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REVIEW

Fighting nosocomial infections with biocidal non-intrusive hard and soft surfaces

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Abstract

Approximately 7 million people worldwide acquire a healthcare associated infection each year. Despite aggressive monitoring, hand washing campaigns and other infection control measures, nosocomial infections (NI) rates, especially those caused by antibiotic resistant pathogens, are unacceptably high worldwide. Additional ways to fight these infections need to be developed. A potential overlooked and neglected source of nosocomial pathogens are those found in non-intrusive soft and hard surfaces located in clinical settings. Soft surfaces, such as patient pyjamas and beddings, can be an excellent substrate for bacterial and fungal growth under appropriate temperature and humidity conditions as those present between patients and the bed. Bed making in hospitals releases large quantities of microorganisms into the air, which contaminate the immediate and non-immediate surroundings. Microbes can survive on hard surfaces, such as metal trays, bed rails and door knobs, for very prolonged periods of time. Thus soft and hard surfaces that are in direct or indirect contact with the patients can serve as a source of nosocomial pathogens. Recently it has been demonstrated that copper surfaces and copper oxide containing textiles have potent intrinsic biocidal properties. This manuscript reviews the recent laboratory and clinical studies, which demonstrate that biocidal surfaces made of copper or containing copper can reduce the microbiological burden and the NI rates.

Key words: Nosocomial infections; Health acquired infections; Copper; Copper oxide; Biocides; Surfaces; Microbiological burden

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INTRODUCTION

A nosocomial, or hospital-acquired, infection is a new infection that develops in a patient during hospitalization. Nosocomial infections (NI) are a worldwide problem that occur both in developed and in developing countries. For example, in the United States approximately 2 million patients annually contract an infection while being hospitalized[1], and it is the fourth among the causes of death in the United States only behind heart disease, cancer and stroke[2]; in Europe in 2007 there were about 3 million healthcare associated infections (HAI), of which approximately 50 000 resulted in death[3]; in Germany alone around 500 000 to 600 000 NI occurred during 2006[4]; methicillin-resistant *Staphylococcus aureus* (MRSA) infections alone are estimated to affect more than 150 000 patients annually in the European Union[5]; in Australia, more than 177 000 NI occur per year[6]; in the province of Quebec, Canada, the rate of NI is estimated to be

around 11%[7]; and the rates of NI in developing countries are even higher[8-11].

NI can be bacterial, viral, fungal, or even parasitic[12-15]. Some of the most common nosocomial pathogens are staphylococci (especially *Staphylococcus aureus*), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Escherichia coli* (*E. coli*), *Clostridium difficile* (*C. difficile*), *Streptococcus* species, Enterobacter species, Acinetobacter species, Klebsiella species, influenza virus and noroviruses[16-21]. The prevalence rates of pathogens that cause NI and have a high level of resistance to antibiotic treatments, such as multidrug-resistant (MDR) *P. aeruginosa*, extended-spectrum β-lactamase producing Enterobacteriaceae, MDR Acinetobacter baumannii, MRSA, and vancomycin resistant enterococci (VRE), are constantly increasing around the globe[22-28], creating a serious threat to the spread and treatment of infectious diseases, because the resistant pathogens are significantly more difficult to treat (e.g.,[29]).

Many measures to reduce the risk of pathogens transmission are sought by health care officials, physicians and scientists. These include improvement of national surveillance of NI, use of aggressive antibiotic control programs to reduce the spread of antibiotic-resistant strains, healthcare staff education for improved hygiene, isolation of infected patients, ultraviolet light sterilization, use of disposable equipment, development of patient care techniques to reduce risks of infection, improved cleaning techniques, improvement of cleaning equipment and sanitary facilities, increase in nursing and janitorial resources and better nutrition (e.g.,[30-34]). It is estimated that by using several of the above strategies simultaneously about one third of NI may be eliminated[35,36]. These measures are not the scope of this review and are widely described elsewhere in the literature (e.g.,[31,37-40]). But it is clear that even in clinical settings where all or most of these measures are implemented, the rates of NI are still too high, and thus new approaches to further fight these infections need to be explored.

NI may occur *via* several manners. It is recognized by the infection control community that the most important and frequent modes of transmission of nosocomial pathogens are through direct-contact between an infected or colonized person (e.g., health worker, visitor or patient) and a susceptible host[41-44], and indirectly *via* contaminated intrusive medical devices[44-49], from the patient's own flora from one part of the host's body to another[50], and *via* airborne particles[21,51-55].

In addition to the above well described modes of transmission of nosocomial pathogens, others[56] and we[57] hypothesised that contaminated textiles in hospitals might be an important source of microbes contributing to endogenous, indirect-contact, and aerosol transmission of nosocomial-related pathogens. Textiles are an excellent substrate for bacterial and fungal growth under appropriate moisture and temperature conditions, and it was shown that bacteria and fungi can survive for prolonged periods in hospital fabrics[58,59]. Microbial shedding from the body occurs continuously[60]. Microbial shedding is greater in patients[54,61]. Thus a bacterium, when shed into a textile fabric between the patient and the bed, either on his pyjama, pillowcase, sheet, or mattress, would readily proliferate since the moisture and temperature in the textile microenvironment would promote its proliferation. Others and we presented data that substantiate this premise[62-65]. Importantly, it was found by others that bed making releases large quantities of microorganisms into the atmosphere and the bacteria levels in the air fall back to background levels only after approximately 30 min[52,66-68]. The released bacteria were shown to contaminate adjacent surfaces, such as bed sheets, over bed tables, and patients' clothing, and even adjacent rooms *via* the air-conditioning systems. Similar results were reported following undressing and redressing of patients[69].

The contribution of contaminated hard surfaces, such as floors, bedrails, bedside tables and door knobs, to NI has been demonstrated too (e.g.,[70-80]). Similarly, contaminated textiles, such as contaminated sheets and pyjamas, in addition to being a source of aerosol transmission of microorganisms, can also directly contaminate the hospital personnel[56,76,81,82]. Hospital staff, even by using protective equipment such as gloves, can contaminate them by touching the contaminated textiles or contaminated surfaces and then transferring the microorganisms to other patients directly or indirectly by contaminating other surfaces, such as door knobs[76,83]. For example, it was found that 65% of the nurses who performed activities on patients with MRSA in wounds or urine, contaminated their nursing uniforms or gowns with MRSA. This in turn, can readily contaminate the clothing and hands of healthcare workers[54,76,83]. High similar contamination of gloves and gowns with MDR *Acinetobacter baumannii* by healthcare workers interacting with colonized patients has also been reported[84]. Furthermore, it was found that 42% of personnel with no direct contact with patients contaminated their gloves by touching contaminated surfaces[76].

Thus, we further hypothesized that use of antimicrobial textiles, especially in those that are in close contact with the patients, may significantly reduce bioburden in clinical settings and consequently reduce the risk of NI[57]. Being all surfaces biocidal in a hospital environment would further reduce the risk of pathogen transmission and NI since most common nosocomial pathogens can remain viable on surfaces for months[43,85]. Indeed, it has been shown that environmental disinfection interrupts the transmission of microbial pathogens[79,80,83,86,87]. However, there are increasing concerns that routine surface disinfection procedures in health care settings are frequently inadequate and possibly counterproductive[88,89]. Consequently, the notion that having potent safe biocidal non-intrusive hard and soft surfaces in medical settings, in direct or indirect contact with patients, capable of reducing the microbiological burden that would significantly contribute to reduction in transmission of nosocomial pathogens, is gaining recognition by the scientific community. This review focuses on the studies demonstrating that hard and soft surfaces containing copper reduce the

microbiological burden in clinical settings and the NI rates.

COPPER HAS POTENT BIOCIDAL PROPERTIES

Copper and copper compounds have a wide spectrum of antibacterial, antifungal and antiviral properties (reviewed in[90,91]). The wide range of microorganisms, including gram negative and gram positive bacteria, yeast, fungi and enveloped and non-enveloped viruses, that have been shown to be killed by copper or copper compounds, are summarized in Table 1. Importantly, copper surfaces or copper compounds have also been shown to be efficacious against hard-to-kill spores[92-98].

Copper exerts its toxicity to microorganisms through several parallel mechanisms, which eventually may lead to the microorganisms' death even within minutes of their exposure to copper[94,99-106]. These include plasma membrane permeabilization, membrane lipid peroxidation, alteration of proteins and inhibition of their biological assembly and activity and denaturation of nucleic acids[90,91]. In general, the redox cycling between Cu^{2+} and Cu^{1+}, which can catalyze the production of highly hydroxyl radicals, with subsequent damage to lipids, proteins, DNA and other biomolecules[90,107], makes copper further reactive and a particularly effective antimicrobial. Interestingly, two different "kill modes", under dry and wet conditions, have been attributed to copper surfaces[101,102,104,105].

BIOCIDAL SOFT SURFACES IN THE HEALTHCARE ENVIRONMENT

Copper oxide is a non-soluble form of copper that, similarly to other copper compounds, has potent wide spectrum biocidal properties[90]. It has, therefore, been chosen as the active copper form to be introduced into textile fibres from which woven and non-woven fabrics can be produced[64,108,109]. These copper-impregnated products possess permanent broad-spectrum anti-bacterial, antifungal and antiviral properties that are not affected by washings[64,91,99,108-112] (Table 1). This technology, for example, enables the production of biocidal fabrics (which inter alia kill antibiotic resistant bacteria)[64,91,108,109], antifungal socks (which inter alia alleviate symptoms of athlete's foot)[108,113], anti-viral masks and filters (which inter alia deactivate HIV-1, Influenza A and other viruses)[99,106,110,111], and anti-dust mite mattress-covers (which may reduce mite-related allergies)[108,114].

As explained in the previous chapter, we hypothesized that contaminated beddings may be an important overlooked source of nosocomial pathogens and therefore the use of potent biocidal beddings, especially pyjamas and sheets, that are in contact with the patients, may significantly reduce bioburden in clinical settings and consequently reduce the risk of NI[57]. Indeed, a pilot study with 30 patients, who slept overnight on regular sheets and then overnight on sheets containing copper-oxide demonstrated a statistically significant lower bacterial colonization on the copper-oxide containing sheets than on regular-sheets[64], clearly supporting our hypothesis.

Importantly, the development of biocidal textiles with the purpose of using them in clinical settings to reduce HAI is gaining momentum and other biocidal active ingredients have or are being explored. These include Cliniweave®[115], organofunctional silane[116], citric acid[117], silver[118,119], triclosan[120], quaternary ammonium compounds[121], chitosan and zeolite[122,123]. For biocidal textiles to be introduced into the hospital textiles they should have wide spectrum antimicrobial, antifungal and antiviral properties, be effective against the already existent antibiotic resistant microorganisms involved in NI, not allow for the development of microorganisms against the active component in them, be efficacious for the life of the material, not be affected by commercial washings, not cause skin irritation or sensitization and be safe to humans following continuous dermal exposure. Some of the above active ingredients have thus been found not to be appropriate for use in hospital related applications (e.g.,[120,124]).

Until recently, only a few trials in clinical settings have been performed with biocidal textiles. It was found that bioburden was significantly lower on garments worn by nurses when the garments were made from a silver and copper containing antibacterial fabric[125]. The antibacterial textiles were tested in two hospital units, an oncology surgery unit and an intensive care unit. Each garment was provided with a piece of test fabric sewed either on the right or left side of the garment, while the regular fabric of the garment on the other side was used as a control. Thirty garments were tested in each unit. They were all sterilized, so they would be free of bacteria at the beginning of the experiment. The nurses wore the same number of garments with the treated area on the left side 1 d and on the right side the following day. Both active and control sides of each garment were sampled simultaneously and the bioburden determined. The number of colony forming units (CFU) was significantly lower on the bioactive patches than on the control areas. The mean reduction rate was about 30% for the 60 garments tested. Reduction of about 50% of bioburden on sheets containing copper oxide compared to regular sheets, when used overnight by general ward patients, was demonstrated[64]. Similarly, reduction of bioburden on blankets containing a bound organofunctional silane was also reported[116]. Recently in a 16 wk, blinded cross-over clinical trial that compared levels of bacterial contamination, a significantly fewer MRSA colonies were detected on scrubs impregnated with nano-sized particles that increase the surface tension of the scrubs than on standard scrubs (http://www.vestexprotects.com/press/view/8-Vestagen-Announces-Completion-of-First-Clinical-Trial-of-Vestex). In contrast, a study that compared the contamination rates of silver containing jackets and pants

Table 1 Demonstrated biocidal efficacy of copper

	Hard surface	Soft surface	Other	Ref.
Bacteria				
Acinetobacter baumannii[1]	+	+	+	[130,164] UR[2]
Acinetobacter calcoaceticus/baumannii	-	-	+	[93,94,165]
Acinetobacter johnsonii	+	-	-	[105]
Acinetobacter lwoffii	-	-	+	[166]
Bacillus cereus	+	-	+	[101,167-169]
Bacillus globigii	-	-	+	[92]
Bacillus subtilis	-	+	+	[165,169-175]
Bacillus macerans	-	-	+	[176]
Brachybacterium conglomeratum	+	-	-	[105]
Brevibacterium	-	+	-	UR
Campylobacter jejuni	+	-	-	[129]
Citrobacter freundi	-	-	+	[165,177]
Clostridium difficile	+	-	+	[93,97,98]
Clostridium tyrobutyricum	-	-	+	[95]
Corynebacterium xerosis	-	+	-	UR
Deinococcus radiodurans	+	-	-	[101]
Desulfovibrio desulfuricans	-	-	+	[178]
Edwardsiella tarda	-	-	+	[179]
Enterobacter aerogenes	-	-	+	[168,180]
Enterobacter cloacae	+	+	+	[127,128,168,175]
Enterococcus sp.[1]	-	-	+	[93]
Enterococcus faecalis[1]	+	+	+	[64,108,112,136,137,168,180]
Enterococcus faecium[1]	+	-	-	[127,128,137,155,181]
Enterococcus gallinarum	+	-	-	[137]
Enterococcus hirae	+	-	-	[182]
Escherichia coli	+	+	+	[64,100,101,105,108,109,112,127,128,133,139,147,155,165, 168-172,181,183-193]
Klebsiella pneumoniae	+	+	+	[112,130,165,193-195]
Kocuria marina	+	-	-	[105]
Kocuria palustris	+	-	-	[105]
Legionella pneumophila	+	-	+	[93,140,159,196-198]
Listeria monocytogenes	+	+	+	[64,140,180,199,200]
Mycobacterium tuberculosis[1]	+	-	-	[130]
Micrococcus luteus	+	+	-	[105,127,128] UR
Morganella morganii	-	-	+	[177]
Pantoea stewartii	+	-	-	[105]
Photobacterium leiognathi	-	+	-	[112]
Proteus mirabilis	-	-	+	[194]
Proteus vulgaris	-	-	+	[168]
Pseudomonas aeruginosa	+	+	+	[112,127,128,130,144,164,167,168,171,172,175,201,202]
Pseudomonas fluorescens	+	-	-	[199]
Pseudomonas nitroreducens	-	-	+	[169]
Pseudomonas oleovorans	+	-	-	[105]
Pseudomonas putita	-	-	+	[203]
Pseudomonas striata	+	-	-	[176]
Salmonella spp.	+	+	+	[64,129,165,183]
Salmonella typhi	+	-	+	[141,174,177,190,194,203,204]
Salmonella typhimurium	+	-	-	[141,142,199,201]
Sarcina lutea	-	-	+	[167]
Serratia marcescens	-	-	+	[171]
Shewanella putrefaciens	+	-	-	[199]
Shigella dysenteriae	-	-	+	[194]
Shigella flexnerii	+	-	+	[165,174,177,204]
Sphingomonas panni	+	-	-	[105]
Staphylococcus aureus[1]	+	+	+	[64,93,94,105,108,109,112,127,128,130,131,134,138,165,167-172, 175,181,184,199,200,205,206]
Staphylococcus epidermidis	+	+	+	[105,168,191,195,207] UR
Staphylococcus haemolyticus	+	-	-	[105]
Staphylococcus hominis	+	-	-	[105]
Staphylococcus warnerii	+	-	-	[105]
Stenotrophomonas maltophilia	-	-	+	[164]
Streptococcus faecalis	-	+	-	[175]
Streptococcus pyogenes	-	-	+	[168]
Streptococcus sp.	-	-	+	[165,208]
Vibrio cholerae[1]	+	-	+	[141,190,209]
Yersinia pseudotuberculosis	-	-	+	[180]

Xanthomonas compestris	-	-	+	[202]
Fungi/Yeast				
Alternaria brassicae	-	-	+	[202]
Aspergillus bransilensis	-	+	-	UR
Aspergillus carbonarius	-	-	+	[210]
Aspergillus flavus	+	-	+	[96,172,203,204]
Aspergillus fumigatus	+	-	+	[96,211]
Aspergillus niger	+	+	+	[96,114,172,202,211-214]
Aspergillus oryzae	-	-	+	[212]
Candida albicans	+	+	+	[64,96,104,108,109,112-114,130,168,169,173,193,204,211,214,215]
Candida glabrata	-	-	+	[168,180,194,204]
Candida krusei	-	-	+	[168]
Candida parapsilosis	-	-	+	[168]
Candida tropicalis	-	-	+	[168,180]
Cronobacter sakazakii	-	-	+	[216]
Cryptococcus neoformans	-	-	+	[211]
Culvularia lunata	-	-	+	[195]
Epidermophyton floccosum	-	-	+	[211]
Fusarium culmonium	+	-	-	[96]
Fusarium oxysporium	+	-	+	[96,202]
Fusarium solani	+	-	+	[96,195,204]
Microsporum canis	-	-	+	[204,211]
Myrothecium verrucaria	-	-	+	[212]
Penicillium chrysogenum	+	-	-	[96]
Pleurotus ostreatus	-	-	+	[185]
Pycnoporus cinnabarinus	-	-	+	[185]
Rhizoctonia bataicola	-	-	+	[195,203]
Rhizoctonia solani	-	-	+	[213]
Rhizopus stolonifer	-	-	+	[203]
Saccharomyces cerevisiae	+	-	+	[103,104,169,217]
Torulopsis pintolopesii	-	-	+	[215]
Trichoderma viride	-	-	+	[212]
Trichophyton longifusus	-	-	+	[204]
Trichophyton mentagrophytes	-	+	+	[113,114,194,212]
Tricophyton rubrum	-	+	+	[113,211]
Tricophyton schoenleinii	-	-	+	[194]
Virus				
Avian influenza	-	+	+	[111,205]
Adenovirus type 1	+	+	-	[99,218]
Bacteriophages	-	-	+	[219-223]
Coxsackie virus types B2 and B4	+	-	-	[218]
Cytomegalovirus	-	+	-	[99]
Echovirus 4	+	-	-	[218]
Herpes simplex virus	-	-	+	[219,220]
Human immunodeficiency virus	-	+	+	[99,108,110,224]
Infectious bronchitis virus	-	-	+	[225]
Influenza A	+	+	-	[99,111,135]
Junin virus	-	-	+	[220]
Measles	-	+	-	[99]
Parainfluenza 3	-	+	-	[99]
Poliovirus	+	-	+	[222,226]
Pichinde	-	+	-	[99]
Punta Toro	-	+	-	[99]
Respiratory syncytial virus	-	+	-	[99]
Rhinovirus 2	-	+	-	[99]
Simian rotavirus SA11	+	-	-	[218]
Vaccinia	-	+	-	[99]
West nile virus	-	+	-	[108]
Yellow fever	-	+	-	[99]

[1]Tested also against antibiotic resistant pathogens; [2]Unpublished data.

and of standard textile clothing used by 10 emergency workers did not find any significant difference in the extent of microbial contamination between the textiles[119]. It may be that a larger sample size was required to prove the silver containing fabric efficacy. It should be taken into consideration that in contrary to *in vitro* conditions, a continual re-inoculation with pathogens occurs during real-life health care scenarios. In addition, the killing of the microorganisms is not on contact, as it takes time for the biocidal textiles to kill the exposed microorganisms. Thus, obtaining sterile hospital or health-care associated fabrics by biocidal textiles in a healthcare environment

cannot be expected. Obviously, trials demonstrating that the use of biocidal textiles does not only reduce bioburden in clinical settings, but also reduces NI rates, still need to be conducted.

BIOCIDAL HARD SURFACES IN THE HEALTHCARE ENVIRONMENT

On February 2008 the USA Environmental Protection Agency (EPA) permitted the USA Copper Association to make public health claims and state that copper alloy products kill 99.9% of disease causing bacteria within 2 h and continue to do so when re-exposed[126]. This approval has now been given to 355 different copper alloys (including brass and bronze) following many years of independent laboratory testing based on rigorous EPA approved protocols. Copper is the only hard surface metal that has received approval by the EPA to make antimicrobial public health claims. In addition to the tests conducted by the USA Copper Association in order to obtain the approval for the registered health claims, the biocidal properties of copper surfaces was demonstrated by many others as well[96-98,100-102,104,105,127-142]. As can be seen in Table 1, copper surfaces can be regarded as a wide spectrum biocidal surface, as it has been found to be efficacious against a wide array of gram positive and negative bacteria, fungi and viruses. The biocidal efficacy of copper surfaces increases with the copper concentration[97,101,104,127,128,130,133,134,137,139], exposure periods[96-98,100-102,104,127-130,133-135,137,139,140,143], humidity[127,128,131,136] and temperature[98,129,131,133,144]. The higher the microorganism inoculum load is the longer it takes to reach complete elimination of the exposed microorganisms[133,134,137]. In contrast to stainless steel, which is the metal most widely used in hospital care environments, copper surfaces are highly reactive, and thus residual soil and build-up of microbial cells is more likely to occur in copper surfaces than on stainless steel[145]. Different cleaning solutions or products may have different effects on the continual efficacy of the copper surfaces[145] and thus the right cleaning and appropriate cleaning protocols of copper surfaces need to be developed[102].

Importantly, the significant contribution of copper surfaces to the reduction of bioburden in clinical settings has recently been demonstrated[132,146,147]. One trial was conducted in the United Kingdom[146], one in South Africa[147] and one in Germany[132].

In the United Kingdom study[146] the efficacy of copper surfaces to reduce bioburden was examined in a busy acute medical ward, which included gastroenterology patients, and a cross-over model was utilized. A toilet seat, tap handles and a ward entrance door push plate each containing copper (60%-70% copper content) were sampled for the presence of microorganisms and compared to equivalent standard, non-copper-containing items in the same ward. The items were installed at least 6 mo prior to the commencement of the study to allow both healthcare workers and staff to become accustomed to the copper containing items. The hospital staff followed their standard cleaning routines, which included disinfection of both the control and test fixtures approximately every 2 h. The items were sampled once weekly for 10 wk at 07:00 and at 17:00 to determine the number of microorganisms present following quite and busy time periods, respectively. The following specific indicator bacteria were quantified: methicillin-sensitive *Staphylococcus aureus* (MSSA), MRSA, VRE, *C. difficile* and *E. coli*. After 5 wk, the copper-containing and non-copper-containing items were interchanged to exclude any possibility of bias according to preferential use of any particular item based on location. Median numbers of microorganisms harbored by the copper-containing items were between 90% and 100% lower than their control equivalents at both sampling time-points, the microbial loads being highly statistically significantly different between the matched tested items (P values ranging from < 0.05 to < 0.0001). Three of the indicator microorganisms (MSSA, VRE and *E. coli*) were only isolated from control items. MRSA and *C. difficile* were not isolated during this study.

In the South Africa study[147], a comparative controlled study was conducted at a busy walk-in primary healthcare clinic in a rural region. Two similar adjacent consulting rooms were chosen. One was fitted with copper sheets (99.9% pure copper) on desk and trolleys that were in constant contact with staff and patients and on top of cupboards and windowsills where contact was less frequent. The other room remained with its original surfaces that did not include any copper surfaces. Cleaning procedures were the same for both rooms and no disinfectants were used. Samples for microbiological determinations were taken from 5 equivalent touch surfaces from each room. Sampling was undertaken for a period of 4 and a half days every 6 wk by the same person for a period of 6 mo. Samples were taken before cleaning (at 7 am), post cleaning but pre consultation (at 8 am) and post consultation (at 4 pm). The temperature and humidity in both sampling rooms were comparable during the study period covered - winter, spring and summer. The average number of consultations in each room during each sampling series during the 6 mo study was similar (65 study and 68 control room). Statistically significantly lower overall mean total CFU for all copper surfaces, including those in constant contact with staff and patients and those with less frequent contact, were found ($P < 0.001$), being the mean reduction 71%.

In the German study[132], an oncological/pneumological and a geriatric ward was used to test the efficacy of copper surfaces in reducing bioburden. All touch surfaces in patient bed rooms, rest rooms and staff rooms were replaced with new surfaces composed of metallic copper-containing alloys, while matched rooms, where no changes were made in the touch surfaces, served as controls rooms. All surfaces were routinely cleaned each morning with a disinfectant. The trial lasted 32 wk, 16 in the summer and 16 in the winter. During both test periods of 16 wk, the total number of CFU on metallic cop-

per-containing surfaces was 63% of that on the control surfaces ($P < 0.001$). When analyzing per surface area, the differences were significant for door knobs, which had the highest overall microbial load. Bacterial loads in push plates and light switches were similar between the test and control samples. Interestingly, after disinfection of the copper and control surfaces, microbial repopulation of the surfaces was significantly delayed on copper alloys ($P < 0.05$).

In addition to the above studies, a clinical study was undertaken to compare the surface microbial contamination associated with pens constructed of either a copper alloy or stainless steel used by nurses on intensive care units. A significantly lower level of microbial contamination was found on the copper alloy pens[148].

Another study, conducted in the UK, investigated the efficacy of using biocidal hard surfaces impregnated with a silver based technology in reducing microbial contamination in a real-life hospital environment[149]. Two outpatient units were included in the 18 mo study. One unit was refurbished with the silver containing products, which included door knobs, blinds, tiles, sack holders and light switches. The other unit contained untreated items and served as a control. Both units were similar in terms of volume of people and layout and were subjected to similar standard cleaning practice. Both units were allowed to function for 12 mo before microbiological swabbing commenced. Swabs were collected over a 5-mo period from both units. The CFU counts in the unit containing the silver impregnated products were between 62% to 98% lower than the matched unit. CFU counts from the silver-treated materials were between 70% (fabrics) to 99% (laminates) lower than untreated equivalents. In addition, the bacterial contamination on untreated products in the ward containing the silver-impregnated products was on average 43.5% lower compared with untreated matched products in the control unit.

The above described trials clearly demonstrate that biocidal hard surfaces found in heath-care settings offer the potential to significantly reduce the number of microorganisms in the clinical environment and thus reduce the risk of HAI. However, the use of biocidal surfaces should not act as a replacement for cleaning in clinical areas, but as an adjunct in the fight against HAI.

IS MICROBIAL RESISTANCE TO COPPER A CONCERN?

Bacterial resistance is a major concern in infection control, as exemplified by the highly antibiotic resistant bacteria (with up to 2200-fold decreased sensitivity to the antibiotic (e.g.,[150]) that have evolved in less than 50 years of antibiotic usage, making infected patient treatment extremely difficult (e.g.,[29]). Thus, the possibility of development of resistance to biocides is a real concern[151,152]. Importantly, as opposed to antibiotics, in spite of copper being a part of the earth for millions of years, and being used by humans from the beginning of the civilization, no microorganisms that are highly resistant to copper have been found, but only microorganisms with reduced copper sensitivity (increased copper tolerance). For example, Enterococci bacteria isolated from the gut of pigs, which were fed for many months with high concentrations of copper in their diet, were 7 fold less susceptible to copper than Enterococci bacteria isolated from pigs not fed with copper[153,154]. The increased tolerance to copper is achieved by the induction of an efflux pump in the tolerant bacteria[154]. Outstandingly, the Enterococci and *E. coli* tolerant bacteria isolated from pig farms following the use of copper sulfate as feed supplement were rapidly killed when spread in a thin, moist layer on copper alloys with 85% or greater copper content or under dry conditions[155]. Tolerance, but not resistance, was found in nitrifying soil microorganisms exposed to Cu for nearly 80 years under field conditions[156]. Similarly, the spray of copper-containing compounds for years on vegetable and fruit crops to limit the spread of plant pathogenic bacteria and fungi, has favored the spread of copper tolerant genes among saprophytic and plant pathogenic bacteria[157]. The increased tolerance to copper was found to be associated with the amount of soluble copper and not with the total amount of copper[158]. Thus, even in soils where the concentration of copper was very high, but in a non-soluble form, no increase in tolerance to copper was observed[158]. The copper active ingredient used in the biocidal textiles is copper oxide, a non-soluble form of copper. Importantly, no resistant bacteria evolved *in vitro* when consecutively exposed to repeated fabrics containing 1% copper oxide[112]. Interestingly, bacteria were isolated from copper-containing surfaces and some exhibited prolonged (1 to 3 d) survival on dry but not on moist copper surfaces[105]. None of these isolates strains was copper resistant in culture[105]. Survival on copper-containing surfaces appeared to be the consequence of either endospore formation, survival on patches of dirt, or a special ability to endure a dry metallic copper surface.

The reason why no resistance to copper, but only tolerance, is found in microorganisms exposed to constant relatively high doses of copper, may be because copper exerts its biocidal/antimicrobial activity not through one mechanism (as most antibiotics), but through several parallel non-specific mechanisms[90,91]. As briefly mentioned previously, these mechanisms include: (1) denaturation of nucleic acids by binding to and/or disordering helical structures and/or by cross-linking between and within nucleic acid strands; (2) alteration of proteins and inhibition of their biological assembly and activity; (3) plasma membrane permeabilization; and (4) membrane lipid peroxidation. Furthermore, widespread appearance of bacteria tolerant or resistant to copper contact killing appears unlikely as plasmid DNA is completely degraded after cell death by contact killing, preventing the transfer of resistance determinants between organisms[137] and copper contact killing is very rapid precluding the acquisition of

Figure 1 Use of copper in the detailed products, which are in direct or indirect contact with patients, may significantly contribute to the reduction of nosocomial pathogen loads and nosocomial infections. HEPA:

resistance during cell division[102].

Thus, even though some organisms have mechanisms of tolerance to excess copper as described above, in general, all microorganisms cannot cope when exposed to high concentrations of copper and are irreversibly damaged. As a result, despite having been present throughout human history, and despite repeated historic use of copper as an antimicrobial agent over the centuries, copper was and remains a broad-spectrum biocidal/antimicrobial compound and yet no bacteria fully resistant to copper have been discovered.

CONCLUSION

Similar to the efficient control of Legionella infections and the reduction of molds and yeasts that has been achieved in hospital systems by simply incorporating copper-silver ionization devices into the hospital water distribution systems[159-161], the use of soft and hard surfaces containing biocidal copper in products such as those described in Figure 1, may play an important role in reduction of NI in hospital care environments. Furthermore, as NI are now spreading out from the hospital environment into the community (e.g.,[162,163]), the use of textiles, such as those impregnated with copper oxide, and hard surfaces containing a high percentage of copper, may not only significantly contribute to the reduction of HAI, but may also confer protection when used in homes for the elderly and in other environments where immune compromised individuals are at high risk of contracting infections.

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