

Control and Mitigation of Healthcare-Acquired Infections: Designing Clinical Trials To Evaluate New Materials and Technologies

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Abstract

Hospitals clean environmental surfaces to lower microbial contamination and reduce the likelihood of transmitting infections. Despite current cleaning and hand hygiene protocols, hospital-acquired infections (HAIs) continue to result in a significant loss of life and cost the U.S. healthcare system an estimated \$45 billion annually. Stainless steel and chrome are often selected for hospital touch surfaces for their “clean appearance,” comparatively smooth finish, resistance to standard cleaners, and relative effectiveness for removing visible dirt during normal cleaning. Designers use wood surfaces for aesthetics; plastic surfaces have become increasingly endemic for their relative lower initial cost; and “antimicrobial agents” are being incorporated into a variety of surface finishes.

This paper concentrates on environmental surface materials with a history of bactericidal control of infectious agents and

focuses on the methods necessary to validate their effectiveness in healthcare situations. Research shows copper-based metals to have innate abilities to kill bacteria in laboratory settings, but their effectiveness in patient care environments has not been adequately investigated. This article presents a research methodology to expand the evidence base from the laboratory to the built environment. For such research to have a meaningful impact on the design/specifying community, it should assess typical levels of environmental pathogens (i.e., surface “cleanliness”) as measured by microbial burden (MB); evaluate the extent to which an intervention with copper-based materials in a randomized clinical trial affects the level of contamination; and correlate how the levels of MB affect the incidence of infections acquired during hospital stays.

Key Words: *Healthcare-acquired infections, HAI, antimicrobial surfaces, copper, EPA registration, transmission of pathogens, hospital cleanliness, medical intensive care units, clinical outcomes*

Preferred Citation: Sharpe, P. A., & Schmidt, M. G. (2011). Control and mitigation of healthcare-acquired infections: Designing clinical trials to evaluate new materials and technologies. *Health Environments Research & Design Journal*, 5(1), 94–115.

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Note: Funding for the research in this paper was from a Department of Defense contract, as detailed in the acknowledgments at the end of this article.

Introduction

The ubiquity of bacteria, fungi, and viruses within healthcare settings, coupled with the incidence with which infections are acquired during hospitalization, contributes to an additional an-

nual estimated \$45 billion in direct hospital costs for healthcare-acquired infections (HAIs) in the United States alone (Scott, 2009). Despite best efforts to promote good hand-hygiene practices, the cleansing of healthcare surfaces, and the use of contact precautions and isolation protocols (Rutala, Weber, & HICPAC, 2008; Siegel, Rhinehart, Jackson, & Chiarello, 2007), infections acquired during hospital stays are the most common complication of hospital care (Scott, 2009) and one of the most serious patient safety concerns. Among patients who acquire an infection during a hospital stay, 29.8% were readmitted within 30 days for an infection or complication, compared to 6.2% readmission of patients without prior HAIs (Martin, 2011). Nationally, an estimated 1.7 million HAIs occur each year, leading to about 100,000 deaths (Klevens, Edwards, & Gaynes, 2008).

Objectives

This paper:

- Reviews the published scientific literature on these topics
- Argues for the adoption of a baseline concentration of bacteria associated with common high-touch surfaces in the hospital setting
- Presents a research methodology to develop an expanding body of evidence that inherently antimicrobial surfaces—specifically those based on copper metals—may well present synergies with current cleaning strategies and/or material choices for the built environment
- Offers a common research methodology to build on the evidence base, and from which new materials, strategies, and appliances for controlling HAIs might be assessed

It is anticipated that the information provided here will empower manufacturers, designers, specifiers, and owners to make evidence-based decisions regarding the potential benefits and positive synergies that design interventions might contribute to existing standards of cleaning and infection control.

Background—The Built Environment

Hand hygiene, patient screening, isolation, and the cleaning of hospital surfaces, typically assessed after terminal cleaning, are established healthcare interventions designed to mitigate the rates and acquisition of HAIs. Concomitant design interventions in the built environment have also achieved limited success by increasing the use of single-patient rooms and/or the strategic placement and installation of sinks and/or alcohol dispensers to facilitate hand hygiene. Because building transitions can be difficult to clean and microbes often persist, the design of healthcare equipment and furnishings has focused on increasing the use of smooth surfaces and open configurations to facilitate efficient cleaning and to reduce opportunities for debris to accumulate, especially fluids in corners, cracks, and crevices. Often such features are promoted as “antimicrobial” rather than, more appropriately, “cleanable.”

Recently, copper-based surfaces have been advanced as a complement to standard cleaning methods to control the bacterial burden associated with high-touch surfaces within healthcare environments. A range of alloys containing more than 60% of copper have been registered by the U.S. Environmental Protection Agency (EPA)

for their ability to kill six disease-causing bacteria: *E. coli* O157:H7, *Staphylococcus aureus*, Methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-resistant *Enterococcus faecalis* (VRE), *Enterobacter aerogenes*, and *Pseudomonas aeruginosa*. Incorporating one of these EPA-registered alloys into healthcare equipment or furnishings allows public health claims that the surfaces kill these bacteria. The standards required are rigorous. First, the alloy must demonstrate antimicrobial efficacy as a sanitizer. Second, the antimicrobial efficacy of the copper alloy does not diminish or wear away over time. And third, the copper alloy must be able to continuously reduce bacterial concentration when a test surface is re-inoculated, without cleaning or disinfecting the surface between inoculations.

Over the past few years, manufacturers have also begun to incorporate agents such as nano-silver matrices and triclosan or silane chemicals into coatings and/or additives, suggesting their “antimicrobial” benefits. These systems rely on leaching technologies that have not been recognized nor registered with the EPA for their ability to kill harmful pathogens; as such, it is not permissible to make public health claims for them. The only claims that the EPA has recognized for these coatings and additives are listed under an EPA *treated article exemption*, which allows manufacturers to claim that the articles treated with such additives resist odor, staining, or discoloration caused by bacteria, and/or that they protect the treated article itself (such as a plastic computer keyboard or bed rail, coated steel or aluminum doorknob, or an impregnated fabric curtain or

furniture covering) from degradation caused by bacteria. More importantly, and central to understanding how the treated article exemption operates when considering these agents as a means of infection control, according to EPA exemption notice 40 C.F.R. § 152.25(a), these additives are exempt from making any implied or explicit public health claim that they are capable of killing human pathogens. Consequently, until data are provided to support such claims, they should not be considered to have the ability to reduce bacterial burden on surfaces.

Review of Hospital Cleanliness

The literature associated with the cleanliness of environmental surfaces covers a wide range of topics: (a) the effectiveness of current cleaning practices from the perspective of how daily and discharge/terminal cleaning mitigate microbial reservoirs that can conduct bacteria from the environment to the patient, resulting in either colonization or infection; (b) how quickly microbial bioload returns to environmental surfaces following cleaning; (c) metrics and tools to assess cleanliness and the associated levels of risk if cleaning metrics are not achieved; and (d) the introduction of cleaning systems and/or the augmentation of existing protocols utilizing disinfectants to enhance the effectiveness of cleaning.

Why We Clean Environmental Surfaces

In the mid-1800s, based on a theory that contagious diseases resulted from individual interactions with the environment, Florence Nightingale led the promotion of strict adherence to hygiene and sanitation practices in hospitals to reduce

infection rates (Harvard University, 2011). The assumption was that, if the available microbial burden (MB) (on linens, clothing, hands, environmental surfaces, medical instruments, etc.) was lessened, the risk of spreading pathogens would decrease. Nowadays, healthcare facilities have cleaning protocols in place to achieve a degree of cleanliness below the risk levels associated with transferring infectious bacteria among patients, staff, visitors, and environmental surfaces. The Centers for Disease Control and Prevention (CDC) Guideline for Disinfection and Sterilization of Healthcare Facilities, 2008 (Rutala et al., 2008) describes the “ultimate goal of their recommendations” as reducing the rates of HAIs through the appropriate use of both disinfection and sterilization.

Role of the Built Environment in the Transmission of Pathogens

The Guideline (Rutala et al., 2008) incorporates a disinfection strategy devised more than 25 years ago by E. H. Spaulding based on the predicted degree of risk involved in the use of inanimate objects. Objects classified as *critical*, or at high risk for infection, include items that enter sterile tissue, such as surgical instruments, catheters, and implants. *Semi-critical* items (such as respiratory therapy and anesthesia equipment and endoscopes) come in contact with mucous membranes or nonintact skin. In the Spaulding hierarchy, *noncritical* (i.e., low-risk) items typically come in contact with skin but not mucous membranes.

Environmental surfaces, including bed rails, bedside tables, and patient furniture, fall within

Spaulding’s noncritical category (Kohn et al., 2003; Schulster & Chinn, 2003). The guidelines note that these objects could potentially contribute to secondary transmission by contaminating the hands of healthcare workers or by contacting medical equipment that subsequently contacts patients (Agency for Healthcare Research and Quality, 2011; Bhalla et al., 2004; Favero & Bond, 2001; Ray, Hoyen, Taub, Eckstein, & Donskey, 2002; Sattar, Jacobsen, Springthorpe, Cusack, & Rubino, 1993; Sattar, Lloyd-Evans, Springthorpe, & Nair, 1986; Ward et al., 1991; Weaver, Michels, & Keevil, 2008). The CDC Guideline did not argue that environmental surfaces substantially contributed to infection transmission. Recent work has begun to provide evidence that suggests otherwise.

The environment may act as a reservoir for pathogens that cause healthcare-associated infections (Boyce, Havill, Otter, & Adams, 2007). VRE is capable of prolonged survival on hands, gloves, and environmental surfaces and may serve as a potential reservoir for nosocomial transmission (Noskin, Stosor, Cooper, Peterson, 1995). Inadequately disinfected reusable equipment has been reported to be a source of nosocomial infection, particularly with regard to MRSA and VRE (Maki, 1995).

Persistence of Pathogens on Surfaces

Infectious bacteria can survive on environmental surfaces for days, weeks, or months. Noncritical equipment used in the medical environment can serve as fomites, harboring microorganisms that can be transmitted and contribute to nosoco-

mial infections and hospital outbreaks. MRSA, VRE, and Gram negatives can survive on inanimate objects such as hospital equipment for many months. Spore-forming bacteria, including *Clostridium difficile* (*C. diff.*), can also survive for months. The longer a nosocomial pathogen persists on a surface, the longer it may be a source of transmission and thus endanger a susceptible patient or healthcare worker (Boyce et al., 2007; Falk, Winnike, Woodmansee, Desai, & Mayhall, 2000; Kramer, Schwebke, & Kampf, 2006; Martinez, Ruthazer, Hansjosten, Barefoot, & Snyderman, 2003; O'Doherty, Murphy, & Curran, 1989; Schabrun & Chipchase, 2006).

Bacteria can be transferred to the hands of healthcare workers even without direct patient contact. When clean or gloved hands touch contaminated objects, they become contaminated with similar organisms, which can then potentially be transmitted to other surfaces and people (Duckro, Blom, Lyle, Weinstein, & Hayden, 2005; Hayden, Blom, Lyle, Moore, & Weinstein, 2008). Items frequently touched by healthcare workers or patients are often contaminated by such pathogens in the rooms of affected patients. Contaminated surfaces contribute to the transmission of healthcare-associated pathogens by serving as sources of hand/glove contamination among healthcare workers and by the direct spreading of pathogens to susceptible patients. An increasing body of evidence suggests that the enhanced cleaning/disinfection of environmental surfaces can reduce the transmission of these pathogens (Boyce, 2007).

How Well Are Surfaces Being Cleaned?

A high percentage of environmental surfaces reportedly are not cleaned well after patient-discharge (terminal) cleaning. Carling has conducted numerous trials indicating that, on average, immediately after terminal cleaning has been completed, only about 50% of surfaces have been adequately cleaned (Carling, Parry, & Von Beheren, 2008; Carling et al., 2008; Carling, Von Beheren, Kim, & Woods, 2008). One study cultured bed rails, telephones, call buttons, doorknobs, toilet seats, and bedside tables from hospital rooms housing patients with VRE or *C. diff.* infections. Ninety-four percent of the rooms housing VRE patients were widely contaminated with VRE, and 100% of rooms housing *C. diff.*-infected patients were widely contaminated with *C. diff.* spores (Eckstein et al., 2007).

Environment as Source of Transmission

Dancer (2009) notes that for many years, experts believed that contaminated environmental surfaces in hospitals did not play a significant role in transmitting pathogens to patients; however, recent studies provide increasing evidence that contaminated hospital surfaces may be a source of the transmission of pathogens. Other examples of the environment serving as a vector of infection include: (a) Kramer and others (2006) reported that, in hospitals, surfaces with hand contact are often contaminated with nosocomial pathogens and may serve as vectors for cross-transmission; (b) Stiefel and colleagues (2011) found that in patient rooms with MRSA carriers, healthcare workers are just as likely to contaminate their hands (gloves) from commonly touched envi-

ronmental surfaces as from direct contact with patients' skin sites; (c) Boyce, Potter-Bynoe, Chenevert, and King (1997) demonstrated that nurses frequently acquired MRSA on gloves after touching surfaces near colonized patients; and (d) Bhalla and colleagues (2004) found that 53% of hand-imprint cultures were positive for one or more pathogens after contact with surfaces near hospitalized patients. Patients in rooms previously occupied by individuals with infections are at higher risk of acquiring an infection than if a previous occupant did not have an infection. Shaughnessy and others (2011) report that if patients are admitted to patient rooms where previous patients had *C. diff.*, they have a higher risk of acquiring that pathogen.

Metrics for Assessing Hospital Cleanliness

Conditions for the growth of bacteria are ever present in the majority of food processing environments. Food, by its nature, contains high levels of organic material and, as such, can facilitate the formation of a conditioning film to which bacteria, fungi, and viruses can readily adhere (Zottola & Sasahara, 1994). Consequently, the food industry has a well-established MB baseline that food preparation surfaces cannot exceed (Moore & Griffith, 2002). The level of five total aerobic colony-forming units (CFU) per square centimeter (cm²) was established because it was determined that when levels exceeded this concentration, foods that came in contact with such surfaces might cause people to become ill.

Unfortunately, such standards of hospital cleanliness are in their infancy. Dancer points out that

often the only method used in evaluating the quality of hospital cleaning is visual assessment, which does not necessarily correspond with microbiological risk (Dancer, 2004; Malik, Cooper, & Griffith, 2003) and that environmental contamination can contribute to the transmission of MRSA (Dancer, 2008). Mulvey and colleagues (2011) evaluated several methods for monitoring hospital cleanliness to establish a benchmark that could offer guidance regarding the risk that the environment presents to patients. They too concluded that visual assessment could not serve as a reliable metric of infection risk to patients, and that high-touch surfaces should be subjected to a direct method that monitors the overall levels of microbial dirt present on surfaces. Based on measurements of MB, they suggested a concentration < 2.5 aerobic colony counts/cm² as a benchmark for assessing hospital cleanliness immediately after terminal cleaning. A ward-crossover study investigating the effect of enhanced cleaning indicated a significant reduction in total aerobic counts on touch surfaces, a lower number of samples to reach the proposed hygienic standard (2.5 CFU/cm²) considered acceptable, and a reduction of MRSA acquisition by patients (Dancer, White, Lamb, Girvan, & Robertson, 2009).

Other Cleaning Strategies

Because current cleaning and barrier strategies have been ineffective at reversing trends in nosocomial infection, several new strategies are being advanced. These include the promotion of better cleaning through education, training, monitoring, and/or using checklists or fluorescent dye indicator systems as part of behavioral

modification programs; more frequent cleaning; the addition and better placement of sinks and alcohol dispensers; and employing technological solutions to facilitate the distribution of disinfectants such as hydrogen peroxide vapor, gaseous ozone, and/or ultraviolet light room throughout the built environment. Although these cleaning strategies may have merit, many of them can be conducted only when a patient is not in the room, may require costly equipment, and/or necessitate that the room be sealed off and remain out of service for anywhere from half an hour to several hours. Some of these chemicals can have a deleterious effect on plastics and other items in the room.

It is also important to note that, no matter the effectiveness of the preceding strategies and how diligently cleaning protocols are followed, in active clinical environments, pathogens “resurface” with relative ease and, in many cases, thorough cleaning of patient rooms is not scheduled until after patient discharge. A recent study reported that disinfection of patient-occupied bed rails with quaternary ammonium disinfectants reduced the MB from 95% to 98% within half an hour of application. However, bacterial levels returned to pre-disinfectant levels within 2 to 6 hours after disinfection (Schmidt, Attaway, et al., 2011).

In another study, the disinfection of standard control surfaces made of plastic and aluminum were compared with similar objects covered with bactericidal metallic copper alloys. Here again the experimental and control surfaces were

disinfected once a day, and the respective bio-burdens were assessed at prescribed intervals of 3, 6, and 9 hours (Dancer et al., 2009). Before cleaning, the total bacterial burden observed was significantly lower on the surfaces covered with metallic copper than the burden measured on the control objects. Cleaning effectively deburdened the surfaces of infectious bacteria regardless of the material covering the surface. Unsurprisingly, within hours after cleaning, bacteria were again found on the surfaces. However, differences were observed in the rates at which bacteria recolonized the copper and control surfaces. For objects covered with an antimicrobial alloy of copper, the rate of recolonization was 12.4 CFU/hour to 14.2 CFU/hour (summer vs. winter) compared to 22.5 CFU/hour to 33.0 CFU/hour (summer vs. winter) on the control (plastic and aluminum) surfaces. The authors point out that in active clinical environments, once-a-day cleaning alone is not enough to keep surface contamination at bay.

Research Methodology To Expand the Evidence Base

The proposed research methodology outlines the need for comprehensive clinical trials to investigate the potential benefits of using inherently antimicrobial surfaces in addition to current infection-reduction practices. Because HAIs continue to be a major concern for patients and healthcare providers, new materials should be evaluated as an alternative to materials that hospitals commonly use in the built environment—plastics, stainless steel, chrome, solid composite surfaces, wood, and/or powder coatings.

Study Objectives

The overall purpose of such investigations is to expand the evidence base regarding the extent to which an inherently antimicrobial surface can:

- Impart positive benefits to reduce both MB and the associated risk of infection transmission.
- Have a synergistic effect on infection-reduction practices, including but not limited to hygienic protocols and behavioral and design interventions.
- Reduce the number and/or types of infections observed beyond the capability of commonly employed infection-reduction methodologies.
- Provide a sufficient base of evidence to encourage suppliers to offer objects that imbue surfaces with the inherent ability to kill infection-causing bacteria, and the design, specifying, clinical, and payer communities to work together to implement such technologies in infection-protection programs to lead to better clinical outcomes and provide an immediate and tangible consequence for reducing HAIs.

Hypotheses

- In regularly cleaned and maintained patient rooms in medical intensive care units (ICUs), the material composition of the environmental surface (touch surface) itself can influence the level of MB at any given time.
- Selecting touch-surface materials that inherently mitigate MB can augment hand-washing and cleaning protocols to minimize the risk of developing microbial reservoirs capable of transmitting infections.
- As a consequence of reduced MB, the rate of HAIs will decrease.

Description of Clinical Trials

The proposed comprehensive study is currently underway at several healthcare centers in the United States, funded by a grant from the Department of Defense (DOD) under the aegis of the Telemedicine and Advance Technology Research Center. These multiphase multihospital trials were designed to confirm the antimicrobial performance of copper surfaces in real-world settings and expand on prior investigations by

- Providing diverse institutional settings and healthcare populations to ensure statistical significance.
- Encompassing industry-accepted infection control practices, already instituted at these institutions, which include both design and procedural interventions. Each ICU has single-patient rooms with hand-washing sinks and alcohol dispensers in each room and utilizes MRSA admission screening with subsequent contact precautions. Other interventions are employed to varying degrees at the three hospitals, including barrier protocols (gloves and gowns) for visitors, VRE screening, and “bundling” interventions for and the regular chlorhexadine bathing of patients. (In clinical practice, *bundling* is a set of interventions that, when grouped and implemented together, can have greater impact than when performed individually. Bundling evidence-based practices can promote better outcomes and improve patient care.)
- Focusing on daily cleanliness rather than evaluation following terminal cleaning. Assessments based on random sampling take into account how microbial flora from pa-

tients, staff, and visitors affect surface contamination—taking a real-life “snapshot” of the relative cleanliness of the built environment as it relates to ICUs.

- Establishing a causal link between the cleanliness of environmental surfaces and infection rates—i.e., the likelihood of *not* acquiring an infection in the course of routine hospital care. Many designers and hospital administrators have indicated that these data will be crucial to their evaluation of the clinical data and any subsequent course of action.
- Including a range of typical cleaning practices as independent variables—i.e., not influenced or altered by the research design. As noted previously, several proposed interventions for reducing HAIs are based on instituting new cleaning technologies (chemicals, nontouch systems) and/or enhanced training, educational, and/or monitoring programs.
- Incorporating healthcare-grade components manufactured from existing suppliers to the healthcare industry (where practical). This is intended to provide equipment and furnishings that will meet the structural integrity, durability, cleanability, and overall aesthetics (i.e., a “clean look”) requirements of hospitals.

Why Copper Is Being Proposed for Intervention

Environmental Protection Agency

Recognition of Copper

The copper-based surfaces being advanced for these clinical trials were chosen for the intervention because they represent the only (solid-surface) class of EPA-registered material that

is active (and available) on a 24-hour basis and between discharge cleanings (EPA, 2008). Such touch-surface materials should be considered a complement to, not a substitute for, other standard cleaning methods.

The evaluation of solid copper-alloy materials by the EPA mandated three test protocols to assess (1) their antimicrobial efficacy as a sanitizer, (2) the durability of their efficacy, and (3) their ability to continuously reduce bacterial contamination when a surface is re-inoculated, without cleaning or disinfecting the surface between inoculations. EPA-mandated tests were conducted by a Good Laboratory Practices test facility using six disease-causing bacteria: *E. coli* O157:H7, *Staphylococcus aureus*, MRSA, VRE, *Enterobacter aerogenes*, and *Pseudomonas aeruginosa*.

The efficiency with which antimicrobial materials act is often attributed to log reduction of the population present at the time the viability of the bacteria being evaluated was measured. Many challenges are associated with this test because bacteria can be inactivated by many mechanisms. Because water is necessary for all life, dehydration is a common means of killing bacteria. The rate of death, an exponential function, can easily be visualized by plotting the concentration of viable bacteria present in a population as a function of time on a semi-log scale. The efficacy with which copper inactivates bacteria over time is shown in Table 1.

The EPA tests used stainless steel as the control surface. Although not indicative of how these

EPA Efficacy Tests					
Test 1¹	Stainless steel	Initial Inoculum^a	Final^b	Log Reduction	
	As a sanitizer	Copper ^e	350,000,000	4,900,000	2 log
Test 2²	Before wear cycles	Stainless steel	350,000,000	0	8 log
		Copper nickel ^f	500,000,000	1,700,000	2 log
Test 3³	After wear cycles	Stainless steel	500,000,000	30	8 log
		Copper nickel ^f	500,000,000	430,000	3 log
	Continuous reduction after repeat contamination	Stainless steel	Initial Inoculum^a	Final^c	Log Reduction
		Copper ^e	500,000,000	30	7 log
Test 3³	Continuous reduction after repeat contamination	Stainless steel	Cumulative Inocula^a	Final^d	Log Reduction
		Copper ^e	5,200,000	29,000,000	--
			5,200,000	35	5 log

1. U.S. EPA (2011b)

2. U.S. EPA (2011c)

3. U.S. EPA (2011a)

a. Inocula = CFU/mL

b. After 120 minutes

c. 120 minutes after 12 wet and dry abrasion cycles and repeat inoculations over 24 hours

d. 120 minutes after 8 repeated inoculations over 24 hours with no cleaning between them

e. Contains 99.9% copper

f. Contains 90% copper

Table 1. Survival of MRSA on Copper Alloys Employing EPA Testing Criteria.

surfaces function in clinical environments, in each of the EPA tests the stainless steel remains well above the metric advocated by Dancer, Mulvey, and colleagues (Dancer et al., 2009; Mulvey et al., 2011) as a benchmark for assessing hospital cleanliness immediately after terminal cleaning. In the test of copper as a sanitizer, viable MRSA was absent on the copper test coupon where an eight-log reduction was observed after the 120-minute test.

The EPA testing criteria required the use of high loading concentrations of bacteria between one and one hundred million CFU per milliliter (ml) (10^6 to 10^8). Such inocula, present as a wet suspen-

sion, are designed to determine the efficacy with which solid surfaces can inactivate or kill bacteria after a prescribed period of time (2 hours). Santo and colleagues (2011) report that under dry conditions, copper surfaces exhibit bactericidal properties within minutes.

Other Surfaces and Coatings

The antimicrobial efficacy of several coatings and additives, including silver-, triclosan-, and silane-based, were reviewed prior to selecting the copper-alloy materials for use in the clinical trials. The only claims that the EPA recognized for these coatings and additives were listed under an EPA “treated article exemption,” which allows a

manufacturer to claim that the articles treated with these additives resist odor, staining, or discoloration caused by bacteria and/or they protect the treated article itself, such as a plastic computer keyboard or bed rail, a coated steel or aluminum doorknob, or an impregnated fabric curtain or furniture covering from the degradation caused by bacteria. More importantly, according to EPA exemption notice 40 C.F.R. § 152.25(a), and central to our understanding of how the treated article exemption operates when considering these other agents as a means of infection control, this EPA classification states that these additives are prohibited from making any implied or explicit public health claim that they have an ability to actually kill human pathogens.

In laboratory evaluations, these coatings and additives were typically examined using the Japanese Industrial Standard Z2801, which was developed to measure the survival of bacterial cells held in intimate contact (using polyethylene film) and incubated for 24 hours at 95 °F under conditions of saturating humidity. When these materials are tested under ambient temperature and humidity conditions typical of healthcare settings, silver ion-containing polymers exhibit no meaningful antimicrobial efficacy against MRSA inocula following 24 hours of exposure (Industrial Microbiological Services Ltd., 2005; Michels, Noyce, & Keevil, 2009).

Copper-based metals (copper alloys) are the only class of solid surface materials that meet EPA test protocols, which require *efficacy as a sanitizer, residual self-sanitizing activity, and continuous reduction of bacterial contamination* for antimicrobial

capacity. They are the only solid materials that the EPA registers to make public health claims that the surfaces themselves have inherent properties to kill infectious bacteria that EPA registers (Blackburn, 2011; EPA, 2011a–c).

Investigations of Copper in Healthcare

Settings

Over the past few years, several research studies have introduced copper surfaces into hospital spaces to establish the extent to which the antimicrobial effectiveness of copper in EPA laboratory testing translates to an actual reduction in MB in clinical environments. These relatively small-scale studies have reported on the effect of using copper-based surfaces in healthcare environments, and they have shown a consistent and significant reduction in MB compared to standard touch-surface materials. Several are discussed below.

Medical Ward, Birmingham, United Kingdom

In a 10-week pilot study at Selly Oak Hospital, several frequently touched metal surfaces (chrome and aluminum) were replaced with copper alloys to compare the number of microorganisms on each. Items such as door push plates and faucet handles were sampled twice a day (7 a.m. and 5 p.m.) for 10 weeks in a medical ward (Casey et al., 2010). After 5 weeks, the copper and control surfaces were switched to minimize the possibility of preferential use of either item based on location. Overall, the copper-containing items harbored between 90–100% fewer microorganisms (median values) than their control equivalents in both the morning and evening samplings. (See Table 2.)

<i>Item Samples</i>	<i>Median CFU/Control Surface</i>		<i>Median CFU/Copper Surface</i>	
Push plate (7 a.m. reading)	45*	(0–195)**	0 *	(0–6)**
Push plate (5 p.m. reading)	15	(0–84)	6	(0–30)
Cold faucet handle (7 a.m.)	75	(0–870)	0	(0–30)
Cold faucet handle (5 p.m.)	45	(0–510)	0	(0–30)
Hot faucet handle (7 a.m.)	66	(0–5,050)	0	(0–30)
Hot faucet handle (5 p.m.)	30	(0–360)	0	(0–390)

* Median CFU ** (CFU range)

Table 2. Median CFU Counts on Copper-Containing Items Compared to Controls in the Clinical Setting. *Source:* Casey et al. (2010).

The researchers concluded that these results demonstrate that copper offers the potential to significantly reduce the number of microorganisms in the clinical environment, and the use of copper, in combination with optimal infection prevention strategies, may consequently reduce the risk of patients acquiring infections in hospital and other healthcare environments.

Intensive Care Units, Calama, Chile

In a 2009 clinical trial at the Hospital del Cobre, objects with copper-alloy touch surfaces were introduced into medical ICUs to assess the ability of these materials to reduce the total MB associated with critical touch surfaces. Three paired (copper and control) rooms were compared, by measuring the MB on bed rails, over-bed tables, chair arms, intravenous (IV) poles, and bed levers.

The results of this clinical trial demonstrated an approximately 90% reduction in the number of microorganisms on the copper items compared to

the controls surfaces, and a reduction in the total MB was seen for each class of microbe evaluated. Furthermore, the antimicrobial activity of copper persisted throughout the study. Average MB counts in rooms with copper touch surfaces were significantly lower than in rooms without copper surfaces. *Staphylococci* were the predominant microorganisms isolated, and copper was effective in reducing the *Staphylococcus* MB (Prado et al., 2010). (See Table 3.)

Over the 30-week sampling period, compared with the respective control surface, copper was effective in reducing MB from 82% to 92%; the average of the *Staphylococcus* burden on the copper surfaces was significantly lower than on the noncopper surfaces; and copper substantially reduced the inherent Gram-negative burden on all of the objects.

An interesting finding in these trials was the effectiveness with which copper reduced MB in an extremely dry environment. With silver-ion tech-

Percentage Reduction on Copper Surfaces*

Item	Compared to Control Surfaces
Bed rail	91%
Bed lever	82%
Chair arm	92%
Tray table top	83%
IV pole	88%

*Proportion of CFU/100 cm² as measured on control and copper surface

Table 3. Comparison of Copper and Control Surfaces. *Source:* Prado et al. (2010).

nologies, suppliers report that moisture in the air (or direct contact with moisture, like a sneeze) activates the release of silver ions to the surface at a slow and steady rate, and the silver ions exchange with other positive ions (often sodium) from the moisture in the environment, effecting a release of silver (Stinson, 2011). The Hospital del Cobre de Calama is located in a semi-desert area in the north of Chile, where humidity levels range between 7.2% and 19.7%. At these low moisture levels, copper alloys reduced MB, on average, by 90%.

Outpatient Clinic, Manhasset, New York

In a 15-week pilot study at an outpatient practice in the Division of Infectious Disease at North Shore Long Island Jewish Health System, a pilot study was conducted in 2010 to assess the ability of copper to reduce the MB on the tray tables and arms of phlebotomy chairs (Hirsch et al., 2010). Approximately two thirds of the outpatients were HIV positive; the remainder consisted of general infectious disease patients.

The plastic trays and wooden chair arms on two of three phlebotomy chairs in the clinic, each in a separate room, were retrofitted with an EPA-registered copper-nickel alloy. The alloy was inlaid into the tops of wooden chair arms (leaving the wood sides intact), and the trays were fabricated entirely from the copper

alloy. The chair arms and tray surfaces were cultured twice each week from three chairs, two retrofitted with copper plus one control, for 15 weeks. Every 5 weeks the chairs rotated between the three rooms to minimize the possibility of preferential use based on location.

The study reported that copper significantly lowered the MB found on the tray and chair-arm surfaces, with a median reduction of 88% for total bacteria on the tray tops and 90% on the inlaid copper-alloy tops of the chair arms. They observed that the significant and consistent reduction in MB approached the microbiocidal activities observed under ideal laboratory conditions, where rates greater than 99.9% are the norm for claims asserting microbiocidal activity. The majority of the microorganisms identified were *Staphylococci*.

Two additional observations from this study included:

1. The majority of MB levels on the copper chairs were below the level thought to represent a risk

	Arm Top		Tray Top		Arm Sides	
	Wood	Copper	Composite	Copper	All-Wood Chair Arm	Wood Adjacent to Copper
Total Bacteria*	1,305	135	1,290	150	Total Bacteria*	1,095 330
Percentage reduction	-90%		-88%		Percent reduction	-70%
Staph*	480	30	390	60	Staph*	795 270
Percentage reduction	-94%		-85%		Percent reduction	-66%

* Median CFU/100 cm²

Table 4. Bioburden on Phlebotomy Chairs. *Source:* Hirsch et al. (2010).

to patients (< 2.50 CFU/cm²) (Dancer, 2004, 2009; Mulvey et al., 2011), and the majority of samples collected on the wood and plastic composite surfaces were above this risk level.

2. MB on the wooden sides of the copper alloy chair arm (copper tops, wooden sides) were 66% lower than those on the all-wood (top and side) chair arms. The researchers suggest that this potential “microbiological halo” effect should be studied further.

Similarly, patients and healthcare workers who used chairs with copper trays were subjected to a 15-fold lower risk than patients using chairs with composite trays. The MB on copper trays was reduced by 88% compared to the composite plastic surface (Ray et al., 2002; Rutala et al., 2008).

Status of Proposed Clinical Trials

The DOD-funded clinical trials identified above

are in progress, and official findings have not yet gone through final internal reviews with subsequent peer review and publication. However, several poster presentations and talks relating to the research have been presented at infection-control, healthcare, and design conferences over the past year or so. The following discussion addresses the methodology and some preliminary findings that have been covered in these public forums.

Methods

Setting

Research is being conducted in medical ICUs at three hospitals: the Medical University of South Carolina (six rooms), the Memorial Sloan Kettering Cancer Center (six rooms), and the Ralph H. Johnson Veterans Administration (VA) Medical Center (4 rooms). This mix provides distinct patient populations serving immune-compromised patients (cancer hos-

pital), a general patient population (academic teaching hospital), and (mostly male) veterans (VA hospital). ICUs are all single-patient occupancy, and sinks and alcohol dispensers are installed in each room.

Objects Measured for Cleanliness

In Phase I of the clinical trials, six categories of high-touch surfaces were sampled to determine levels of microbial contamination. These objects included a patient bed (tops of side rails), over-bed table (tabletop), IV stand (poles and/handles), visitors' chair (arms), nurse call button, and various computer data input devices (keyboard surface on laptop, mouse, and/or touch-screen monitor bezel). Surfaces were cultured once each week for a collective total of 119 weeks for which baseline data were collected from approximately 6,500 surfaces.

Phase II Intervention

After baseline data were collected, the six objects (in half of the test rooms in each hospital) were equipped with copper-alloy surfaces. The MB was monitored as before in control rooms as well as copper-outfitted rooms for an additional collective 83 weeks. The "copperized" surfaces included bed rails (99.99% copper-containing alloy), over-bed tray tables (90% copper alloy), chair arms (90% copper alloy), call buttons (70–95% copper alloys), data input devices (90% copper alloy), and IV poles (75–95% copper alloys). The varieties of copper alloys used were selected from a range of approved materials included under EPA registration that would hold up well to standard hospital cleaners.

Sampling Methodology

In a review of the role that contaminated surfaces play in the transmission of nosocomial pathogens, Otter, Yezli, and French (2011) observe that since the 1970s, when studies suggested that the hospital environment contributed negligibly to the endemic transmission of nosocomial pathogens, the routine surveillance of the hospital environment came to be regarded as unjustified, and the frequency of routine environmental sampling declined from three-quarters of U.S. hospitals in 1975 to virtually none today. However, because of the ever-expanding literature that holds microbes from the built environment responsible for HAIs, this study incorporated a quantitative sampling of the microbes present on common, high-touch surfaces to assess and better understand the relationship between burden and infection acquisition and/or colonization. Briefly, 100-cm² surfaces were sampled on each object included in the trial and tested for total microbes, total Staphylococci, total Gram negatives, MRSA, and VRE.

Patient Room Cleaning

Over the course of the trials, EPA-approved cleansers/disinfectants have been used to facilitate the routine cleaning and terminal cleaning of the patient rooms as prescribed by the manufacturers of the disinfectants. The clinical trials neither controlled nor adjusted internal infection control practices or the routine of the environmental service teams at the three hospitals. Standard cleaning protocols included the daily cleaning of ICUs, additional cleanings as necessary, and cleanings subsequent to the discharge or transfer

of patients. Daily routines at two of the hospitals involved routine once-a-day cleanings. The third hospital has instituted a twice-daily cleaning protocol in each of its ICUs as a consequence of an outbreak early in the trial, and it continues this protocol.

Discussion: Findings and Design Implications

Initial findings from the ongoing clinical trial appear to complement several of the other, smaller studies reported in the literature where copper was introduced into healthcare surfaces. In this multihospital trial, the copper alloys have had a positive effect on reducing MB in the healthcare built environment. Salgado and colleagues (2010) describe preliminary results that closely match the copper efficacy from the North Shore Hospital, Hospital del Cobre, and Selly Oak research summarized above.

Accordingly, over the first 9 weeks that copper objects were placed in rooms from the three participating hospitals:

- Copper-containing surfaces were effective in reducing the total MB of the patient ICU room by 87%.
- The MB on the copper bed rails was 99% lower than on comparative plastic rails.

Although MRSA and VRE were frequently isolated from the plastic control surfaces, they were never isolated from any of the copper objects in the ICUs at the various sites.

At the 2011 World Health Organization International Conference on Prevention and Infection Control, additional preliminary trial data were reported, subject to further peer review in the published literature (Schmidt, Salgado, et al., 2011).

Pre-Intervention

Prior to interventions with copper surfaces, all the objects sampled in the control arm of the study produced average MB levels significantly higher than the minimum risk for transferring infectious bacteria. (See Table 5.) The sampled bacterial lev-

<i>Item</i>	<i>Bacterial Contamination on Control Surfaces^a</i>
Bed rails (plastic)	13,028 CFU/100 cm ²
Nurse call button (plastic)	6,253 CFU/100 cm ²
Data input device (plastic)	5,404 CFU/100 cm ²
Chair arm (wood)	3,989 CFU/100 cm ²
Tray table top (composite laminate)	2,557 CFU/100 cm ²
IV stand (stainless or chrome)	791 CFU/100 cm ²
Associated risk level ^b	250 CFU/100 cm ²

a. Total 1,200 rooms sampled. Average CFU from all surfaces sampled in each category.

b. According to baseline metrics in table sources.

Table 5. Bacterial Contamination on Control Surfaces. Source: Dancer (2004, 2009); Mulvey et al. (2011).

els ranged from about three times the benchmark risk level from the IV poles to 50 times the risk level, on average, for the bed rails. This differential is understandable because the beds represent the area where patients receive all their care while in the ICU, and they do not interact with the poles from the IV stands.

Post-Intervention

After copper components were introduced in the ICUs, comparative samples were taken over the course of 83 weeks. On random sampling, the bed rails, representing the object closest to the patient and a surface with the highest frequency of patient, staff, and visitor contact, yielded a 97% reduction in total bacteria compared to the plastic bed rails in the control rooms. And the average MB of 174 CFU/100 cm² was below the benchmark risk level for transmission.

Patient Outcomes

In the last phase of the clinical trials, concurrent with measuring comparative MB on copper and control objects is the monitoring of patient data. This includes the acquisition of infections and/or colonization by MRSA and VRE during an ICU stay, average length of stay, the number of readmissions, and metrics identifying patient condition when entering the ICU. The study is incomplete; full data are still being analyzed, and findings are being reviewed by a team of independent investigators. However preliminary findings report a:

- 40% reduction in the relative risk of acquiring an HAI among patients in copper rooms ($N = 651, p = .039$)

- 61% relative risk reduction in HAIs among patients who occupied a bed with copper rails 100% of their time in the ICU compared to patients who occupied beds with plastic rails during their ICU stay ($N = 541, p = .006$)
- 69% relative risk reduction among patients who received a 100% copper dose (i.e., all six of the objects in the room were copper during the patient's entire stay in the ICU) compared to patients with no exposure to copper items during their stay ($N = 462, p = .008$)

Although only partial findings from these trials have been reported, researchers are indicating that in the medical ICUs investigated, and on the sample size (and P values) included to date, the limited placement of inherently antimicrobial copper surfaces is showing a:

- Consistent and significant reduction in the levels of bacteria in hospital settings
- Reduction in the rates of HAIs in medical ICUs
- Rate of reduction linked to the frequency of exposure to copper-based metals.

As more comprehensive datasets are developed and correlations and analyses from these trials are completed, full findings will be detailed in medical journals. From a designer's perspective, an expansion of these preliminary findings should provide a better picture of how the integration of inherently antimicrobial surfaces:

- Can improve the ongoing level of cleanliness in patient-occupied ICUs—attributable to combined daily cleaning, terminal cleaning, and episodic cleaning

- Will correlate with an associated reduction in the risk of transmitting infections, possibly including correlations of surface cleanliness to:
 - Type of surface (e.g., copper, plastic, wood, stainless steel, chrome, powder coating)
 - Type of pathogenic organism
 - Category of hospital (including population served, geographic and seasonal influencers, etc.)
 - Cleaning protocols (e.g., frequency of cleaning and types of cleaners)
 - Amount of copper in the ICU and patient exposure (i.e., “dose” of copper)

While the research from these trials is developing patient data to correlate copper intervention with patient outcome(s), more detailed information should become available to healthcare specifiers regarding the:

- Incidence of HAIs
- Incidence of hospital-acquired colonizations
- Length of stay
- Correlation of infections to:
 - Copper “dosage” (total copper surface area in room)
 - Whether certain objects in a patient room have a greater or lesser effect on patient outcomes
 - The effect that patient age, condition on admission to the ICU, and direct exposure to copper surfaces each have on patient outcomes

Implications Beyond These Trials

From a design standpoint, it is important to note that these results were additive to other infection-

control implementations (single-patient rooms, sinks, alcohol dispensers, patient screening, etc.) that were already in place in the clinical trial hospitals. Should the conclusions apply to other areas of the hospital, then employing inherently antimicrobial surfaces could represent a significant enhancement to mitigating infectious bacteria in hospitals. For example, by instituting a best practices approach that implemented cleaning and hand hygiene designs and protocols, the California Healthcare-Associated Infection Prevention Initiative showed a 3.2% reduction in HAIs. With many of these best practices already in place, the initial findings from the clinical trials indicate an additional double-digit reduction in infections.

Although the relative infection rate in ICUs is generally higher than in hospitals at large, patients in ICUs are typically immobile, and their interaction with the built environment is limited. ICUs typically do not have hand railings or bathrooms (e.g., no grab bars, sinks, faucets, paper dispensers, shelves, towel racks). Patients typically do not ambulate (e.g., while gripping an IV pole); they remain in bed rather than in a patient chair; and there is little interface with over-bed tables, television remotes, telephones, or computers. This type of investigation needs to expand beyond the medical ICU to include, but not be limited to, the effect of inherently antimicrobial materials in general wards where patients have greater interaction with other objects in the built environment. Investigations should research their effect in emergency and recovery rooms, pediatric and neonatal units, dialysis centers, burn

units, transplant units, and cancer centers with immune-compromised patients. Healthcare environments that arguably receive less day-to-day hygienic oversight than hospital patient rooms, such as visiting areas, long-term care rehabilitation centers, outpatient clinics, and elder care facilities, should also be investigated.

Conclusions

HAIs represent a substantial cost in lives lost, prolonged rehabilitation, lost wages, toll on families, and dollars spent on healthcare. Recently published studies indicate that the contaminated environment of the patient room plays a significantly larger role in the pathogenesis of HAIs than previously thought.

Although the design community has focused predominantly on interventions to facilitate hand hygiene, the pre-intervention findings from the multihospital clinical trial discussed here indicate that everyday levels of surface contamination in active ICUs are significantly higher than levels considered to represent a risk for the transmission of infections. These findings, along with other studies, suggest that more attention must be directed toward equipment, furnishings, and building designs that can help first facilitate and then enhance environmental disinfection.

The post-intervention study findings, though preliminary, show that by incorporating inherently antimicrobial (copper-based) surfaces into common high-touch surfaces in a patient room and continuing regular cleaning routines, site-specific levels of contamination are lowered by

more than 90%, thus mitigating the potential risk of transmitting infectious bacteria. More importantly, the study's initial findings indicate significant reductions in HAIs, with the rate of reduction linked to the frequency of exposure to copper-based materials.

This review cites several studies that advance the idea of a "critical" threshold of MB, below which the acquisition of HAIs is unlikely. Additional research is needed to build the evidence supporting this concept. If such a threshold could be universally recognized, approaches to hospital room cleaning could be standardized and monitored with the goal of improving patient outcomes and reducing length of stay.

The inherent antimicrobial activity of copper surfaces offers a potentially unique advantage to reduce the rate of HAIs independent of conventional environmental cleaning approaches in that disinfection mediated by copper is continuous rather than episodic. The random room sampling described in the clinical trials reinforces this.

The findings in this paper should be considered with the understanding that standard hospital hygienic care, including cleaning, disinfecting, and hand washing, depend on behavioral practices. Studies continually show both compliance with and the effectiveness of these practices to be highly variable, often requiring constant reinforcement to maintain minimal observance.

Designing healthcare surfaces that are easy to clean is important. Designs that consider the

placement of sinks and alcohol dispensers coupled with appropriate educational and monitoring programs can also help to increase compliance and effectiveness. However, the incorporation of surface materials with inherent bactericidal properties used in synergy with current design interventions and hygienic practices offers a new paradigm for healthcare design that will lead to better outcomes.

Acknowledgments

This research project is being conducted under contract with the U.S. Army Medical Research and Materiel Command, Contract No. W81X-WH-07-C-0053. The views, opinions, and/or findings presented here are those of the author(s) and should not be construed as an official U.S. Department of the Army position. The program is managed through the Advanced Technology Institute (ATI), Charleston, South Carolina. Special acknowledgment to the clinical, research, and support staff at the three participating medical centers for design and implementation of the clinical trials, and to the CDA for their metallurgical expertise related to the copper-based equipment and furnishings. Dr. Freeman is the independent statistical consultant. The clinical trial team includes:

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