSA on ICU admission and those known to have MRSA were placed in contact precautions; targeted decolonisation, which added 5 days of chlorhexidine (2% no-rinse chlorhexidine cloths) once a day bathing and 5 days of twice a day mupirocin (2%) nasal ointment for those known to have MRSA; or universal decolonisation, in which screening was stopped and all patients received 5 days of twice a day mupirocin and daily chlorhexidine baths for their entire ICU stay. Randomisation was stratified to optimise balance in inpatient volume and baseline prevalence of MRSA carriage, as described elsewhere.¹⁰ Contact precautions were applied in all groups for patients known to harbour MRSA and for other indications per national guidance.¹¹ All participating adult ICUs in a hospital were assigned the same randomisation strategy. Chlorhexidine bathing instructions included cleansing of the perineum with additional cleaning of the 6 inches (15 × 24 cm) of tubes, drains, and lines closest to the skin, including urinary catheters. Periodic observations of staff to assess compliance with the protocol were completed by each intervention unit every 3 months.

Outcomes

We evaluated the secondary outcomes of high-level bacteriuria ($\geq 50\,000$ colony forming units [CFU]/mL due to a bacterial uropathogen), high-level candiduria ($\geq 50\,000$ CFU/mL), and any bacteriuria due to a bacterial uropathogen per 1000 ICU-attributable patient days. The CFU/mL threshold for high-level bacteriuria was chosen because several microbiology laboratories reported maximum CFU/mL as 50 000–100 000 or 50 000 or more. We did not assess lactobacillus, gardnerella, corynebacterium, streptococci (other than group B streptococcus), coagulase-negative staphylococcus (other than *Staphylococcus saprophyticus*), and anaerobes because they are unlikely uropathogens.

Outcomes were based on microbiology laboratory results obtained from the Hospital Corporation of America's centralised electronic data warehouse. We specified, a priori, analyses stratified by sex because of the known higher risk of infection in women from endogenous flora.^{6, 7} Outcomes were defined as the first culture per person that met the outcome definition and was attributed to being in an ICU, which meant the collection date occurred longer than 2 days after ICU admission through to 2 days after ICU discharge. Transfer of finalised data from the microbiology laboratories serving trial hospitals was confirmed at an error rate of less than 1%.

Descriptive data were limited to microbiology data, demographic data, and diagnostic and procedure codes. We did not have data for use of urinary catheters. We captured the frequency that urinary cultures were sent (irrespective of negative or positive result) per 1000 ICU attributable patient days. For the last 17 months of the intervention period (May 1, 2010, to Sept 30, 2011), we also gathered the proportion of urinary outcomes that had a concurrent blood culture sent or a white blood cell count of 12×10^3 per μL or more within 2 days of the urine culture. White blood cell counts were collected to provide supporting evidence of infection since access to vital signs and antibiotics were not available. Finally, we obtained surgical procedures and comorbidity information based on International Classification of Disease (ICD) version 9 administrative codes, including the Romano comorbidity index.¹² All descriptors were assessed by group, stratified by period (baseline vs intervention), and sex.

Statistical analysis

Main results show as-randomised, unadjusted analyses. We used proportional hazards models to assess all outcomes, with shared frailties to account for clustering within hospital, as previously detailed in the primary analysis of this trial.^{10, 13, 14} Frailties are similar to random intercepts in mixed effects models and allow every hospital to have a unique infection rate. The intervention effect was estimated by group-by-treatment period interactions, which assess the differences between differences in hazards between the baseline and intervention periods and between the study groups. Phase-in period data were excluded from all analyses. When the null hypothesis of equal changes across the groups was rejected, we examined pairwise comparisons between each of the treatment groups and the control groups. We did not compare the sex effects because separate male and female analyses were planned a priori.

Sensitivity analyses included multivariable covariate adjusted models and as-treated models. Adjusted models accounted for age, sex, race, type of insurance patients had, comorbidities (ICD-9 codes), and surgery during admission to hospital. Analyses were done with SAS version 9.3.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Figure 1: Study profile of the REDUCE MRSA trial

N indicates the number of patients in the intervention period in the specified group. Reproduced from Huang and colleagues,³⁰ by permission of the *New England Journal of Medicine*. ICU=intensive care unit. MRSA=meticillin-resistant *Staphylococcus aureus*. Group 1=screening and isolation. Group 2=targeted decolonisation. Group 3=universal decolonisation.

	Baseline (12 months), n=48 390 admissions with ICU stay			Intervention (18 months), n=74 256 admissions with ICU stay		
	Screening and isolation	Targeted decolonisation	Universal decolonisation	Screening and isolation	Targeted decolonisation	Universal decolonisation
Patient admissions with ICU stay*						
Total	15 816	15 218	17 356	23 480	24 752	26 024
Women	7473 (47.2%)	7176 (47.2%)	8320 (47.9%)	11 170 (47.6%)	11 688 (47.2%)	12 367 (47.5%)
Men	8342 (52.7%)	8042 (52.8%)	9036 (52.1%)	12 310 (52.4%)	13 064 (52.8%)	13 650 (52.5%)
Attributable ICU patient days*						
Total	63 135	57 418	69 668	88 222	92 978	101 603
Women	29 153 (46.2%)	26 690 (46.5%)	32 248 (46.3%)	41 931 (47.5%)	42 745 (46.0%)	46 729 (46.0%)
Men	33 978 (53.8%)	30 728 (53.5%)	37 420 (53.7%)	46 291 (52.5%)	50 233 (54.0%)	54 874 (54.0%)
Hospital stay (days)						
Total	7 (5-12)	7 (5-12)	8 (5-12)	7 (5-12)	7 (5-12)	7 (5-12)
Women	8 (5-12)	7 (5-12)	8 (5-12)	7 (5-12)	7 (5-12)	7 (5-12)
Men	7 (5-12)	7 (4-12)	8 (5-12)	7 (4-12)	7 (4-12)	7 (5-12)
ICU stay (days)						
Total	3 (2-5)	3 (2-5)	3 (2-5)	3 (1-5)	3 (2-5)	3 (2-5)
Women	3 (2-5)	3 (2-5)	3 (2-5)	3 (2-5)	3 (2-5)	3 (2-5)
Men	3 (2-5)	3 (2-5)	3 (2-5)	3 (1-5)	3 (2-5)	3 (2-5)
Age (years)						
Total	65 (52-77)	66 (53-77)	65 (51-77)	65 (52-77)	66 (53-77)	65 (52-77)
Women	66 (52-79)	68 (54-79)	66 (52-79)	66 (52-78)	68 (54-79)	66 (53-78)
Men	64 (52-75)	65 (52-76)	63 (51-75)	64 (52-75)	65 (52-75)	63 (51-75)
Non-white race						
Total	4099 (25.9%)	3368 (22.1%)	5354 (30.8%)	6092 (25.9%)	5805 (23.5%)	8240 (31.7%)
Women	2033 (27.2%)	1645 (22.9%)	2616 (31.4%)	3034 (27.2%)	2762 (23.6%)	3939 (31.9%)
Men	2066 (24.8%)	1723 (21.4%)	2738 (30.3%)	3058 (24.8%)	3043 (23.3%)	4295 (31.5%)
Comorbidity index†						
Total	3 (1-5)	3 (1-5)	2 (1-5)	3 (1-5)	3 (1-5)	2 (1-5)
Women	3 (1-5)	3 (1-5)	2 (1-5)	2 (1-5)	3 (1-5)	2 (1-5)
Men	3 (1-5)	3 (1-5)	3 (1-5)	3 (1-5)	3 (1-5)	3 (1-5)
Diabetes						
Total	4949 (31.3%)	5027 (33.0%)	5327 (30.7%)	7458 (31.8%)	8085 (32.7%)	8186 (31.5%)
Women	2354 (31.5%)	2350 (32.7%)	2482 (29.8%)	3486 (31.2%)	3798 (32.5%)	3782 (30.6%)
Men	2595 (31.1%)	2677 (33.3%)	2845 (31.5%)	3972 (32.3%)	4287 (32.8%)	4400 (32.2%)
Renal failure						
Total	3170 (20.0%)	3107 (20.4%)	3299 (19.0%)	4774 (20.3%)	5494 (22.2%)	5133 (19.7%)
Women	1385 (18.5%)	1324 (18.5%)	1433 (17.2%)	2066 (18.5%)	2384 (20.4%)	2189 (17.7%)
Men	1785 (21.4%)	1783 (22.2%)	1866 (20.7%)	2708 (22.0%)	3110 (23.8%)	2942 (21.6%)
Cancer						
Total	1651 (10.4%)	1641 (10.8%)	2455 (14.1%)	2328 (9.9%)	2664 (10.8%)	3393 (13.0%)
Women	612 (8.2%)	653 (9.1%)	1021 (12.3%)	897 (8.0%)	1033 (8.8%)	1393 (11.3%)
Men	1039 (12.5%)	988 (12.3%)	1434 (15.9%)	1431 (11.6%)	1631 (12.5%)	2000 (14.7%)
Liver failure						
Total	539 (3.4%)	664 (4.4%)	680 (3.9%)	947 (4.0%)	1019 (4.1%)	1097 (4.2%)
Women	187 (2.5%)	267 (3.7%)	255 (3.1%)	371 (3.3%)	385 (3.3%)	403 (3.3%)
Men	352 (4.2%)	397 (4.9%)	425 (4.7%)	576 (4.7%)	634 (4.9%)	694 (5.1%)
Surgery during admission						
Total	6413 (40.5%)	5879 (38.6%)	8244 (47.5%)	9092 (38.7%)	9320 (37.7%)	12 021 (46.2%)
Women	2812 (37.6%)	2595 (36.2%)	3771 (45.3%)	3948 (35.3%)	4027 (34.5%)	5426 (43.9%)
Men	3601 (43.2%)	3284 (40.8%)	4473 (49.5%)	5144 (41.8%)	5293 (40.5%)	6591 (48.3%)

Data are n, n (%), or median (IQR). ICU= intensive care unit. *Data are missing for eight patients (one patient in screening and isolation group at baseline with four attributable ICU patient days, and seven patients in universal decolonisation at intervention with 17 attributable days). †Romano comorbidity index.^{3,38}

Table 1: Baseline characteristics of the intensive care unit population enrolled, by arm and sex*

Results

From June 24, 2009, to Dec 10, 2009, 55 hospitals were screened and recruited and from this total, 45 (82%) hospitals were enrolled into the REDUCE MRSA trial (figure 1). 45 hospitals (78 adult ICUs) in 16 states were randomly assigned to one of three different prevention strategies for MRSA (figure 1). 43 hospitals (74 ICUs) initiated the assigned intervention; but two hospitals (four ICUs) randomly assigned were excluded from analyses because they met pre-existing exclusion criteria, which was noted before the intervention started. One targeted decolonisation hospital withdrew after the intervention started and is included in as-randomised but not as-treated analyses.

122 646 ICU patients were admitted to participating hospitals during the study, 48 390 in the baseline period (Jan 1, 2009, to Dec 31, 2009) and 74 256 during the intervention period (April 8, 2010, to Sept 30, 2011). Patient characteristics were generally similar across the three groups and between baseline and intervention periods for all patients and when stratified by sex (table 1). Patients in the universal decolonisation group were more likely to be non-white, have cancer, and undergo surgery. As previously described, 10 reasonably high compliance was achieved across the groups.

For ICU-attributable high-level bacteriuria, no significant difference was reported between the groups in the relative hazards comparing intervention with baseline periods (table 2), either overall or when stratified by sex (figure 2). However, a non-significant reduction was noted in the HR for men in the universal decolonisation group.

	Hazard ratios (95% CI)			Overall trial (p value)
	Group 1	Group 2	Group 3	
High-level bacteriuria (≥50 000 CFU/mL)				
All patients	1.02 (0.88–1.18)	0.88 (0.76–1.02)	0.87 (0.77–1.00)	0.26
Women	0.97 (0.80–1.17)	0.83 (0.70–1.00)	0.93 (0.79–1.09)	0.49
Men	1.09 (0.85–1.40)	1.01 (0.79–1.29)	0.78 (0.63–0.98)	0.12
High-level candiduria (≥50 000 CFU/mL)				
All patients*	1.14 (0.95–1.37)	0.99 (0.83–1.18)	0.83 (0.70–0.99)	0.05
Women	1.09 (0.88–1.36)	1.00 (0.81–1.24)	0.94 (0.76–1.16)	0.62
Men†	1.21 (0.88–1.68)	1.01 (0.73–1.39)	0.63 (0.45–0.89)	0.02
Any bacteriuria				
All patients	0.95 (0.84–1.09)	0.92 (0.80–1.04)	0.86 (0.77–0.97)	0.52
Women	0.91 (0.77–1.08)	0.86 (0.73–1.01)	0.95 (0.82–1.10)	0.70
Men‡	1.01 (0.81–1.25)	1.04 (0.83–1.30)	0.74 (0.61–0.90)	0.04

Group 1=screening and isolation. Group 2=targeted decolonisation. Group 3=universal decolonisation. CFU=colony forming units. *Pairwise analysis: Group 2 versus Group 1, p=0.27; Group 3 versus Group 1, p=0.01. †Pairwise analysis: Group 2 versus Group 1, p=0.42; Group 3 versus Group 1, p=0.006. ‡Pairwise analysis: Group 2 versus Group 1, p=0.85; Group 3 versus Group 1, p=0.04.

Table 2: Results from proportional hazard models for as-randomised, unadjusted, urinary tract infection outcomes

By contrast, there were significant differences between reported high-level candiduria among the groups overall, and among men, but not women (table 2, figure 2). The difference among men was due to reductions in candiduria in men in the universal decolonisation group who had a significantly greater reduction in hazard than men in the screening and isolation group (table 2).

In assessment of any bacteriuria, no significant overall differences were recorded, but again there were differences among men in whom universal decolonisation produced a significantly greater hazard reduction than screening and isolation treatment (table 2, figure 2). In all outcomes, HR estimates for reduction in urine colony count for universal decolonisation in men were similar (HRs 0.63-0.78), even though the finding was not significant for high-level bacteriuria. For women, HR estimates did not suggest meaningful reductions in any treatment outcome (0.93-0.95).

Results from adjusted analyses were highly similar in significance and magnitude to as-randomised findings. When the analyses were restricted to the 38 hospitals that could be randomised to all three groups (removing five hospitals with mandatory screening laws), hazard estimates remained stable, but the p value for any bacteriuria in men was below significance ($p=0.09$; data not shown).

Table 3 details the frequency with which urine cultures were sent and the count and rates per 1000 ICU attributable days of all outcomes. In general, across the baseline and intervention periods for the three groups, urine cultures were sent at a similarly variable rate for women (43-50 per 1000 ICU patient days) as for men (41-54 per 1000 ICU patient days). However, the outcome rates of high-level bacteriuria, high-level candiduria, and any bacteriuria were consistently at least double for women than men (table 3). For high-level bacteriuria, 925 (72%) of 1287 ICU patients had either a white blood cell count of 12×10^3 per μL or higher or concurrent blood cultures sent compared with 1186 (74%) of 1607 with any bacteriuria, 729 (88%) of 833 with high-level candiduria, and 39 271 (58%) of 67 618 without any outcome. In men, 79% (364 of 460) of high-level bacteriuria, 88% (211 of 241) of high-level candiduria, and 81% (477 of 588) of any bacteriuria events were associated with either a concurrent blood culture submission or a raised white blood cell count. In women, these values were 68% (561 of 827) of high-level bacteriuria, 88% (518 of 592) of high-level candiduria, and 70% (709 of 1019) of any bacteriuria events that were associated with either a concurrent blood culture submission or a raised white blood cell count.

In the universal decolonisation group, men had fewer cultures sent to the laboratories during the intervention period (44.7 per 1000 ICU patient days) than during the baseline period (53.5 per 1000 ICU patient days). Additionally, of the cultures sent, fewer outcomes were noted in the intervention period than the baseline period, particularly for any bacteriuria (8.9% vs 9.9%).

The distributions of bacterial pathogens from high-level bacteriuria and any bacteriuria in men and women, by group and period (baseline or intervention), are shown in the appendix. *Escherichia coli* and *enterococcus* were the two most common uropathogens reported in both men and women.

Seven adverse events (two in targeted decolonisation, five in universal decolonisation) were reported in seven patients involving mild pruritus or rash after use of chlorhexidine, two of which involved the perineum. All adverse events were rapidly resolved upon discontinuation of chlorhexidine.

Figure 2: Effect of trial interventions on high-level bacteriuria (A–C), high-level candiduria (D–F), and any bacteriuria (G–I) in all patients, women, and men In all plots, the circles show the hazard ratios (HRs; 95% CI) of the intervention effect at individual hospitals, with the size of the circles illustrating the relative number of patients contributing data to the trial at that hospital. Error bars next to the circles provide the overall group-specific HR and confidence interval derived from proportional hazards models. Black dots are the group-specific point estimates of the HR. Dotted lines represent an HR of 1.0 for the follow-up vs baseline period. These estimates are as-randomised and unadjusted for covariates, but account for clustering within hospital.

Discussion

Our findings suggest that universal decolonisation could be a potentially new and effective strategy for the prevention of overall bacteriuria and high-level candiduria in only male ICU patients (panel).

Despite established guidance for UTI prevention, 15, 16 data show that UTIs have not abated.^{24, 25} In fact, the USA reported a slight rise in UTIs between 2009 and 2012.²⁵ Thus, advancements in effective UTI prevention strategies are needed.

Although the decolonisation intervention included both once a day chlorhexidine bathing and a short course of mupirocin ointment, the presumption is that chlorhexidine was the primary source of the reduction because MRSA is an uncommon source of bacteriuria and that the use of chlorhexidine in the groin and perineum would be the expected method by which bacteria and candida would be usually reduced. These findings contrast with prior smaller-scaled, quasi-experimental, ICU chlorhexidine studies that assessed UTI as a secondary outcome and did not find a benefit with this prevention strategy.^{26, 27}

Although low-level bacteriuria and candiduria are generally indicators of colonisation rather than infection, the reality is that clinicians often treat these findings with antimicrobial drugs.^{9, 28} This is particularly true in

ICUs where every effort is made to address potentially reversible illnesses in a patient who is critically ill. Additionally, ICU sedation precludes physicians from knowing if the patient has frequency, urgency, or dysuria; as a result clinicians might treat patients out of uncertainty. Whether the exclusion of low-level bacteriuria and candiduria from the USA's definition of reportable UTIs will affect urine culturing or

	Baseline 12 months			Intervention 18 months		
	Screening and isolation	Targeted decolonisation	Universal decolonisation	Screening and isolation	Targeted decolonisation	Universal decolonisation
All patients						
Attributable ICU patient days	63 135	57 418	69 668	88 222	92 978	101 603
Urine cultures sent per 1000 patient days	50.8	43.8	51.9	49.0	42.1	44.8
High-level bacteriuria, n (rate*)	301 (4.7)	316 (5.4)	396 (5.7)	420 (4.8)	446 (4.9)	501 (5.0)
High-level candiduria, n (rate*)	197 (3.1)	196 (3.4)	229 (3.3)	299 (3.4)	310 (3.4)	266 (2.6)
Any bacteriuria, n (rate*)	391 (6.2)	372 (6.5)	506 (7.4)	517 (5.9)	543 (5.9)	638 (6.4)
Women						
Attributable ICU patient days	29 153	26 690	32 248	41 931	42 745	46 729
Urine cultures sent per 1000 patient days	49.9	47.2	50.2	49.1	43.4	44.9
High-level bacteriuria, n (rate*)	193 (6.7)	213 (8.0)	252 (8.0)	265 (6.4)	280 (6.7)	337 (7.4)
High-level candiduria, n (rate*)	138 (4.8)	136 (5.2)	156 (4.9)	206 (5.0)	209 (5.0)	201 (4.4)
Any bacteriuria, n (rate*)	245 (8.5)	249 (9.5)	309 (9.9)	321 (7.8)	338 (8.1)	422 (9.4)
Men						
Attributable ICU patient days	33 978	30 728	37 420	46 291	50 233	54 857
Urine cultures sent per 1000 patient days	51.5	40.8	53.5	48.9	41.0	44.7
High-level bacteriuria, n (rate*)	108 (3.1)	103 (3.3)	144 (3.8)	155 (3.3)	166 (3.3)	164 (3.0)
High-level candiduria, n (rate*)	59 (1.7)	60 (1.9)	73 (1.9)	93 (2.0)	101 (2.0)	65 (1.2)
Any bacteriuria, n (rate*)	146 (4.3)	123 (3.9)	197 (5.3)	196 (4.2)	205 (4.1)	216 (4.0)
ICU=intensive care unit. *Rate provided as per 1000 at-risk patient days specific to each outcome.						
Table 3: Total and positive urinary cultures during baseline and intervention periods						

antimicrobial prescribing is yet to be seen, but evidence suggests that treatment is disconnected from mandatory reporting requirements.²⁹ Finally, low-level bacteriuria is well known to progress to high-level bacteriuria in patients with a catheter.³⁰ Irrespective, further interventions to address hospital-associated UTIs are still needed.

The finding of a benefit in men and not women from a topical decolonisation strategy is probably accounted for by anatomical differences. In men, topical chlorhexidine application can produce sustained reductions in the bioburden near the urethral meatus, whereas in women the urethral meatus is far less amenable to sustained reductions in endogenous flora by bathing, even though our protocol included perineal cleaning with chlorhexidine. The REDUCE MRSA protocol included explicit training and compliance observations for cleaning the proximal 6 inches of all urinary catheters, as well as other lines, drains, and tubes, with chlorhexidine during once a day bathing. This cleaning could have further mitigated the bacteriuria and candiduria risk in ICU patients with urinary catheters. Differential effects by sex due to improper aseptic technique in placement or access of urinary catheters would not be expected.

Although universal ICU decolonisation seems to only protect men from bacteriuria and candiduria, its value should be interpreted in the greater context of its comprehensive benefit in reducing ICU-associated infections. Clinical trials, including the REDUCE MRSA trial, have shown that universal ICU decolonisation with chlorhexidine alone or plus mupirocin can reduce highly antibiotic-resistant pathogens as well as reduce all cause bloodstream infections, central line-associated bloodstream infections, and blood culture contamination.^{10,22,23,31} The reduced reservoir of uropathogens might partly explain the reduced bacteraemia

and contamination of patient care environments and on health-care workers' hands.³² These findings thus add selective prevention of bacteriuria and candiduria in men to the growing list of potential benefits that might be attributed to universal decolonisation approaches with chlorhexidine in adult ICUs.

Reported significant reductions in bacteriuria in male ICU patients receiving universal decolonisation seemed to be due to both a reduction in the proportion of urine cultures that suggested bacteriuria and the frequency that urine cultures were sent to laboratories. A reduction in the frequency that urine cultures yielded a uropathogen suggests that when infectious signs and symptoms prompted physicians to send cultures, they were less likely to find bacteriuria and candiduria in men. The change in frequency of sending samples suggests a possible reduction in infectious signs and symptoms that would trigger clinicians to send urine cultures, such as fever or a raised white blood cell count in blood or in a urinalysis because most patients in the ICU settings are sedated and would not verbalise their symptoms. Although the practice is discouraged, clinicians might also regularly send urine cultures solely or cloudy or malodorous urine noted in urinary catheters, which could be reduced in response to prevention of bacteriuria or candiduria. Nevertheless, these reasons are speculative in this study since the pragmatic trial did not include any chart review or other determination of clinical assessment.

Such reductions in bacteriuria or candiduria were not reported in female patients, which, although anticipated, is unfortunate because women had double the number of UTIs compared with men. This higher prevalence of UTIs in women has been previously described in ICU patients and those admitted to hospital with urinary catheters.^{6, 7, 33} It could also be associated with the known frequency of pre-admission asymptomatic bacteriuria, particularly in women, which could magnify over time in the presence of a urinary catheter.³⁴

We do not have an explanation for the absence of a significant reduction in high-level bacteriuria in men in ICUs, although chlorhexidine would not be expected to prevent sources of bacteriuria that did not originate from the body surface—eg, if bacteria or candida were introduced during procedures or inappropriate manipulation of catheters. Another explanation might be that insufficient high-level bacteriuria outcomes occurred to confirm an effect since we note that the estimated reductions in HR for this outcome were similar to the other outcomes. Thus, decolonisation might not effect catheter-associated UTI rates that need high colony counts of uropathogens.

For pragmatic purposes in the ICU setting, our study and others have used outcomes solely based on microbiological results showing a uropathogen.^{6, 7} Patients are often sedated in the ICU and cannot verbalise their symptoms, so we used an objective definition that did not require reporting of symptoms. Even though we do not know the proportion of these events that were associated with clinical signs, such as fever, we reported that about 80-90% of events (infection or colonisation) in men and 70-90% of events in women across the three outcomes were associated with either a concurrent blood culture submission or an elevated white blood cell count, suggesting that the patient was broadly cultured presumably in response to a clinical trigger. Since physicians often treat bacteriuria, this outcome may reduce antibiotic use.^{9, 28, 29}

Additional limitations of this study included the fact that knowledge about antibiotics (which can prevent bacteriuria or increase candiduria) or the presence of urinary catheters were not readily available for analysis. We also did not measure the adherence to present infection prevention standards for the placement, access, maintenance, and prompt removal of urinary catheters; but we note that the Hospital Corporation of America (Nashville, TN, USA) did have a robust corporate Aim-For-Zero campaign that was actively encouraging attention to these practices in all hospitals in all groups of the REDUCE MRSA trial. Although we did not measure practice adherence, fortunately differences in culturing or prevention practices across groups are largely accounted for by comparing each hospital's outcome rates to its own baseline, providing some reassurance that the benefit is attributable to decolonisation rather than baseline variation in casemix or clinical practices across groups. Nevertheless, to the extent that the rationale for sending clinical cultures differed between the baseline and intervention periods, the results could over or underestimate the effect of

decolonisation on isolation of an uropathogen. Finally, these findings show the patient population of a large, single health system of community hospitals in the USA, but its generalisability to other hospitals and health systems remains to be seen.

In conclusion, universal decolonisation prevented 37% of high-level candiduria and 26% of bacteriuria events in male ICU patients. Further studies will be needed to determine if these reductions translate to other clinical correlates of UTI. Nevertheless, this reduction is likely to be generally achievable in most hospitals given the pragmatic nature of this study being completed in mostly community hospitals.^{10, 35} Although vigilance against emerging resistance will be needed, reports of chlorhexidine resistance are rare and the minimum inhibitory concentrations found are far below the 20 000 μ g/mL of chlorhexidine applied to the skin by 2% chlorhexidine cloths. These data add to the growing benefits of universal decolonisation in preventing healthcare-associated infections in the ICU setting.

Panel: Research in context Systematic review

Several recent systematic reviews into chlorhexidine bathing in intensive care units (ICUs) have concluded that once a day chlorhexidine bathing reduces bloodstream infections, including central-line-associated bloodstream infections, as well as meticillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococcus (VRE) colonisation and infection.^{17–20} We searched PubMed for “chlorhexidine” (MeSH Terms), “randomized controlled trial” (publication type), AND “ICU”, and found five additional trials on this topic. These included one brief single-centre study that did not find a reduction in a composite of health-care-associated infection and four large trials that reported significant reductions in MRSA and VRE carriage and acquisition, as well as significant reductions in all-cause health-care-associated bloodstream infections.^{10,21–23} One of the four trials included the parent REDUCE MRSA trial of this secondary analysis. The REDUCE MRSA trial, which was the largest such trial so far, reported a 37% reduction in MRSA carriage and a 44% reduction in all-cause bloodstream infections. We know of no previous randomised controlled trials involving chlorhexidine bathing that have assessed whether body and perineal chlorhexidine cleansing affected bacteriuria or candiduria.

Interpretation

As a secondary analysis of the largest adult ICU chlorhexidine bathing trial so far, we identified a 37% reduction in high-level candiduria and a 26% reduction in all bacteriuria events in male ICU patients. Selective benefit in men is likely because of anatomical differences that allow for persistent antiseptic effect following perineal cleansing. Whereas candiduria and bacteriuria are often markers of urinary colonisation, they are nevertheless frequently treated with antimicrobials, particularly in patients who are critically ill.

Although whether daily chlorhexidine bathing reduces antimicrobial use is yet to be assessed, our study extends the already proven benefits of antiseptic bathing in reducing bloodstream infection and carriage in addition to infection due to multidrug-resistant organisms, which now include reduction of candiduria and bacteriuria in male patients.

Contributors

SSH contributed to study design, study conduct, data analysis, and manuscript drafting. ES, MKH, and JAJ contributed to study design, study conduct, and manuscript review. KK contributed to study design, data analysis, statistical analysis, and manuscript review. JS and TRA contributed to data analysis and manuscript review. JM, JH, JL, AG, REK, KH, and JBP contributed to study conduct and manuscript review. RP and RAW contributed to study design, study conduct, data analysis, and manuscript review.

Declaration of interests

SSH, ES, MKH, KK, TRA, JM, JH, AG, REK, KH, JAJ, JBP, and RAW are completing a clinical trial (ABATE Infection Trial) in which participating hospitals receive contributed product from Sage Products and Molnlycke. This disclosure arose after the conduct and analysis of the original REDUCE MRSA Trial. No product was contributed for the REDUCE MRSA Trial. SSH, MKH, KK, TRA, JL, AG, REK, KH, RP, and RAW report grants from Agency for Healthcare Research and Quality (HHS2902010000081 and HHS29032007T) and the US CDC Prevention Epicentres Program (1U01 C1000344), during the conduct of the study. ES was on the scientific advisory board for 3M (no longer active) and has been on the speaker's bureau for Sage Products (no longer active) in the past 3 years. JS declares no competing interests.

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