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Major Article

Potential effectiveness of copper surfaces in reducing health care–associated infection rates in a pediatric intensive and intermediate care unit: A nonrandomized controlled trial

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Background: Studies have consistently shown that copper alloyed surfaces decrease the burden of microorganisms in health care environments. This study assessed whether copper alloy surfaces decreased hospital-associated infections in pediatric intensive and intermediate care units.

Methods: Admitted infants were assigned sequentially to a room furnished with or without a limited number of copper alloyed surfaces. Clinical and exposure to intervention data were collected on a daily basis. To avoid counting infections present prior to admission, patients who stayed in the hospital <72 hours were excluded from analysis. Health care–associated infections (HAIs) were confirmed according to protocol definitions.

Results: Clinical outcomes from 515 patients were considered in our analysis: 261 patients from the intervention arm of the study, and 254 from the control arm. Crude analysis showed an HAI rate of 10.6 versus 13.0 per 1,000 patient days for copper- and non–copper-exposed patients, respectively, for a crude relative risk reduction (RRR) of 0.19 (90% confidence interval, 0.46 to -0.22). Conducting clinical trials to assess interventions that may impact HAI rates is very challenging. The results here contribute to our understanding and ability to estimate the effect size that copper alloy surfaces have on HAI acquisition.

Conclusions: Exposure of pediatric patients to copper-surfaced objects in the closed environment of the intensive care unit resulted in decreased HAI rates when compared with noncopper exposure; however, the RRR was not statistically significant. The clinical effect size warrants further consideration of this intervention as a component of a systems-based approach to control HAIs.

Health care–associated infections (HAIs) are a major public health concern causing significant morbidity and mortality that could be, to some finite extent, prevented. Progress in reducing HAIs has been achieved through the implementation of low technology and low-cost interventions, such as hand hygiene and disinfection of the environment. However, the full efficacy that each approach offers has not been fully realized for many different reasons.[1]

Handwashing is considered the single most effective intervention for controlling infection; however, compliance rates continue to be an issue.[2] Environmental cleaning and disinfection have been overlooked since Spaulding[3] categorized noncritical items as less important in the chain of events leading to infection. Asepsis and antiseptics have completely changed the landscape such that we need to target new reservoirs, new mechanisms of transmission, and new microorganisms. Recently, strong evidence has been generated suggesting that near-patient high-touch surfaces may act as important reservoirs for some hospital pathogens causing HAIs.[4,5]

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In controlled in vitro experiments, and during the conduct of pragmatic clinical trials, copper alloys have consistently displayed a profound and persistent antimicrobial activity.[6-8] Salgado et al[9] evaluated the antimicrobial activity of copper in the context of whether or not lower microbial burdens proximal to the patient would result in lower acquisition rates of HAI and learned that through the reduction in microbial burden on selected surfaces and components in the rooms of patients, a subsequent and significant reduction of HAI rates was observed. However, the study was conducted in adult medical intensive care units, and therefore it remains to be seen how the reduced bacterial burden might impact the HAI rates in different clinical settings and in different patient populations.

The methodologic challenges for estimating a significant reduction in HAI rates, as influenced by copper surfaces in different clinical settings, are manifold. First, a randomized controlled trial (RCT) seems to be the ideal design but presents the following challenges: (1) masking the intervention is challenging; (2) randomization is complicated because the intervention does not act at the level of the individual but rather on the microbes proximate to the care being provided; and (3) for busy critical health care units it may not be feasible to randomly assign patients to a particular room based on their medical need. Further, the very definition of the primary outcome required from such studies, acquisition of an HAI, is problematic because although ideal and detailed definitions of HAIs suited for epidemiologic purposes exist, their utility is limited as a consequence because they are not easily abstracted from medical records with the level of precision expected from a binary outcome. HAI definitions can also vary according to the population involved (eg, bloodstream infections associated with immunocompromised vs immunocompetent patients), from country to country, and from many other perspectives.[10]

In the work from Salgado et al,[9] they reported results of an RCT aimed at estimating the effect of copper-surfaced objects on HAI and colonization rates in adult patients admitted to the intensive care units of 3 hospitals in the United States. They found that the limited introduction of 6 copper components resulted in a statistically significant reduction of HAI rates and methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant *Enterococcus* colonization in the intervention arm of the study compared with the control arm. The observed HAI incidence rates were 0.071 and 0.123 for the intervention and control groups, respectively, with a relative reduction risk (RRR) of 0.42. These promising results encouraged us to run a similar trial with respect to the number of copper components introduced as an additional component of a comprehensive infection control strategy in a different setting to compare estimates of the intervention effect. Our trial objectives were 2-fold. The first, for which results were recently published,[11] compared the microbial burden alleviated by the intervention (the limited introduction of copper components) with the microbial burden associated with the control surfaces. The second, addressed here, was to measure the clinical impact that copper alloy surfaces had on the HAI acquisition rates seen in 2 pediatric intensive care settings.

METHODS

Study design and setting

This study was conducted using a nonrandomized, unmasked, controlled clinical trial. The protocol was registered before the initiation of the study (ClinicalTrials.gov identifier no. NCT01678612). Although the study design was not ideal, it was deemed meritorious and was conducted under the umbrella of a pragmatic trial.[12,13]

The study was conducted in the pediatric intensive care unit (PICU) and intermediate pediatric care unit (PIMCU) of the Roberto del Rio Hospital, Santiago, Chile, which is a 249-bed tertiary hospital. Recruitment lasted 12 months. Eligible participants were all patients admitted to the study site. Although we would analyze only patients staying >3 days in the ward, we included all patients in the study because we could not judge beforehand the length of the patient's stay. The only exclusion criterion was lack of informed consent. The PICU has 6 two-bed rooms and 2 single-bed rooms. The PIMCU has 1 four-bed rooms, 5 three-bed rooms, and 2 single-bed rooms.

Intervention

Half of the rooms (n = 8) were furnished with copper-surfaced items, and the other half remained unchanged. Intervened rooms were located in the space in an alternate fashion.[10] The selected items surfaced with copper were bed rails, bed rail levers, intravenous poles, sink handles, and the nurses' workstation. Handwashing procedures and cleaning routines remained the same before and throughout the study period. The hand hygiene compliance rate of health care workers was assessed by staff not affiliated with the trial and was reported quarterly as a measure of health care worker adherence to the established protocol for hand hygiene before and after patient contact. For the period of the trial, the mean compliance rate for the health care workers observed in the units (N = 153), expressed as the percentage of individuals that complied entirely with the hospital standards for intensive care unit wards, was 93% (range, 80%-100%).

Assignment to experimental arm

On admission, to each unit, patients were sequentially assigned to either an intervened or control room. Swapping patients from one unit to the other was discouraged but was allowed for compelling medical reasons; however, the protocol stated that patients should move to the same type of room (intervened or control) as originally assigned.

Ethics and regulatory requirements

Written informed consent was obtained from each parent or legal guardian within 24 hours of admission. This study was conducted in accordance with the Helsinki Declaration, the International Conference on Harmonization Guidance for Good Clinical Practice, and applicable national regulations. The study protocols and informed consent form were approved by the research ethics committee overseeing clinical research at the local site.

Measurements

Demographic and clinical data were collected at entry for all eligible patients. Thereafter, clinical data regarding installation and removal of invasive catheters (central venous catheters, indwelling urinary catheters, and tracheal intubation for mechanical ventilation), instauration of antimicrobial therapy, room location, and HAI suspicion status were collected on a daily basis until patient discharge from the unit. An inventory log was designed to keep track of the presence or removal of items with and without copper surfaces from their original assigned room.

Bacterial burden was measured on selected surfaces (bed rails, cribs, and faucet handles) from both groups on a bimonthly basis during study duration. Detailed results of this aim of the study are reported elsewhere.[11]

Outcome

The primary outcome of the study was the diagnosis of an HAI event associated with patient stay within the PICU or PIMCU. According to broadly accepted criteria, signs and symptoms should appear on or after the third calendar day of admission to the facility.[14] HAI definitions used were the standard definitions used by the National Surveillance System of the Ministry of Health of Chile.[15] However, to evaluate the reliability of the results, an independent review of the source documents was conducted on a subset of the study subjects (122/515; 24% records) on completion of the study. The reviewer was blinded to the assignment of the patient to the intervention or control group and to the occurrence or not of an acquisition of an HAI, the primary outcome.

Safety

Although the anticipated risk of harm associated with the study was very low, possible skin or other allergic reactions to either the patients or hospital staff were monitored during the study. Mortality data were also collected.

Statistical methodology

Sample size was estimated on the basis of available local data. An expected HAI incidence rate of 14.4 per 1,000 patient days for the control group was derived from figures from the study wards reported to the HAI National Surveillance System along with a short retrospective study of administrative data from the previous year. The historical number of patients admitted annually to the local site was approximately 1,100, resulting in an expected number of 7,500 patient days for the study duration. Allowing for a 10% dropout from the analysis, we estimated that approximately 3,400 patient days would be required per group to yield an approximate 85% statistical power to show a 50% reduction of the HAI rate in the intervention group compared with the control group, with a 2-sided type I error of 0.05 within the 12 months allotted for the trial. The analysis was planned on an intention-to-treat basis because some protocol deviations regarding actual exposition to copper (objects removed or displaced) were expected. Considering that repeated infections on the same patient are not independent events, the analysis counted solely the first HAI observed on each patient. A κ statistic was derived to assess agreement between original HAI determinations and those for the validated subsample. A Poisson regression model was planned to control for selected variables according to clinical considerations. R package version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analyses.

RESULTS

Study population

A total of 1,012 patients were admitted to the PICU-PIMCU during the 12 months of study duration (November 12, 2012-November 15, 2013). To avoid counting possible infections present prior to admission, patients who stayed in the hospital <72 hours were excluded from analysis. The distribution of patients within each arm of the study and unit of admission is shown in Figure 1. Demographic and relevant clinical features of enrolled patients are described in Table 1. In spite of patients not being randomized when allocated to the study group, fair balance between baseline characteristics was observed. In particular, regarding aspects that increase the likelihood of developing an HAI, for example, specific pre-existing conditions and the number of patients with invasive medical catheters and time of exposure to invasive medical devices.

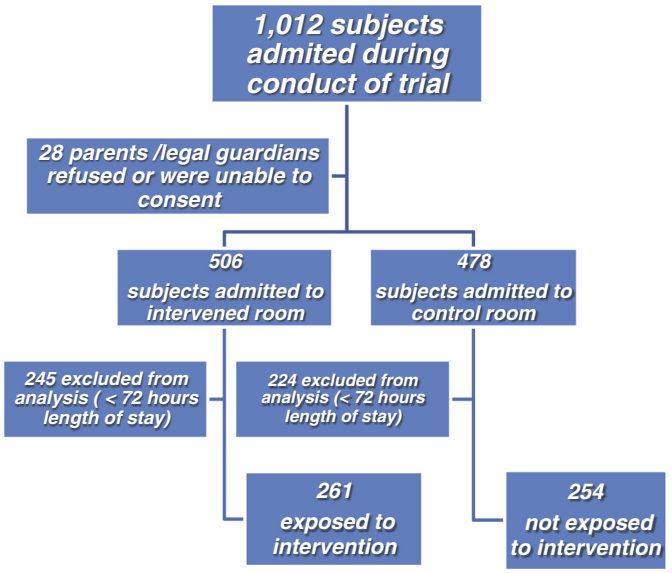

Fig 1. Flow diagram of patient data used for analysis. There were 1,012 patients available for consent for subsequent enrollment during the trial period within the pediatric intensive care unit and intermediate pediatric care unit of the Hospital Roberto del Rio, Santiago Chile.

Setting considerations and adherence with study protocol

The mean bed occupancy rate during the study period was 70% (monthly range, 14%-121%) for the PICU and 43% (monthly range, 12%-94%) for the PIMCU. In the PICU, during July and August, the bed occupancy rate was >100% (22 and 14 days, respectively, or 85% of the time). This meant that, in the best interest of the patients, additional noncopper beds were placed in some intervened rooms of the PICU. Moreover, during the same winter months, some patients allocated to copper-surfaced beds were moved to noncopper rooms, representing an estimated deviation of the protocol of 12% over the corresponding 868 patient days of the busiest winter months. Shortly after the initiation of the trial, it became apparent that the patients from the 4-bed room of the PIMCU (control arm room) should be excluded from the trial because they were classified as long-term or chronic patients. The patients associated with this room were excluded from subsequent analyses because their inclusion would skew the overall study occupancy rate and patient demographics.

Analysis of primary outcome

Overall, 65 patients developed 91 medical conditions compatible with the protocol definition of an HAI, 32 patients were from the intervention group and 33 from the control group, resulting in an HAI incidence rate of 10.6 and 13.0 per 1,000 patient days, respectively, which corresponds to an 0.19 RRR of HAI for patients exposed to copper-surfaced objects compared with control patients. In addition, as prescribed in the study protocol, a Poisson regression model was fitted to control for selected variables according to clinical considerations. The offset parameter was the log of the number of patient days in each group (intervention and control). Two variables (ie, number of days with invasive catheters [indwelling urinary catheter, central venous catheter, and endotracheal intubation], age) were the covariates that best fit the

model. The adjusted estimate of the effect provided by the incorporation of copper into the built clinical environment from the fitted model was an RRR of 0.26 (90% confidence interval, 0.48 to -0.06) (Table 2).

Forty-two patients developed only 1 HAI during the study period, 21 developed 2 HAIs, 1 developed 3 HAIs, and 1 developed 4 HAIs. Only the first HAI event was considered in the primary analysis.

Table 1
Demographic and clinical characteristics at study entry & postadmission characteristics

Characteristic	Intervention	Control	*P* value
Patients consented PICU and PIMCU, n	261	254	
Patients treated in PICU, n (%)	130 (50)	149 (59)	.05
Sex (male), n (%)	141 (54)	146 (58)	.48
Age, n (%)			
≤ 1 y	133 (51)	144 (57)	.22
> 1 y	128 (49)	110 (43)	
Median age (y)	1	1	
Age range (y)	0-16	0-17	
Pre-existing conditions			
None	67	79	.46
Oncology-immunodeficiency	11	6	
Gastrointestinal ostomy	8	7	
Cardiovascular malformation	5	5	
Other	9	5	
Absence of devices at admission, %	83%	85%	.55
Active antimicrobial therapy at admission, %	17	13	.18
Frequent causes of admission, %*			
Respiratory	57	60	.16
Infectious	49	52	
General surgery recovery	12	6	
Neurologic/neurosurgery	10/7	10/6	
Trauma/burn	5/3	2/3	
Sepsis: shock/oncology	5/6	9/4	
Post admission characteristics			
LOS			
Median LOS, d	4	4	
Range LOS, d	1-100	1-91	
Patients with IUCs	150	128	
Total days IUC	680	640	
No. of patients with CVCs	144	133	
Total days CVC	1,087	1,131	
No. of patients with ETT	158	130	
Total days ETT	731	729	

CVC, central venous catheter; *ETT*, endotracheal intubation; *IUC*, indwelling urinary catheter; *LOS*, length of stay.
*Sum of the percent may be >100% because each patient may have >1 pre-existing condition at the time of admission.

Urinary tract infection (UTI) and bloodstream infections were the most common types of HAI. Patients who developed HAI events in the intervened arm of the study had pre-existing conditions more frequently than patients in the control group and had longer lengths of stay (Table 2).

The data associated with Table 3 illustrate the type of infection and the pathogens isolated among HAI cases encountered in the room containing copper components and control rooms. Three patients displaying the symptoms of pneumonia were diagnosed solely using clinical criteria because all samples cultured were negative. This is a commonly observed occurrence with cases of suspected pneumonia. All 3 corresponded to patients assigned to the intervention arm of the study. A clear imbalance is observed in the number of UTI cases being more frequent in patients assigned to the control arm.

Independent review of source documents

An independent expert (blinded to the experimental assignment) reviewed the medical records, nurse charts, and laboratory results of 122 patients. Fifty four were HAI cases, and 68 were matched non-HAI cases. Matching parameters were length of stay, sex, and unit of admission. Each patient was classified as case or noncase according to an algorithm (previously established by the expert), which included number of days with fever, polymerase chain reaction levels, source of cultures, type of microorganisms isolated, and so forth. A test for agreement (κ score) gave an estimate of 0.41, which can be considered moderate agreement.

Secondary analyses

The potential influence of bed occupancy over time on the occurrence of cases was explored. Excess occupancy rates (>100%) were only observed in the PICU; therefore, we analyzed PICU alone in a subgroup unplanned analysis. Figure 2 summarizes the distribution of HAI occurrence, bed occupancy rates, and surface bacterial burden measured over the study period. Median bacterial burden in the control rooms fluctuated at high levels, somewhat following occupancy rates within the PICU ward, whereas median bacterial burden in intervened rooms stayed steadily low. Although HAI cases in the intervention group seem to occur more or less randomly over time, HAI cases in the control group show a clustering trend during July-August (7 and 14 cases for the copper and noncopper group, respectively), coinciding with an isolated increase of median bac-

Table 2
Primary end point: hospital-associated infection density rates

Primary endpoint	Intervention	Control	Relative risk reduction (90% CI)
Total HAI cases	32	33	
HAI by care unit, PICU/PIMCU	26/6	28/5	
Patient days	3,012	2,531	
Incidence rate, no. of HAIs per 1,000 patient days	10.6	13.0	0.81 (0.50-1.32)
Presence of pre-existing condition at time of HAI acquisition			
Yes	15	6	
No	17	27	
Median length of stay, d	22	12	
Range	3-158	4-96	
No. of HAI cases	43	48	
Bloodstream infection	15*	11	
Urinary tract infection	9	16	
Pneumonia	7†	4†	
Surgical site infection	1†	2†	

CI, confidence interval; *HAI*, health care–associated infection; *PICU*, pediatric intensive care unit; *PIMCU*, intermediate pediatric care unit.
*One case without microbiologic confirmation.
†Three cases without microbiologic confirmation.

Table 3
Infection type and pathogen associated with HAI

Type of infection	Intervention rooms (copper)	Control rooms
BSI	15 infections	11 infections
	Fungal infections	Fungal infections
	Candida albicans: 1	Gram-positive infections: 5
	Gram-positive infections: 9	*S aureus*: 2
	Staphylococcus aureus: 1	*S epidermidis*: 3
	Staphylococcus epidermidis: 3	Gram-negative infections: 6
	Staphylococcus haemolyticus: 2	*K oxytoca*: 2
	Staphylococcus hominis: 2	*Klebsiella pneumoniae*: 3
	Staphylococcus pyogenes: 1	*Haemophilus influenzae*
	Gram-negative infections: 4	type B: 1
	Klebsiella pneumoniae: 3	
	Enterobacter cloacae: 1	
PNEU	7 infections	4 infections
	Culture negative: 3	Culture negative: 0
	Fungal infections	Fungal infections: 0
	Candida parapsilosis: 1	Gram-positive infections: 1
	Gram-positive infections: 1	*S pneumoniae*
	Streptococcus pneumoniae	Gram-negative infections: 3
	Gram-negative infections: 2	*P aeruginosa*: 1
	Pseudomonas aeruginosa: n = 1	*H influenzae* type B: 2
	Haemophilus influenzae type B: 1	
UTI	9 infections	16 infections
	Fungal infections: 0	Fungal infections: 1
	Gram-positive infections: 2	*C albicans*: 1
	Enterococcus faecalis: 2	Gram-positive infections: 3
	Gram-negative infections: 7	*E faecalis*: 3
	Escherichia coli: 5	Gram-negative infections: 13
	Klebsiella oxytoca: 1	*E coli*: 8
	Pseudomonas aeruginosa: 1	*K pneumoniae*: 2
		Proteus mirabilis: 1
		E cloacae: 1
SSI	1 infection	2 infections
	Fungal infections: 0	Fungal infections: 1
	Gram-positive infections: 0	*Candida lusitaniae*
	Gram-negative infections: 1	Gram-positive infections: 1
	Escherichia coli	*S aureus*: 1

BSI, bloodstream infection; *HAI*, health care–associated infection; *PNEU*, pneumonia; *SSI*, surgical site infection; *UTI*, urinary tract infection.

terial burden on intervened rooms and also with occupancy rates >100%.

Safety analysis

Adverse effects were not observed among the health care workers or patients exposed to copper-surfaced items. There was no indication of excess mortality identified during the study. Eight patients died during their course of care in the copper arm of the study, whereas 9 patients died during the course of care in the control arm of the study, accounting for an overall mortality rate of 2%.

DISCUSSION

In this pragmatic clinical trial, an intervention consisting of placing selected copper alloy surfaced components in the environment in close proximity to patients admitted to the PICU and PIMCU showed a moderate 19% (crude) to 26% (adjusted) reduction of incident HAI rates compared with the control arm of the study. Although not statistically significant, the reduction to the HAI acquisition rate in the copper arm suggests that the reductions to the proximate environmental microbial burden near the patient warrant further investigation. This study represents only the second such RCT investigating a relationship between the environmental microbial burden and HAI acquisition. Here a pediatric population was used to investigate this relationship. The copper components were found to be equivalently effective in their ability to control the proximate microbial burden to those used in the adult trial.[9,11]

Although the comparison between the 2 groups failed to achieve significance, we recall the advice offered by Altman and Bland who encourage, "just because results are non-significant does not necessarily follow that the study found nothing of clinical importance."[16] Although the RRR observed in our study was lower than expected, we offer that the actual overall effect that the lowered proximate microbial burden (copper arm of the study) contributed to the HAI acquisition rate in the pediatric units was somewhere between our estimate and the one observed in the published adult intensive care unit trial.[9] Given that HAI acquisition is a complex and multifactorial clinical phenomenon, here the fractional difference observed between the copper intervention and control groups may not exceed the proportion of HAIs facilitated by exogenous cross transmission. Harbarth et al concluded from their work that such cross contamination for HAI acquisition may vary between 16% and 35%.[17] Therefore, under this hypothesis, an extremely efficacious environmental intervention would, at the best, reduce HAI incidence by no more than 30%.

Additionally, protocol deviations were encountered during the course of our study during the winter season. Overcrowding led to misplaced objects and the addition of extra beds and patients into 2 rooms of the PICU. This may have limited the antimicrobial contribution provided by the copper intervention.

Some of our assumptions regarding statistical power calculations were not met. As already described, in the absence of better information, our estimated copper effect was optimistic. Also, the number of patients who failed to meet the minimum length of stay (72 hours) in the unit was underestimated (expected: 10%, observed: 47%). On a positive note, the estimated HAI incidence rate for the control arm for our facility was in close agreement to our estimate. In accordance with the published literature on the exposure of human skin to metallic copper materials, no adverse events were reported in association with the intervention. Similarly, mortality rates were equivalent for both arms of the study.

In summary, and following recommendations on how to report RCT results from pragmatic trials,[18] we conclude that our results are compatible (90% confidence interval) with a 46% decrease or a 22% increase of HAI rates. However, taking into account that there is no biologic plausibility that lower microbial burdens should lead to increases to HAI rates, and that a previous study showed a 42% decrease to the HAI acquisition rate, we offer that copper-surfaced objects offer a potential benefit that needs to be determined with a greater level of precision. Further, not all types of HAIs are likely to be equally influenced by environmental interventions. The results here suggest that there exists a greater effect on incidence rates for pediatric UTIs ($3 \times 1{,}000$ vs $6 \times 1{,}000$ patient days for copper and control groups, respectively). Ideally, a target difference could be defined, as proposed by various methodologists and trialists.[19]

Despite the nonrandomized design of the study, both groups looked fairly comparable from the perspective of the most frequent clinical characteristics likely to introduce bias of some concern. The nonblinded characteristic of the study design was a major concern because, as previously stated, the diagnosis of HAI is a complex process requiring clinical judgment, particularly when a binary end point is lacking (ie, pathogen-positive culture). In this study, the clinicians responsible for assessing the primary outcome did not have access to the study database; therefore, they rapidly lost track of partial results. Controversial end points were adjudicated through a collective discussion among the medical trial team after discharge of the patient. Additionally, the conduct of an independent blind review of medical records associated with positive and negative HAIs offered some assurance regarding the consistency with which the primary outcome was assessed. For the sake

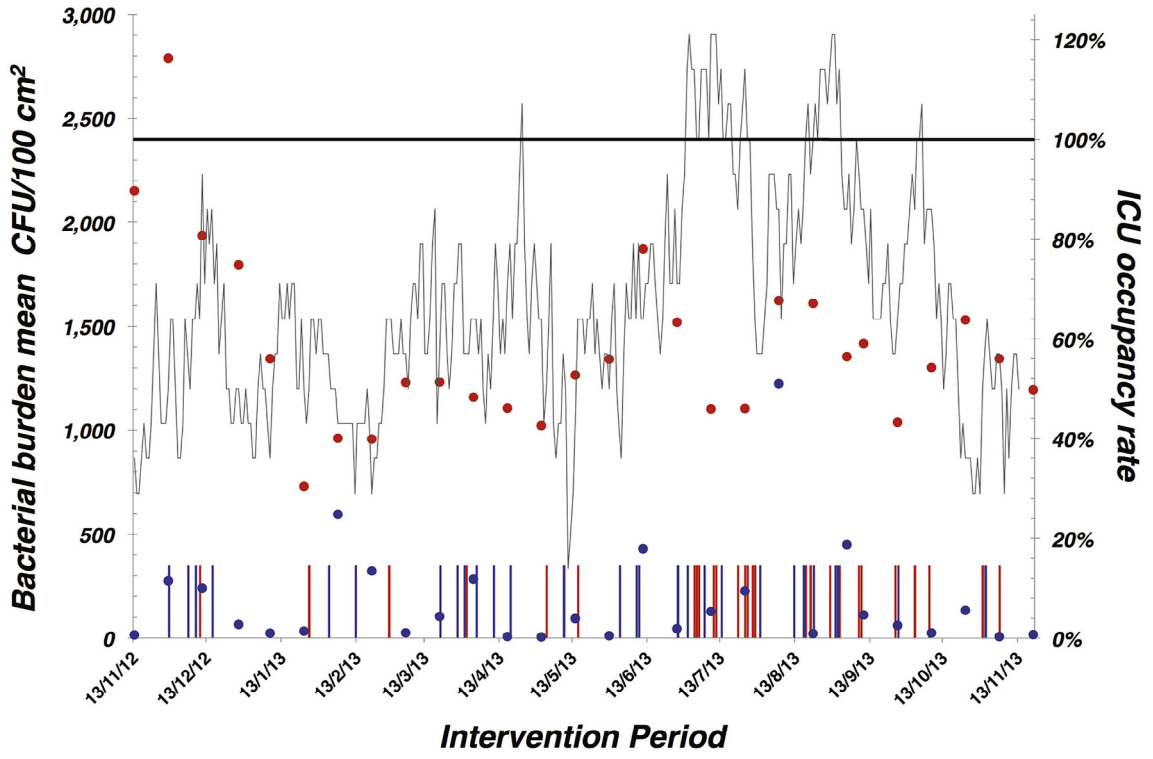

Fig 2. Comparison of room occupancy rates with mean bacterial burden present on sampled objects along with the date of HAI acquisition. The mean bacterial burden associated with sampled objects (bed rails, cradles, and faucet handles; blue circles, copper-intervention objects; red circles, control objects), the date of HAI acquisition, (blue vertical line, HAI acquisition copper arm; red vertical line, HAI acquisition control arm), and the room occupancy rate (solid black line) were plotted against the time (day/month/year) that they were observed. *CFU*, colony forming units; *HAI*, health care–associated infection; *ICU*, intensive care unit.

of clarification, a κ test for agreement of 0.41 must be interpreted as a 41% agreement on top of what could be expected if the rating was performed at random.[20]

Our results are generalizable to PICUs that present with comparable populations in terms of demography, HAI incidence rates, and type of infection reported. For example, the baseline HAI rate in our setting seemed to be a low rate (crude frequency rate of 13%) when compared with reported rates in PICUs of comparable countries, such as Brazil and Peru, where the crude HAI rates reported are 18% and 20%, respectively.[21,22] This low HAI acquisition rate may have also contributed to a lower than expected copper effect.

In thinking about the value proposition that the addition of a limited number of copper components offers to a comprehensive systems-based approach to control HAIs, a consideration of the data from the cost-benefit model developed by York Health Economic Consortium is warranted. Here the authors developed a cost-benefit model that was populated with established datasets relevant to the profiles for UK hospitals. The model assumed a copper size effect of 20% reduction of HAI rates. The model yielded a return of investment of 1 month and a cost per infection averted of £120.[23] Therefore, a target difference of ≥20% reduction of HAIs seems a reasonable size effect from an economic and policy decision perspective, confirming the potential value that our results and copper components offer to a systems-based approach for controlling HAIs.

Considering the methodologic difficulties faced when evaluating this kind of environmental interventions, we concur with Stone et al[24] to give more priority to time series experimental designs because they are best suited to detect temporal and nonindependent events as the ones studied in this clinical trial.

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