LETTERS TO THE EDITOR

The Environment and Healthcare-Acquired Infections: Why Accurate Reporting and Evaluation of Biological Plausibility Are Important

To the Editor—We read with interest the article by Salgado and colleagues,[1] describing a randomized clinical trial involving 614 patients in intensive care unit (ICU) rooms with or without the addition of copper alloy surfaces on 6 frequently touched items in the near-patient environment. The 2 primary outcomes were incidence of (a) any healthcare-associated infection (HAI) and (b) any ICU-acquired colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant enterococci (VRE) detected from surveillance swab samples or clinical cultures. The authors concluded that placing copper surfaces into ICU rooms reduced the risk of HAI by more than 50%. Although this trial represents a substantial amount of laudable work, we have concerns with 3 important issues: (1) the approach taken to reporting study outcomes; (2) lack of information concerning the determination of study end points; and (3) a failure to evaluate the biological plausibility of the findings.

First, the authors created a complex system of 2 single and 4 composite outcomes that included patients who had (a) any episode of HAI; (b) any episode of MRSA or VRE colonization; (c) both HAI and colonization (ie, only patients who had both events); (d) HAI and/or colonization (ie, patients with either HAI or colonization, meaning any event); (e) HAI only without colonization (ie, patients with HAI minus those who had both HAI and colonization); and (f) colonization only without HAI (ie, patients with colonization minus those who had both HAI and colonization). Combined data for both trial arms were available for all outcomes (a)–(f), but separate data for each trial arm were reported only for outcomes (d)–(f), not for (a)–(c). For (d) and (e), there was a significant reduction of events in favor of copper-treated rooms, and for (f), there was a nonsignificant reduction. The statistical significance of composite outcomes (d) and (e) apparently provided the basis for the conclusions. However, we believe that rates stratified by treatment arm for (a) any HAI and (b) any colonization would have been biologically and clinically most relevant. Combining the 2 end points (under d) may not be informative, because the causal pathways for both are biologically different. In addition, outcomes (e) and (f) are unnecessarily complex and appear artificially constructed.

We extracted the missing numbers for the primary end points (a) and (b) from the article. For both noncomposite primary outcomes (a) and (b), the differences were not statistically significant (by χ^2 and Fisher exact tests). A compilation of reported (in the article by Salgado et al[1]) and extracted (not reported) outcomes is shown in Table 1. This has 2 implications. Nonreporting of 2 prespecified primary outcomes for each trial arm constitutes a case of selective reporting,[2] and the conclusion that copper-equipped rooms reduced the rate of any new HAIs (corresponding to primary outcome [a]) is now questionable.

Second, there remains uncertainty over end point determination in this clinical trial with high interobserver variability and disagreement in outcome ascertainment and validation (κ statistics, 0.52). How were new MRSA or VRE acquisitions detected and defined? This is obviously important for the overall outcome, especially because one site was not performing admission screening for VRE, and exclusion of MRSA carriage depended solely on nasal swab samples across all sites. How was colonization defined, as opposed to infection, and what were the specific acquisition rates of MRSA and VRE? The most striking HAI reduction was observed for bloodstream infection (BSI) rates. Were these episodes related to primary or secondary BSI? What were the central venous catheter (CVC)-related BSI rates expressed per 1,000 CVC-days and stratified by treatment arm? Finally, there are insufficient data on compliance with hand hygiene before patient contact, particularly any differences among staff dealing with patients in both types of study room.[3]

Third, we have concerns about the biological plausibility of the main findings. The major source of healthcare-associated pathogens is thought to be the patient's endogenous flora, but an estimated 20% of pathogens are acquired via other transmission routes, such as the environment, and 20%–40% is attributed to cross-infection via the contaminated hands of healthcare personnel.[4-7] Thus, it remains unclear how copper-treated surfaces could have had such a substantial effect on reducing HAIs, taking into account the fact that only 10% of ICU surfaces were copper-equipped and that 13% of control patients were exposed to copper objects. If there was a greater than 50% reduction of HAIs as a result of copper surfaces, this would mean that endogenous origin, exogenous transmission through direct contact, and transmission from all other (noncopper) surfaces were implicated in only a minority of HAIs. This is not consistent with the known pathophysiology of ICU-acquired HAIs, including primary and secondary BSIs.[8]

Anyone doing research can retrieve observations that confront conventional wisdom and challenge existing evidence.[9] The essence of research is venturing into the unknown. Certainly, the possibility that there was an association between overall HAI risk and higher microbial levels from hand-touch sites, whether copper coated or not, was of interest. However, we feel that this study (apparently not registered a priori on an open-access trial registration site) provides more questions

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TABLE 1. Primary and Composite Outcomes for Patients in Rooms with and without Copper-Coated Surfaces

Outcome[a]	No. of patients, by type of room			*P*	
	Copper-coated surfaces (n = 294)	Without copper-coated surfaces (n = 320)	Total (n = 614)	χ^2 test[g]	Fisher exact test
Any HAI event (a)	17[f]	29[f]	46	.12	.13
Any MRSA or VRE colonization event (b)	11[f]	15[f]	26	.56	.69
Both HAI and colonization (c)[b]	7[f]	3[f]	10	.16	.21
HAI and/or colonization (d)[c]	21	41	62	.020	.023
HAI only (e)[d]	10	26	36	.013	.015
Colonization only (f)[e]	4	12	16	.063	.077

NOTE. HAI, healthcare-acquired infection; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci.
[a] Letters in parentheses correspond to those in the text.
[b] Both events occurring in the same patient.
[c] Either HAI or colonization or both (ie, any event).
[d] No. of patients with HAI minus those who had both HAI and colonization.
[e] No. of patients with colonization minus those who had both HAI and colonization.
[f] These numbers were not provided in the original article by Salgado et al[1] and instead were extracted and calculated from the other reported data.
[g] Without Yates correction.

than answers, and we would appeal for additional work on linking antimicrobial surfaces with HAI transmission in ICUs.

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Reply to Harbarth et al

To the Editor—We thank Harbarth et al[1] for their characterization of our work as laudable, but offer the following perspective on their critique of the design and interpretation of data from our study.[2] It is firmly established that hospital-