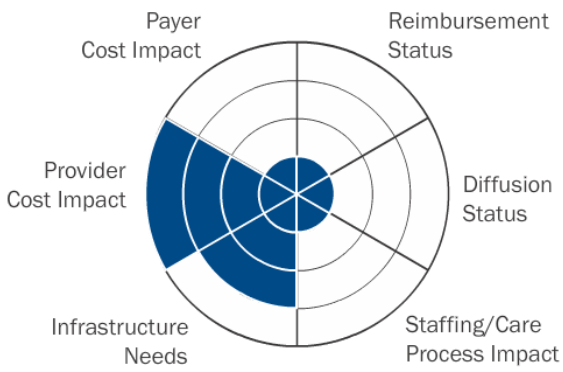
Antimicrobial Copper Surfaces for Reducing Hospital-acquired Infection Risk

HEALTH TECHNOLOGY ASSESSMENT INFORMATION SERVICE™

EMERGING TECHNOLOGY EVIDENCE REPORT

Executive Summary

Antimicrobial copper surfaces used in healthcare settings include surface components made from copper alloys and hard surface materials infused with copper oxides, both of which exert antimicrobial activity by releasing copper ions at concentrations toxic to microorganisms. Antimicrobial copper surfaces are meant to supplement standard cleaning procedures to reduce hospital-acquired infection risk. Their intended benefits include sustained antimicrobial effects independent of human compliance, wear resistance, environmental friendliness and recyclability, and a low risk of adverse events from copper exposure. A disadvantage is that copper materials are priced higher than standard materials used for hospital surfaces.



Parameter Rating and Definition*	Rationale
Reimbursement Status: 1	This technology does not qualify for reimbursement because acquisition of copper surfaces is an infrastructure cost for the provider.
Diffusion Status: 1 Innovative: Use limited to clinical trials or adopted by <10% of healthcare providers expected to use this technology.	ECRI Institute has found some published evidence that at least 17 healthcare facilites in the United States have installed some form of antimicrobial copper alloy surfaces, and 3 hospitals have installed copper-oxide-impregnated hard surfaces. Worldwide, approximately 60 healthcare facilities in more than 20 countries in Europe, Asia, Africa, and South America have reported installing antimicrobial copper alloy surfaces.
Effects on Staffing and Care Processes: 1 Low: Limited staffing changes and/or care process changes needed.	After installing antimicrobial copper surfaces, hospitals need to instruct their cleaning staff on the proper care of copper surfaces, but they do not need to change their cleaning or care processes. If fewer healthcare-associated infections occur, reduced demands on infectious disease/nursing staff are likely.
Infrastructure Needs: 3 Moderate: Some additional infrastructure needed to adopt the technology.	Replacing standard surfaces with antimicrobial copper surfaces in hospital rooms may require temporarily closing some rooms and reducing patient admissions. Installing copper surfaces during new construction would have a negligible impact on time required for construction.
Technology Cost Impact on Providers: 4 Substantial: >$100,000 for acquisition and implementation.	Hospitals absorb the costs of installing antimicrobial copper surfaces. Estimates based on prices for prototype items suggest the per-room installation cost is $7,000 to $15,000. Costs can be lower depending on which items and how many are installed per room. Nonetheless, the initial outfitting of all patient rooms can be a major investment of hundreds of thousands to millions of dollars.
Technology Cost Impact on Payers: 1 Negligible: <$5,000 per patient and/or negligible utilization driving negligible aggregate cost.	Hospitals absorb the costs of installing antimicrobial copper; if these surfaces reduce hospital-acquired infections, hospitals will benefit from not incurring nonreimbursable costs of treating such infections.

*Please see Appendix C for parameter definitions.

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Evidence Summary of Selected Outcomes*

Key Outcomes Assessed**	Evidence Base	Conclusions	GRADE-based Strength-of- evidence Rating*
Rate of hospital-acquired infections	1 RCT: Antimicrobial copper alloy surfaces vs. standard surfaces	Inconclusive: Too few patients assessed	Very low
Mortality rate	1 RCT: Antimicrobial copper alloy surfaces vs. standard surfaces	Inconclusive: Too few patients assessed	Very low

*Note: We grade strength of evidence based on the concepts and methods proposed by the GRADE working group. Please see Appendix A for details.
**No studies were published that made other comparisons of interest: antimicrobial copper surfaces with standard surfaces in conjunction with an enhanced cleaning technology (e.g., hydrogen peroxide vapor and mist generators, ultraviolet irradiators, ozone generators, high-pressure steam cleaners) and copper surfaces in a multi-bed ICU with standard surfaces in a single-bed ICU room. No studies reported on hospital-acquired infection readmissions.
RCT: Randomized controlled trial

Adverse Events

Our searches did not identify any studies that reported adverse events from copper surface exposure in healthcare settings.

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EMERGING TECHNOLOGY EVIDENCE REPORT

Table of Contents

Tables

Antimicrobial Copper Surfaces for Reducing Hospital-acquired Infection Risk

HEALTH TECHNOLOGY ASSESSMENT INFORMATION SERVICE™

EMERGING TECHNOLOGY EVIDENCE REPORT

Overview

Related Names

Proprietary names: CuVerro® antimicrobial copper, CuVerro bactericidal copper, MD-Cu29 antimicrobial copper, MicroGuard™ antimicrobial copper, Revere® antimicrobial copper, Cupron, Cupron Enhanced, Antimicrobial Cupron Enhanced EOS Surface, EOScu, Preventive|Biocidal Surface™, antimicrobial copper CU+®, Arrow HartTM, Century® Copper, CuLean™, CuLorTM, CuSalus®, Schlage®, SafeGripTM

Generic names: antimicrobial copper, antimicrobial copper alloys, copper oxide-impregnated surfaces

Background/Disease

Several studies suggest that antimicrobial copper surfaces can reduce the number of bacteria living on surfaces in hospital settings, such as patient rooms.[1-9] Based on these findings, some healthcare facilities are installing copper surfaces, hoping to reduce the risk of hospital-acquired infections (HAIs) (i.e., infections that patients acquire from the hospital environment when receiving healthcare treatment for other conditions).[10,11]

Bacteria, such as methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE), multidrug-resistant gram-negative bacilli, and Clostridium difficile (C. difficile), are the most common causes of HAIs,[12-14] likely because environmental sources of these bacteria are difficult to eliminate and the conditions they cause are difficult to treat.[14] Less frequently, viruses, fungi, and parasites cause HAIs.[10,12]

The following five types of infections constitute more than 85% of HAIs:[12]

- Catheter-associated urinary tract infection
- Central line-associated bloodstream infection
- C. difficile infection
- Pneumonia
- Surgical site infection

Hospital surfaces serve as a reservoir for pathogenic microbes and may play a key role in the transmission of HAIs.[12,14,15] Pathogenic microbes may persist for weeks or even months on common hospital surfaces, such as bedrails, bed trays, television remote controls, call buttons, chairs, doorknobs, push plates, faucet handles, sinks, medical device controls, and intravenous (IV) poles.[13,15-17] Pathogens on contaminated surfaces can spread directly to patients by touch, or indirectly when a healthcare worker touches a contaminated surface and then touches a patient.[12,14] Touch is the usual means of transmission for HAIs.[12]

Environmental cleanliness and hand hygiene are essential components of HAI control.[14] Standard cleaning procedures include wiping work surfaces with detergents and disinfectants (e.g., alcohols, bleaches, quaternary ammonium salts, phenol) and using devices such as ultraviolet light–emitting robots.[13,14] However, most standard cleaning methods do not provide sustained disinfection, and hospital surfaces may become recontaminated with pathogenic microbes shortly after cleaning.[13,18,19] Hand hygiene, another key component of reducing HAI risk,[12] relies on human behavior, and compliance with this practice may be poor.[12,16]

Despite adoption of standard cleaning procedures and hand-hygiene protocols, HAIs continue to have a big impact on patient care and associated healthcare costs. According to data from the U.S. Healthcare Cost and Utilization Project, HAIs can cause substantial increases in average hospital stay (5.2 days without an HAI versus 24.4 days with an HAI), in-hospital mortality rate (1.5% without an HAI versus 9% with an HAI), and average hospital cost of a hospital stay ($9,377 without an HAI versus $52,096 with an HAI).[20] To address the challenges of HAIs, some hospitals have implemented enhanced cleaning technologies (e.g., use of hydrogen peroxide vapor and mist generators, ultraviolet irradiators, ozone

generators, high-pressure steam cleaners, high-efficiency particulate air filtration devices).[13,14] Antimicrobial copper surfaces have also emerged as a possible means of reducing HAI risk. Although antimicrobial copper may be used in various healthcare settings, this report focuses on its use in hospital inpatient settings.

Incidence and Prevalence

United States

According to the U.S. Centers for Disease Control and Prevention (CDC), HAIs occur in approximately 4% of patients treated in U.S. hospitals.[21] About 722,000 HAIs occur in U.S. acute care hospitals annually, and nearly 75,000 patients with HAIs die during their hospitalizations.[21] More than 50% of HAIs occur outside intensive care units (ICUs).[21]

Worldwide

According to the World Health Organization, approximately 8.7% of hospitalized patients worldwide develop an HAI.[22] HAI rates range from 3.5% to 12% in developed countries and from 5.7% to 19.1% in developing countries.[23]

The European Centre for Disease Prevention and Control reported that the HAI rate in Europe was 7.1% in 2008, which equates to more than 4 million patients.[24,25]

Technology Description

Antimicrobial copper materials used in healthcare applications include copper alloys containing 60.0% to 99.9% copper[15,26,27] and copper oxides (i.e., antimicrobial Cupron Enhanced EOS surfaces) containing 16% copper made by combining copper powder additives and a polymeric substrate to form small particles.[28] Manufacturers incorporate these particles at a specific percentage to produce various copper-oxide-impregnated surface components.[29]

Although copper has been used for centuries for infection control practices, scientists continue to investigate its exact mechanism of action. The cause of cell death is thought to be multifactorial rather than the result of a single universal process.[30] Copper ions "interfere with several microbial metabolic activities and interrupt the integrity of the cellular DNA, the cytoplasmic membrane, and the cell wall."[3] Specifically, copper ions participate in several biochemical reactions, including generating cell-damaging reactive oxygen species through copper's oxidation state change (between Cu[I] and Cu[II]), competing with metal ions for protein-binding sites, and depleting sulfhydryl groups (-SH) in proteins and peptides. These reactions may form the basis for copper's antimicrobial activity.[15,31] Also, upon contact with a microorganism, copper ions may exert killing effects in multiple stages. Copper ions may first rupture cell membranes causing leakage of cellular substances, then inactivate vital enzymes and proteins inside the cell leading to metabolic disruption, and finally degrade cellular DNA.[15,31-33] Researchers speculate that bacteria are unlikely to develop a complete resistance to copper's antimicrobial properties because the killing effect is rapid and involves complete DNA degradation.[15,31,34]

According to the International Copper Association, a nontrading organization in charge of market development and technical services in the copper industry in North America, antimicrobial copper continuously reduces bacterial contamination, achieving 99.9% reduction of gram-negative and gram-positive bacteria within two hours of exposure and that copper surfaces continue to reduce bacterial contamination even after repeated contamination and between routine cleaning for the product's life.[35-37] Research suggests antimicrobial copper may also be effective against viruses and fungi.[38-40]

The surface components made from antimicrobial copper alloys and copper oxide-impregnated materials have similar indications for hospital use, but different physical and chemical properties. Possible antimicrobial copper alloy surfaces include a broad range of metallic components such as IV poles, countertops, grab bars, tray tables, door hardware, carts, handles, sinks, overbed tables, railings, faucet levers, and switch plates.[27,41,42] High temperature and high relative humidity increase the killing effect of antimicrobial copper alloy surfaces.[31] Copper-oxide-impregnated surfaces can be made from a variety of materials in the form of nonporous (not permeable to fluid or air) hard surfaces. The end products made from copper-oxide-impregnated solid surfaces include countertops, bed rails, sinks, shower pans, and foot boards.[29]

Intended Benefits and Potential Disadvantages

Intended benefits of antimicrobial copper include:[26,41,43]

- Sustained antimicrobial effects
- Wear-resistance
- Environmental friendliness and recyclability (copper alloys)
- Antimicrobial effects independent of human compliance
- Product design capabilities and versatility

Also, antimicrobial copper alloy surfaces may reduce cross-contamination by diminishing total bioburden on adjacent, noncopper surfaces.[3,42,44]

Potential disadvantages of antimicrobial copper include:[45,46]

- Higher price than standard hospital surfaces
- A tendency to tarnish over time (i.e., similar to tarnish characteristics of U.S. coins)

Care Setting

Hospital inpatient

Manufacturers

Antimicrobial copper manufacturers include copper alloy manufacturers and copper oxide manufacturers. Antimicrobial copper alloy manufacturers produce copper alloys or mechanically manipulate (e.g., bend, forge, cast, stamp) copper alloys to fabricate surface components. Copper oxide manufacturers produce copper oxide additives or infuse copper oxide additives into various nonmetallic materials (e.g., synthetic polymers, latex, fibers) to produce surface components.

Some antimicrobial copper alloy manufacturers in the United States have joined the Copper Development Association, Inc. (New York, NY, USA).[47] This organization offers memberships to U.S.-based and international copper producers and fabricators who have production facilities in the United States.[48] The Copper Development Association is the U.S. representative in a global network of Copper Centers. The headquarters of this global network is the International Copper Association, Ltd. (New York, NY, USA), which is in charge of guiding policies and market development for the copper industry worldwide.[47,49] The Copper Development Association and International Copper Association jointly promote the correct and efficient use of copper and its alloys in the United States and worldwide.[47]

The Copper Development Association classifies copper alloy manufacturers into copper alloy suppliers that produce copper alloys and component manufacturers that produce various copper components using copper alloys provided by alloy suppliers.[47,50,51] Some companies are both copper alloy suppliers and component manufacturers.[42]

Copper Alloys

ECRI Institute searches identified the following copper alloy suppliers that produce and market U.S, Environmental Protection Agency (EPA)-registered antimicrobial copper alloys and are Copper Development Association members. Other members may have joined since we compiled this list. See Table 1.[52]

Table 1. Antimicrobial Copper Alloy Suppliers

Manufacturer	Product Brand
Olin Brass Family of Companies (Louisville, KY, USA)	CuVerro
A.J. Oster, L.L.C. (Alliance, OH, USA)	CuVerro
Hussey Copper, Ltd. (Leetsdale, PA, USA)	MD-Cu_{29}

Manufacturer	Product Brand
PMX Industries, Inc. (Cedar Rapids, IA, USA)	MicroGuard™
Drawn Metal Tube Company (Thomaston, CT, USA)*	MicroGuard
Revere Copper and Brass, Inc. (Rome, NY, USA)	Revere®

ECRI Institute searches identified the following component manufacturers that have permission to produce and market antimicrobial copper products made from antimicrobial copper alloys in the United States. All public health claims made by component manufacturers on their products are attached to the brands for the alloys used to fabricate the products rather than the brands for the end products. We are unable to identify product distribution information outside the United States. See Table 2.[53]

Table 2. Commercially Available Antimicrobial Copper Components

Manufacturer	Product(s)	Product Brand	Alloy Brand Used
Allegion plc. (Carmel, IN, USA)	Door hardware	Schlage®	CuVerro
A.T. Cross Company (Lincoln, RI, USA)	Pens and writing instruments	Century®	CuVerro
The Colonial Bronze Company, Inc. (Torrington, CT, USA)	Bedside and examination room case goods, caregiver station doors and drawers, grab bars, door handles, cart handles, instrument knobs, levers, handles	CuSalus®	CuVerro
Cu Healthy Products, L.L.C. (Morganton, NC, USA)	Switch plates, door plates, wall plates, sinks and tile, door-opening device	MD-Cu_{29}	MD-Cu_{29}
Drapery Industries, Inc. (Rochester, NY, USA)	Curtain wands	SafeGrip™	CuVerro
Eaton's Copper Wiring Devices (Peachtree City, GA, USA)	Switches, wall plates, commercial grade AC switches, outlet covers	Arrow Hart™	CuVerro
E.B. Bradley Company (Vernon, CA , USA)	Drawer pulls	CuLor™	CuVerro
Elkay Manufacturing Company, Inc. (Oakbrook, IL, USA)	Sinks (single bowl, round, oval, undermount, drop-in), drains, vanity tops	Elkay®	CuVerro
Frigo Design (Brewerton, NY, USA)	Countertops (with or without sinks), tabletops, shower pans, chair arms, door push plates, custom solutions	Frigo Design	CuVerro
Hussey Copper, Ltd. (Leetsdale, PA, USA)	Cabinet pulls, push/pull plates, custom products, sinks, tiles, wall plates, outlet covers	MD-Cu_{29}	MD-Cu_{29}
Just Manufacturing Company, Inc. (Franklin Park, IL, USA)	Healthcare fixtures, scrub sinks, patient suite lavatory sinks, nurse's handwash stations, sensor faucets	Just Manufacturing	CuVerro
Larco, L.L.C., division of ATEK Access Technologies, L.L.C. (Brainerd, MN, USA)	Door access controls, push plate switches, automatic door packages	Coppershield®	CuVerro
Medline Industries, Inc. (Mundelein, IL, USA)	Door and cabinet hardware, push plates, stretcher rails	CuSalus	CuVerro
Midbrook Medical, Inc. (Jackson, MI, USA)	Intravenous (IV) poles, mayo stands, carts, instrument trays, work surfaces, cabinetry	Midbrook Medical	CuVerro
Operator Interface Technology, Inc. (Longmont, CO, USA)	Sealed keyboards with pointing device, keypads, custom solutions	Operator Interface Technology	CuVerro
Pedigo Products, Inc. (Vancouver, WA, USA)	Stretcher rails, linen hampers, trash canisters, mayo stands, IV poles, equipment carts, tables, cabinets	Pedigo®	CuVerro

Manufacturer	Product(s)	Product Brand	Alloy Brand Used
Rocky Mountain Hardware, Inc. (Hailey, ID, USA)	Locksets, knobs, levers, grips, push plates, kick plates, hinges, sinks, faucets, lighting, window hardware, grab bars, towel bars, custom solutions	Rocky Mountain Hardware®	CuVerro
Triangle Brass Manufacturing Company, Inc., (Los Angeles, CA, USA)	Push/pull plates, push/pull bar sets, grips, offset pulls, floor stops, kick plates, panic guards, door holders	Trimco	CuVerro
Tubular Specialties Manufacturing, Inc. (Los Angeles, CA, USA)	Grab bars, towel bars, shower and specialty bars, dispensers (paper towel, facial tissue, toilet paper), soap dishes, waste receptacles, other washroom accessories	TSM	CuVerro
Wagner Architectural Systems, Inc. (Milwaukee, WI, USA)	Railings, grab bars, kick plates, custom solutions	Wagner™	CuVerro

Copper Oxides

EOS surfaces, LLC. (Norfolk, VA, USA) partners with Cupron, Inc. (Richmond, VA, USA) to produce and market Antimicrobial Cupron Enhanced EOS Surfaces made from copper-oxide-impregnated synthetic polymers (e.g., acrylic, polyester). Antimicrobial Cupron Enhanced EOS Surfaces, which contain 16% copper oxides, are suitable for a variety of applications such as handrails, countertops, and integral bowls.[29,54,55]

Regulatory Status

The International Copper Association and Copper Development Association have established an Antimicrobial Copper "Cu+" mark that certifies EPA registration (in the United States) or otherwise experimentally proven antimicrobial activities of copper alloys (worldwide).[47,53] Manufacturers that intend to use this mark in the United States need to obtain permission from the Copper Development Association and register with EPA. Manufacturers that intend to use this mark outside the United States need to obtain permission from the International Copper Association or their local copper center. By using the antimicrobial copper brand, a manufacturer demonstrates its compliance to usage rules required by EPA or the International Copper Association.[47,53,56]

Copper Alloys

United States

In February 2008, the Copper Development Association received EPA registration for antimicrobial copper alloys with the following public health claims:[57]

> Laboratory testing has shown that when cleaned regularly, antimicrobial copper surfaces:
>
> - Continuously reduce bacterial contamination (*Staphylococcus aureus, Enterobacter aerogenes*, Methicillin-Resistant *Staphylococcus aureus, Escherichia coli* 0157:H7, *Pseudomonas aeruginosa, and* Vancomycin-resistant *Enterococcus faecalis*), achieving 99.9% reduction within two hours of exposure.
> - Kill greater than 99.9% of Gram-negative and Gram-positive bacteria* within two hours of exposure.
> - Deliver continuous and ongoing antibacterial* action, remaining effective in killing greater than 99.9% of bacteria* within two hours, even after repeated wet and dry abrasion and re-contamination.
> - Kill greater than 99.9% of bacteria* within two hours, and continue to kill more than 99% of bacteria* even after repeated contamination.

- Help inhibit the buildup and growth of bacteria (*Staphylococcus aureus, Enterobacter aerogenes,* Methicillin-Resistant *Staphylococcus aureus, Escherichia coli* 0157:H7, *Pseudomonas aeruginosa, and* Vancomycin-resistant *Enterococcus faecalis*) within two hours of exposure between routine cleaning and sanitizing steps.

EPA attached the following two conditions to the registration for antimicrobial copper alloys:[57,58]

- The Copper Development Association will prepare and implement an Antimicrobial Copper Alloy Stewardship Plan, including sending written communications to infection control professionals and the public, developing a stewardship website, and establishing an Antimicrobial Copper Alloy Working Group to support the responsible use of antimicrobial copper products; and
- For at least the first 24 months after registration and until the EPA terminates this condition, the Copper Development Association will submit to the EPA sample advertising materials representing advertisements intended for use in the marketplace

According to the Copper Development Association, "although EPA had registered over 500 antimicrobial copper alloys by March 2015, fewer than six of these are used for commercial products and most are nickel-containing alloys."[59]

EPA offers an Antimicrobial Testing Program, which "ensures that EPA-approved hospital sterilants, disinfectants, and tuberculocides in the marketplace continue to meet stringent efficacy standards." EPA classifies registered products into one of the following three categories:

1) Agency Confirmed Efficacy, representing products that have passed the testing and are confirmed as "efficacious hospital disinfectants";

2) Agency Taking Action, representing products that are under EPA testing or regulatory actions;

3) No Post-Market Testing by EPA, representing newly registered products that have not undergone post-market testing.

As of April 2015, antimicrobial copper alloys were classified into "no post-market testing by EPA."

Canada

In Canada, Health Canada's Pest Management Regulatory Agency (PMRA) approval, granted in July 2014, permits alloy suppliers and component makers to market antimicrobial copper products with approved public health claims in Canada after securing the appropriate approvals.[60] PMRA approved product performance claims similar to the EPA-approved claims for the U.S. market.[61] Some suppliers are positioning to secure registration in Canada.[42]

Copper Oxides

United States

In September 2012, Cupron received EPA registration for Antimicrobial Cupron Enhanced EOS Surfaces with the following public health claims:[62]

Laboratory testing has shown that when cleaned regularly, this surface:

- Continuously reduces bacterial contamination (*Staphylococcus aureus, Enterobacter aerogenes*, Methicillin-Resistant *Staphylococcus aureus, Escherichia coli* 0157:H7, and *Pseudomonas aeruginosa*), achieving 99.9% reduction within two hours of exposure.
- Kills greater than 99.9% of Gram negative and Gram-positive bacteria* within two hours of exposure.

- Kills greater than 99.9% of bacteria (*Staphylococcus aureus, Enterobacter aerogenes*, Methicillin-Resistant *Staphylococcus aureus, Escherichia coli* 0157:H7, and *Pseudomonas aeruginosa*) within two hours and continues to kill 99% of bacteria* even after repeated contamination.
- Helps inhibit the buildup and growth of bacteria (*Staphylococcus aureus, Enterobacter aerogenes*, Methicillin-Resistant *Staphylococcus aureus, Escherichia coli* 0157:H7, and *Pseudomonas aeruginosa*) within two hours of exposure between routine cleaning and sanitizing steps.

The EPA registration for Antimicrobial Cupron Enhanced EOS Surfaces has similar attached conditions to those for registration of antimicrobial copper alloys, which include developing a stewardship plan and submitting sample advertising materials to EPA.[62]

Other Countries

Our searches did not identify information on registration or regulation of antimicrobial copper oxides in other countries.

Applications and Directions for Use

Applications

According to EPA, antimicrobial copper surfaces may be used in hospitals, other healthcare facilities, and various public, commercial, and residential buildings. The EPA registration document includes a comprehensive list of applications for antimicrobial copper.[54,57,62] In hospitals, the most common places considered for antimicrobial surfaces include medical ICUs, lavatories, nurses' stations, and common areas (e.g., hallways).[42]

Labeled Directions for Use

EPA requires manufacturers to include the following statement when making public health claims in the United States related to the use of antimicrobial copper alloys or Antimicrobial Cupron Enhanced EOS Surfaces:[45,57,62] Copper surfaces are

> a supplement to, and not a substitute for, standard infection control practices; users must continue to follow all current infection control practices, including those practices related to cleaning and disinfection of environmental surfaces. Antimicrobial copper surfaces have reduced microbial contamination, but they do not necessarily prevent cross contamination.

EPA directions for use also indicate that antimicrobial copper surfaces should be cleaned and sanitized according to standard practices. Cleaning agents typically used for standard surfaces are applicable to antimicrobial copper surfaces. The specific type of cleaning agent used depends on the type of soiling and the sanitization standard. Normal tarnishing or wear of antimicrobial copper surfaces will not impair the antibacterial effectiveness of the products.[57,62]

Antimicrobial copper surfaces should not be waxed, painted, lacquered, varnished, or otherwise coated. Antimicrobial copper surfaces should not be used for any direct food contact or food packaging.[57,62]

Manufacturer-recommended Directions for Use

Regular cleaning that removes dirt and exposes the copper surface is essential to maintain antimicrobial properties. All EPA-registered disinfectant products are acceptable for use on antimicrobial copper surfaces and should be used according to label instructions. It is acceptable to use polishing products to remove natural oxidation, but the surfaces should be cleaned afterward with soap and water or other cleaners containing a surfactant to remove any residue that may be left behind.

For antimicrobial copper alloy surfaces, the Copper Development Association recommends the following three types of cleaning products:[45]

- Hospital detergents that remove grease and soil from surfaces. Users should wash and dry antimicrobial copper alloy surfaces after cleaning with detergents and before applying disinfectants.

- All EPA-registered disinfectants and alternative cleaning technologies. Users should follow labeled instructions when using them on antimicrobial copper alloys.
- Metal polishes and cleaners that remove tarnish and brighten the appearance of copper alloys. After using metal polishes, users should wash antimicrobial copper surfaces with detergents or other surfactant-containing clearers (organic compounds that reduce liquid surface tension) to remove any possible residue.

A Copper Development Association expert who provided comments to ECRI Institute on this technology recommends several specific cleaning products for antimicrobial copper alloy surfaces. For regular cleaning, recommended products include the hydrogen peroxide–based cleaner Clorox hydrogen peroxide, 70% isopropyl alcohol, Virex® II disinfectant cleaner, Oxivir Tb disinfectant cleaner, Peroxy II cleaner, and Scotch-Brite cleaning products (for sinks). For polishing and remediation, recommended products include Wright's copper cream and ZUD cleaner.[59]

Clinical Guidelines and Standards

ECRI Institute searches did not identify any guidelines that specifically mention the use of antimicrobial copper surfaces in healthcare settings to prevent HAIs. Our searches identified the following three relevant general guidelines that address the use of metals, including copper, as microbicides:

- European Society of Clinical Microbiology and Infectious Diseases. Guidelines for the Management of the Infection Control Measures to Reduce Transmission of Multidrug-resistant Gram-negative Bacteria in Hospitalized Patients. 2013. This guideline states the following:[63]

  > Innovative forms of cleaning and decontamination methods for the healthcare environment are constantly appearing. These have an impact on all environmental pathogens, including spore-forming bacilli, but robust evidence supporting their use for the control of MDR-GNB is lacking. There are novel disinfectants such as electrolysed water, and automated systems dispelling steam, hydrogen peroxide, ozone and different types of UV light. Studies to evaluate the impact of antimicrobial surfaces, such as steel, copper, silver and nano-silver particles combined with light-activated titanium dioxide have demonstrated equivocal results on environmental contamination. However, traditional cleaning methods should not be relaxed or abandoned even if new cleaning systems are introduced.

- CDC. *Guideline for Disinfection and Sterilization in Healthcare Facilities.* 2008. This guideline states, "Metals such as silver, iron, and copper could be used for environmental control, disinfection of water, or reusable medical devices or incorporated into medical devices (e.g., intravascular catheters)."[64]
- CDC. *Guidelines for Environmental Infection Control in Health-Care Facilities*. 2003. This guideline mentions copper's biocidal activity in several sections. The statements concerning copper are as follows:[65]
  - Copper-based compounds have demonstrated anti-fungal activity and are often applied to wood or paint. Copper-8-quinolinolate was used on environmental surfaces contaminated with Aspergillus spp. to control one reported outbreak of aspergillosis. The compound was also incorporated into the fireproofing material of a newly constructed hospital to help decrease the environmental spore burden. (*Background Information* section)
  - Alternative methods for controlling and eradicating legionellae in water systems (e.g., treating water with chlorine dioxide, heavy metal ions [i.e., copper/silver ions], ozone, and UV light) have limited the growth of legionellae under laboratory and operating conditions. (*Background Information* section)
  - Use an EPA-registered anti-fungal biocide (e.g., copper-8-quinolinolate) for decontaminating structural materials. (*Recommendation for Environmental Infection Control in Health-care Facilities section*, rated as strongly recommended)

- Evaluate new methods of water treatment, both in the facility and at the water utility (e.g., ozone, chlorine dioxide, copper/silver/monochloramine) and perform cost-benefit analyses of treatment in preventing health-care–associated legionellosis. (*Areas of Future Research* section)

Also, a specific testing protocol for "the evaluation of bactericidal activity of hard, non-porous copper/copper-alloy surfaces" is available on the EPA website.[66]

Other Evidence Reports

ECRI Institute searches identified the following two relevant evidence reports:

- Ontario Agency for Health Protection and Promotion (Public Health Ontario) the Provincial Infectious Diseases Advisory Committee on Infection Prevention and Control (PIDAC-IPC). *Antimicrobial Surfaces to Prevent Healthcare-associated Infections: A Systematic Review*. 2016. This systematic review of studies published through November 2014 reported the following:[67]

  > Evidence suggests that copper surfaces harbor fewer bacteria than non-copper surfaces. Additionally, one study of copper surfaces in an ICU and one study of copper textiles in chronic care showed a reduction in HAI incidence but the quality of this evidence is very low. Confirmation of the association between use of copper surfaces and HAI reduction using higher-quality study designs should be a priority.

- Canada Agency for Drugs and Technologies in Health. *Antimicrobial Copper Surfaces for the Reduction of Health Care–Associated Infections in Intensive Care Settings.* 2015. After considering the evidence from the one-year trial conducted on antimicrobial copper alloy surfaces in ICU rooms in the United States, this report concludes: "Further evaluation is required to confirm a sustained reduction in HAI rates with antimicrobial copper surfaces beyond a one-year time period and whether there are potential limitations in efficacy with soiling, exposure to chemicals, or the presence of surface defects that may act as microbial reservoirs."[68]

Considerations for Hospitals

Staffing Requirements

According to the Copper Development Association, installing antimicrobial copper surfaces does not require special training for construction workers. Implementing antimicrobial copper surfaces has little impact on staffing needs, as hospitals and healthcare facilities will not have major changes in their cleaning practices after adopting copper surfaces other than to instruct cleaning staff on the proper care of copper surfaces.[45,46]

Installation

Replacing standard surfaces with antimicrobial copper surfaces in hospital rooms may require temporarily closing some rooms and coordinating equipment needs during renovations. According to the Copper Development Association, refitting a hospital room with antimicrobial copper surfaces could be quick, depending on the surfaces being installed: handles, locks, push plates, and kick plates take about 30 minutes; electrical supplies take about 20 minutes; and sink taps, traps, and wastes take about 2.5 hours.[46]

Safety

Exposure to copper may cause allergic reactions;[69-71] however, the risks from intermittent skin contact with antimicrobial copper surfaces are generally low.[70,71]

Copper Alloys

We identified three sources of safety information on antimicrobial copper alloys: EPA, PMRA, and a copper industry assessment conducted in Europe.

EPA registers antimicrobial copper alloys under the Federal Insecticide, Fungicide, and Rodenticide Act's "no unreasonable adverse effects" standard, indicating they pose no risks to public health. Copper products have been in use for centuries, and the EPA sees no harm from their use.[58]

According to PMRA, antimicrobial copper alloys do not present an unacceptable risk to human health or the environment under the approved conditions for use. The PMRA registration document states, "The acute toxicity of the end-use products, Antimicrobial Copper Alloys Group I to VI, were low via the dermal route of exposure. They were non-irritating to the skin and eyes, but cause allergic skin reaction; consequently, the hazard signal words 'potential skin sensitizer' are required on the label."[61]

In 2008, the copper industry performed a "voluntary risk assessment" for copper in Europe under the approval of the Italian government's Istituto Superiore di Sanità on behalf of the European Commission and European Union Member States. The assessment concluded: "The use of copper products is in general safe for Europe's environment and the health of its citizens." The European Commission and European Union Member State experts have accepted the conclusion and published it on the European Chemical Agency's website.[33,72]

Copper Oxides

According to Cupron, copper-oxide-impregnated materials have undergone laboratory testing following generally accepted clinical test protocols under standard Good Laboratory Practices conditions. Under these conditions, copper-oxide-impregnated materials demonstrated no toxicity or irritation to the skin, and no adverse events (AEs) were reported.[73]

Training and Credentialing

Manufacturer-sponsored Training

Antimicrobial copper manufacturers do not provide specific training for using antimicrobial copper surfaces. However, the Copper Development Association has established a stewardship website to provide the public with information and support for the responsible use of antimicrobial copper surfaces.[45,74] The following educational publications on antimicrobial copper alloy surfaces are available on the stewardship website:[75]

- "Reducing the Risk of HCAIs - The Role of Copper Touch Surfaces" (a summary of the science with key references)
- "Antimicrobial Copper FAQs"
- "Near-patient Antimicrobial Copper Touch Surfaces for Infection Control - The Business Case"
- "Guidance on Cleaning and Disinfection"
- "Antimicrobial Copper Alloys: Guidance on Selection" (background engineering information)
- "Antimicrobial Copper: A Hospital Manager's Guide"
- "Antimicrobial Copper: A Specifier's Guide"

General Training

The Copper Development Association and EPA do not require specific training regarding the use of antimicrobial copper surfaces.[45] However, hospitals should train cleaning staff and healthcare workers on the proper care and use of antimicrobial copper surfaces (e.g., maintaining regular cleaning), as well as provide general information and educational resources on the technology (e.g., the stewardship website).

Competing and Complementary Technologies

Antimicrobial copper surfaces are intended to complement—not replace—standard cleaning agents and methods, including detergents and disinfectants. Antimicrobial copper surfaces that provide continuous antimicrobial effects in patient-occupied rooms may also complement enhanced cleaning technologies (e.g., hydrogen peroxide vapor and mist generators, ultraviolet irradiators, ozone generators, high-pressure steam cleaners) that provide episodic biocidal effects

on human operation in unoccupied rooms.[13,14] However, hospitals that install antimicrobial copper surfaces may use enhanced cleaning technologies less frequently.[42]

Phase of Diffusion

United States/Copper Alloys

In the United States, use of antimicrobial copper alloy surfaces is in an innovative stage of diffusion. According to the Copper Development Association, as of January 2015, at least 17 U.S. hospitals and healthcare facilities have installed some form of antimicrobial copper alloy surfaces, such as door hardware, cabinet pulls, sinks, stretchers, and IV poles.[42]

United States/Copper Oxides

In the United States, Cupron Enhanced EOS Surfaces are in an early stage of diffusion. As of March 2015, three medical centers have adopted Cupron Enhanced EOS Surfaces.[76,77]

Other Countries/Copper Alloys

Worldwide, antimicrobial copper alloy surfaces are in an innovative stage of diffusion. According to the Copper Development Association, as of May 2015, approximately 60 hospitals and healthcare facilities in more than 20 countries in Europe, South America, Africa, and Asia have installed antimicrobial copper alloy surfaces.[42,78,79] Installations have predominantly taken place in clinical settings where patients are at high risk for infections, such as ICU rooms, pediatric and neonatal units, and cancer centers.[68]

Other Countries/Copper Oxides

We are unable to find diffusion information for copper oxides in other countries.

Future Trends

In addition to copper alloys and copper oxides, other forms of antimicrobial copper are under development. Copper nanoparticles are a new family of copper-based materials that researchers are testing for surface applications by using coating techniques, including thermionic vacuum arc deposition, chemical vapor deposition, and sputtering deposition.[80-83] Some preliminary studies suggest copper nanoparticle-coated surfaces have antimicrobial activity.[80-83] Furthermore, researchers are assessing the biocidal effects of copper-containing liquid formulations and exploring their potential uses in hand sanitizers and cleaning products.[15,84-86] A preliminary study suggests that ultra-microfiber mops and cloths loaded with a copper sulphate-based biocide (CuWB50) may reduce the total viable bacteria count in the hospital environment compared with those moistened with water.[15,86] An antimicrobial copper coating spray is under development and pending EPA approval.[87]

Also, copper may have beneficial biological activities in addition to killing microorganisms. Research has discovered that copper may stimulate wound healing, suggesting a potential use for copper in wound dressings.[88]

Some public venues other than healthcare facilities (e.g., restaurants, residential buildings, fitness training facilities, train stations, school buildings, airports) have begun adopting antimicrobial copper alloy surfaces.[42,89]

Costs

Copper Alloys

Our searches identified limited cost information on antimicrobial copper alloy surfaces from three sources: a business case published by the Copper Development Association, news articles about an actual hospital experience, and retail websites listing price information.

The business case reported an estimated cost of $7,700 to $15,000 per room to convert hospital common surfaces (i.e., bed rails, IV poles, cabinet hardware, chairs, tables, countertops, door levers, grab bars, handrails, light switches, computer mouse devices, keyboards, other data-input devices, sinks, faucets) to antimicrobial copper alloy components.[90] This estimate was based on prototype pricing used to fabricate components specifically for the U.S. Department of

Defense–funded clinical trial before commercial products were available on the U.S. market. Thus, the estimate may not reflect current pricing.

In July 2014, MD-Cu_{29} antimicrobial copper alloy manufacturer Hussey Copper announced that Pullman Regional Hospital (Pullman, WA, USA)—a 95,000-square-foot, level IV trauma center with 25 patient beds, 3 operating rooms, and 24-hour emergency care—replaced more than 1,100 surface items with antimicrobial copper alloy components for a total cost of $7,000.[91] The replaced items were primarily small, low-cost, and durable components, including sink faucet levers in the hallway and restrooms, handles for IV poles, and handicapped-access buttons for double-doors.[92]

Some retail websites list pricing information for antimicrobial copper alloy products used in hospital settings.[93-97] See Table 3 for details.

Table 3. Pricing for Select MD-CU_{29} Antimicrobial Copper Alloy Products

Product	Price/Price Range
Bathroom sinks	$100 to 300
Cabinet pulls	$5 to $12
Drop-in sinks	$279 to $905
Light switch wall plates and electrical outlets	$5 to $8
Pull plates	$46 to $53
Push plates	$12 to $20
Tiles (adhesive or grouted)	$29
Undermount sinks	$175 to $356

Copper Oxides

Our searches identified limited anecdotal cost information on antimicrobial copper oxide surfaces from a news article about an actual hospital experience.[77] Sentara Leigh Hospital (Norfolk, VA, USA) paid approximately $600,000 for 8,000 square feet of Cupron Enhanced EOS Surface to outfit a newly constructed 129-bed hospital building.[77] The installed Cupron Enhanced EOS Surface items included countertops, overbed tables, and bed rails. However, because the hospital received budget approval for standard surfaces before the installation of copper surfaces, the manufacturer may have offered a relatively low price for the Cupron Enhanced EOS Surface items to fit the hospital's budget.[77]

Cost-effectiveness and Considerations

CDC estimates that an HAI adds 19.2 hospital days and $43,000 in treatment costs for an average patient who develops an infection. CDC has also reported that HAIs add $35.7 billion to $45 billion to U.S. healthcare costs annually.[98]

York Health Economics Consortium at the University of York in the United Kingdom conducted a business model–based cost-effectiveness study for implementing antimicrobial copper alloy surfaces.[99] The model used compared the extra expenses for antimicrobial copper alloy surfaces (relative to noncopper surfaces) with the cost savings from decreased HAIs. The calculation was based on the costs of replacing six common hospital surfaces (i.e., bed rails, call buttons, chairs, data devices, IV poles, and overbed tray table) with antimicrobial copper alloy surfaces in a 20-bed ICU room. These cost estimates were based on prices for prototype items made for clinical studies, which may not reflect the cost of purchasing the same items at current market prices. Cost data were reported in U.K. pounds, and we converted them into 2015 U.S. dollars. The model estimated that implementing the six antimicrobial copper alloy surfaces during new construction or renovation would cost $47,500 more than standard surfaces. The estimate for HAI-associated costs was based on an average patient stay of six days,[100] an ICU HAI incidence of 25%,[101,102] an additional stay of six days resulting from HAIs,[103] and a HAI cost of $1,550 per patient per day.[103] Using these data, the model calculated that each year this ICU would have 1,200 patients, 300 HAI events, and $2.8 million of HAI-associated costs. Based on a 20% reduction in HAIs resulting from antimicrobial copper alloy surfaces, the model found that copper surfaces would save $560,000 in

HAI-associated costs per year. The model found that the extra cost of implementing antimicrobial copper alloy surfaces could be recouped in fewer than 2 months and that over 5 years antimicrobial copper alloy surfaces would reduce the number of HAIs by 300 and save almost $2.8 million in HAI-associated costs.

Evidence Review

We reviewed evidence to address the following four key questions:

Key Question 1: Do antimicrobial copper surfaces reduce HAI rates and associated mortality?

Key Question 2: How does the effectiveness of antimicrobial copper surfaces compare with that of standard surfaces in conjunction with an enhanced cleaning technology?

Key Question 3: How does the effectiveness of antimicrobial copper surfaces in a multibed ICU compare with that of standard surfaces in a single-bed ICU room?

Key Question 4: What AEs are reported in studies of antimicrobial copper surfaces?

The study population of interest for this report is patients in hospital inpatient settings. We expect standard cleaning of patient room surfaces regardless of the intervention.

Our evidence review focuses on the following patient-oriented outcomes:

- Rate of HAIs
- Length of hospital stay
- Number of sequelae
- Rate of patient readmission
- Mortality
- AEs

Our literature searches identified several studies that reported on microbial load, microbial burden, or bacterial colonization. We do not include data on these surrogate outcomes in our analysis.

Methods

We searched MEDLINE, EMBASE, the Cochrane Library, CINAHL, and PubMed to identify relevant studies published through January 2016. See *Search Strategy* section below for keywords and subject headings used in this search. We further retrieved relevant information via review of bibliographies/reference lists from peer-reviewed and gray literature. Gray literature consists of reports, studies, articles, and monographs produced by government agencies, private organizations, educational facilities, consulting firms, and corporations.

Study Selection Criteria

ECRI Institute applied the following study-selection criteria to identify appropriate studies that could address the key questions:

- Study must be published in English.
- Study must be reported as a full-length, peer-reviewed article. We excluded abstracts and meeting presentations because they do not give complete results and sufficient detail about methodology to assess the risk of bias, and final results may differ from preliminary results.
- To avoid double counting of patient outcomes, if more than one article has been published to describe the same study, the article must be the latest published report or have the most complete report of an outcome.

- Comparative studies must assess at least 10 patients in each arm. Smaller studies are at greater risk of patient-selection bias and often are not statistically reliable.
- To address Key Question 1, we include randomized controlled trials (RCTs) and comparative studies that compare outcomes in hospital rooms with antimicrobial copper surfaces with those in hospital rooms with standard surfaces.
- To address Key Question 2, we include RCTs and comparative studies that compare the effectiveness of antimicrobial copper surfaces with noncopper surfaces in conjunction with an enhanced cleaning technology.
- To address Key Question 3, we include RCTs and comparative studies that compare the effectiveness of antimicrobial copper surfaces in a multibed ICU with that of standard surfaces in single-patient ICUs.
- To address Key Question 4, the study must report on AEs in patients who were inpatients in rooms installed with antimicrobial copper surfaces.

Included Studies

We identified one RCT that addresses Key Question 1. In this RCT, funded by the U.S. Department of Defense and sponsored by the Copper Development Association, Salgado et al. (2013) enrolled 650 patients at 3 U.S. medical centers and compared outcomes for patients randomly placed in available ICU rooms with or without copper surfaces.[104] The investigators conducted this study in 16 single-patient ICU rooms (8 copper-equipped rooms, 8 non-copper-equipped rooms) at Medical University of South Carolina (Charleston, SC, USA), the Memorial Sloan-Kettering Cancer Center (New York, NY, USA), and the Ralph H. Johnson Veterans Affairs Medical Center (Charleston, SC, USA) between July 12, 2010, and June 14, 2011. The study was conducted at random intervals in patient-occupied rooms. In the copper-equipped ICU rooms, the investigators replaced six different surfaces with items made from antimicrobial copper alloys (e.g., bed rails, overbed tables, IV poles, visitor chair arms, nurses' call button, computer mouse, bezel of the touchscreen monitor, palm rest of a laptop computer). Copper-equipped ICU rooms were located adjacent to non-copper-equipped ICU rooms. All hospitals followed preexisting comparable cleaning protocols using hospital-grade disinfectants. Upon patients' admission, bed-control personnel, who were masked to room conditions (whether a room had copper), randomly assigned patients to an available study room. The patients assigned to copper- and non-copper-equipped ICUs had similar demographic and clinical characteristics (i.e., age, gender, race, infection at admission, APACHE [Acute Physiology and Chronic Health Evaluation] II score), and 47.6% of the patients had infections at admission. Patient-oriented outcomes in this study were rate of HAIs/MRSA or VRE colonization, rate of HAIs without MRSA/VRE colonization, length of stay, and mortality.[104] The investigators considered infections as hospital-acquired if they occurred more than 48 hours after patients' admission or within 48 hours after patients' discharge.[104]

The investigators excluded 5.5% (36/650) of patients from analysis because of incomplete study data: 12/650 patients had missing primary outcome data, 3/650 had missing study room assignment, and 21/650 had missing outcomes data and study room assignment. The authors presented no further information regarding these patients. For the 614 patients in the analysis, 294 had been assigned to the copper-equipped ICU rooms and 320 to the non-copper-equipped ICU rooms.

Strength-of-evidence Assessment

We graded strength of evidence (SOE) for selected patient outcomes that potentially matter the most to decision makers and patients. Our grading approach is based on the concepts and methods proposed by the GRADE working group. We also incorporated the evidence assessment methods used by the Agency for Healthcare Research and Quality's Evidence-based Practice Centers. Our grading approach addressed risk of bias, consistency, directness, precision, magnitude of effect, dose-response gradient, and plausible confounders that would reduce a demonstrated effect. We assigned an evidence grade of "high," "moderate," "low," or "very low" for each selected outcome. The definitions of these evidence grades and more detailed description of the grading methods are provided in Appendix A.

Findings

Key Question 1: Do antimicrobial copper surfaces reduce HAI rates and associated mortality?

The single RCT[104] that addressed this question reported on the HAI rate and/or MRSA/VRE colonization, HAI rate without MRSA/VRE colonization, and MRSA/VRE colonization rate without HAIs. Our outcome of interest is the HAI rate regardless of MRSA/VRE colonization status, and we were able to calculate results for this outcome using the reported data. Our calculation found that the difference in the HAI rate (regardless of MRSA/VRE colonization status) between the study groups was not significant (copper-equipped ICUs: 17/294 [5.8%] versus non-copper-equipped ICUs: 29/320 [9.1%]; p = 0.123). The median length of stay for both groups was four days (p = 0.74). The reported mortality rate was 42/294 patients (14.29%) in copper-equipped ICUs versus 50/320 (15.63%) in non-copper-equipped ICUs (p = 0.64).

No studies reported on the number of sequelae from HAIs or patient readmission rates. No studies assessed Cupron Enhanced EOS Surfaces.

Key Question 2: How does the effectiveness of antimicrobial copper surfaces compare with that of standard surfaces in conjunction with an enhanced cleaning technology?

Our searches did not identify any studies that addressed Key Question 2.

Key Question 3: How does the effectiveness of antimicrobial copper surfaces in a multibed ICU compare with that of standard surfaces in a single-bed ICU room?

Our searches did not identify any studies that addressed Key Question 3.

Key Question 4: What AEs are reported in studies of antimicrobial copper surfaces?

Our searches did not identify any studies that addressed Key Question 4.

Ongoing Clinical Trials

ECRI Institute searches identified two ongoing trials. One assesses antimicrobial copper alloys, and the other assesses Cupron Enhanced EOS Surfaces.

The Antimicrobial Copper Alloy trial is a four-year double-blind RCT underway at the University of California, Los Angeles, (UCLA) sponsored by a grant from the U.S. National Institutes of Health and the Agency for Healthcare Research and Quality. The clinical trial will involve two ICUs at Ronald Reagan UCLA Medical Center. The ICUs will be outfitted with copper, sham stainless steel, or conventional surfaces such as plastic or other types of coatings. Over four years, the surface types will be sampled for bacteria levels, and researchers will compare patient-infection outcomes rates among the three surfaces. The study will also include a cost-benefit analysis.[105,106]

The Cupron Enhanced EOS Surface trial is a one-year comparative study underway at Sentara Leigh Hospital. Cupron, EOS Surfaces, and Sentara Healthcare are funding the study. In this study, researchers have outfitted a newly constructed, 129-bed hospital building with items made from Cupron Enhanced EOS Surfaces, including countertops, overbed tables, and bed rails; an existing hospital building equipped with standard surfaces serves as the control. However, in addition to Cupron Enhanced EOS Surfaces, researchers have also implemented in the study building copper-oxide-impregnated Enhanced EOS, such as bed linens, towels, and gowns, which have not received EPA registration. The study will assess rate of HAIs and number of antibiotics used. The effects of Cupron Enhanced EOS Surfaces will be mixed with those of copper-impregnated textiles in these outcomes.[77,107-109]

Discussion

Several studies of this technology reported on surrogate measures (i.e., microbial load, microbial burden or bacterial colonization). These outcomes are of interest to researchers, manufacturers, and regulatory authorities when they assess a cleaning technology for technical improvements, marketing claims, and regulatory approval determinations. However, because we understand that hospital decision makers want to know how installing antimicrobial copper surfaces will

benefit patients and reduce HAI transmission, we consider only patient-oriented outcomes (i.e., HAI rate, mortality, patient readmission) in our analysis of the effectiveness of antimicrobial copper surfaces.

The single RCT that provided data on HAI and mortality rates had several limitations. The study authors did not report prior rates of HAIs in copper-equipped and non-copper-equipped ICUs before this study started. If a significant difference existed in prior rates, the underlying causes for such a difference may be carried over to the study and confound the results. During the study, because copper items are visually distinct from regular items, neither the healthcare workers nor the patients could be masked to the experimental group assignments. Potential changes in healthcare worker cleaning and care procedures in the presence of copper items could affect HAI rates in the two study groups and confound the results. Also, generalizing the results from a single RCT conducted in ICU rooms to other ICUs or other types of patient areas is not possible. In the ICU setting, inpatients are most vulnerable to HAIs and the magnitude of response — the reduction in the incidence of infections — may be greater than that in settings where patients have lower risks for infections. Furthermore, because of equipment and furniture movement during the study, 53.4% of patients in copper-equipped ICUs had at least one copper item removed, and 13.4% of patients in non-copper-equipped ICUs were exposed to copper items during their stay. Inconsistency in patients' exposure to copper items and the cross-group contamination spread by furniture movement may lessen differences in outcomes between the two study groups.

A recently published systematic review authored by the Ontario Agency for Health Protection and Promotion and PIDAC-IPC[67] reported very-low-quality evidence that copper surfaces reduce HAI rates. Their assessment included the published RCT[104] results indicating a significant reduction of 58% in HAI (without MRSA/VRE colonization) incidence associated with copper surfaces. However, when we calculated HAI rates (regardless of MRSA/VRE colonization status) from this RCT, we found no significant difference between the study groups for this outcome.

Antimicrobial copper surfaces are available for a broad range of hospital surfaces, but which surfaces are the most relevant remains unclear. In the RCT, investigators replaced six hospital common surfaces with copper components, but they did not provide reasons for choosing these surfaces. It remains unclear how outcomes would have been affected if the investigators had chosen a different set of antimicrobial copper alloy surfaces.

Based on the available evidence, we were unable to reach a conclusion regarding the effectiveness of antimicrobial copper surfaces in reducing HAIs and associated mortality. However, results of the ongoing four-year trial on antimicrobial copper alloys at UCLA may provide data to inform conclusions about the effectiveness of this technology as well as a cost-benefit analyses.

Evidence Base Conclusions

This report addresses four key questions. Below are the conclusions for each key question.

Key Question 1: Do antimicrobial copper surfaces reduce HAI rates and associated mortality?

One RCT provided data to address this question (Salgado et al., n = 650).[104] We were unable to determine whether antimicrobial copper surfaces reduced the HAI rate or the mortality rate because too few patients were assessed. Strength of evidence: Very low.

No studies were available on sequelae from HAIs or patient readmission rates.

Key Question 2: How does the effectiveness of antimicrobial copper surfaces compare with that of standard surfaces in conjunction with an enhanced cleaning technology?

Our searches did not identify any studies that addressed this question.

Key Question 3: How does the effectiveness of antimicrobial copper surfaces in a multibed ICU compare with that of standard surfaces in a single-bed ICU room?

Our searches did not identify any studies that addressed this question.

Key Question 4: What AEs are reported in studies of antimicrobial copper surfaces?

Our searches did not identify any studies that addressed this question.

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Classifications

Technology Class

Comparative Effectiveness, Environmental Health, Infection Control

Clinical Category

Preventive

Clinical Specialty

Environmental Medicine, Infectious Disease

UMDNS

Intravenous Poles [12-177]; Intravenous Poles, Ceiling-Mounted [16-504]; Rails, Wall [15-855]; Rails [15-852]; Rails, Commode [15-854]; Bedrails [10-341]; Rails, Bathtub [15-853]; Tables, Overbed [13-963]; Carts [10-635]; Sinks [15-932]; Sheets, Patient Bed, Disposable [32-039]; Sheets, Patient Bed, Reusable [31-688]; Covers, Pillow, Protective [18-047]; Casework, Examination Room [27-087]; Casework, Patient Room [15-900]; Tables [13-949]; Chairs [10-787]; Showers [20-336]; Cabinets [10-526]; Electric Receptacles [27-930]; Sinks, Surgical Scrub [15-936]; Surgical Scrub Stations [15-733]; Sinks, Examination/Treatment [15-934]; Tables, Instrument [13-959]; Instrument Trays [12-143]; Hamper Stands [15-838]; Hampers [15-839]; Waste Receptacles [14-424]; Lights [12-347]; Keypads [23-170]; Computer/Computerized System Keypads [23-171]; Scrub Dresses [13-520]; Scrub Pants [27-808]; Scrub Suits [13-524]; Scrub Tops [27-807]; Scrub Suits, Disposable [13-526]; Scrub Suits, Reusable [13-527]; Stretchers, Portable [13-818]; Stretchers, Mobile, Hospital [16-786]; Stretchers, Mobile [13-816]; Stretchers [13-814]

MeSH

Catheter-Related Infections; Copper; Cross Infection; Disinfectants; Infection Control; Protective Clothing; Staphylococcal Infections; Anti-Bacterial Agents; Disinfection; Gram-Negative Bacterial Infections; Staphylococcal Infections; Equipment Design; Surgical Wound Infection; Pneumococcal Infections; Pneumonia; Equipment and Supplies, Hospital; Urinary Tract Infections; Stretchers

ICD-9-CM

Other and unspecified infection due to central venous catheter [999.31]; Bloodstream infection due to central venous catheter [999.32]; Urinary tract infection, site not specified [599.0]; Methicillin resistant Staphylococcus aureus in conditions classified elsewhere and of unspecified site [041.12]; Other specified bacterial infections in conditions classified elsewhere and of unspecified site, other gram-negative organisms [041.85]; Intestinal infection due to clostridium difficile 008.45 Pneumonia, organism unspecified [486]

ICD-10 coding is pending

FDA SPN

CHAIR AND TABLE, MEDICAL [KMN]; DISINFECTANT, MEDICAL DEVICES [LRJ]; STAND, INFUSION [FOX] TRAY, SURGICAL, INSTRUMENT [FSM]; DRESS, SURGICAL [FYE]; SUIT, SURGICAL [FXO]; STRETCHER, HAND-CARRIED [FPP]; STRETCHER, WHEELED [FPO]

HCPCS

Toilet rail, each [E0243]; IV pole [E0776]; Bath tub wall rail, each [E0241]; Over-bed table [E0274]

SNOMED CT

Nosocomial infectious disease [19168005]; Postoperative wound infection [58126003]; Clostridium difficile infection [186431008]; Catheter-associated urinary tract infection [700372006]; Infection associated with catheter [440653007]; Infection due to vancomycin resistant enterococcus [406575008]; Methicillin resistant Staphylococcus aureus infection [266096002]; Pneumonia [233604007]; Nosocomial pneumonia [425464007]; Antibacterial agent [419241000]; Antibacterial drugs [346325008]; Copper [66925006]; Copper [422528000]; Cross infection [36406009]; Disinfectant [311942001]; Bedside rails [37953008]; Bathtub rails [48096001]; Cart [85455005]; Table [86407004]; Hospital shower bath [45984009]; Electrical outlet [18100009]; Lamp [34160005]; Stretcher [89149003]

Publication History

Date	Action	Comments
2/05/2016	Published	Initial publication

Search Strategy

OVID syntax (EMBASE and MEDLINE were searched together):

1. Copper:dn OR copper:ti,ab
2. (e.coli or mrsa or vre or vancomycin-resistance or 'methicillin-resistant staphylococcus aureus infection'/de or 'antibiotic resistance'/de or vancomycin-resistant-enterococcus or 'Escherichia coli infection'/de OR (bacteria* NEAR/1 infection*)) AND (healthcare OR health-care OR hospital*)
3. cross infection'/de or 'hospital infection'/de or 'infection control'/de or nosocomial infection* or 'infection prevention'/de OR 'healthcare associated infection'/de
4. ('hospital acquired' OR 'healthcare acquired' OR 'healthcare associated' OR 'health care acquired' OR 'health care associated') NEAR/2 infection*
5. 'antiinfective agent'/de AND (healthcare OR health-care OR hospital*)
6. 'hospital subdivisions and components'/exp AND infection*
7. 'Furniture'/exp OR 'hospital design'/de
8. (Antimicrobial copper OR anti-microbial copper) AND (infection* OR 'hospital equipment'/de)
9. 1 AND (2 OR 3 OR 4 OR 5 OR 6 OR 7)
10. 9 OR 8]]

This search may be executed in PubMed using the following strategy:

1. Copper[mh] OR copper[tiab]

2. (e.coli OR mrsa OR vre OR vancomycin-resistance OR "methicillin-resistant staphylococcus aureus"[mh] OR "drug resistance, microbial"[mh] OR "vancomycin resistance"[mh] OR "Escherichia coli"[mh] OR (bacteria* AND infection* AND (healthcare OR health-care OR hospital*))
3. "cross infection"[mh:noexp] OR "infection control"[mh:noexp]'/de OR nosocomial infection* or "infection/prevention and control"[mh]
4. hospital acquired infection* OR healthcare acquired infection* OR healthcare associated infection* OR health care acquired infection* OR health care associated infection*
5. "antiinfective agents"[mh:noexp] AND (healthcare OR health-care OR hospital*)
6. "hospital departments"[mh] AND infection*
7. "Interior design and furnishings"[mh] OR "hospital design and construction"[mh]
8. (Antimicrobial copper OR anti-microbial copper) AND (infection* OR "equipment and supplies, hospital"[mh])
9. #1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7)
10. #9 OR #8

Appendix A. Strength-of-evidence Assessment Methods

We grade strength of evidence (SOE) for selected patient outcomes in this report. Our grading approach is based on the concepts and methods proposed by the GRADE working group. Our approach also incorporates the evidence assessment methods adopted by the Agency for Healthcare Research and Quality's Evidence-based Practice Centers. Detailed descriptions of the GRADE and EPC methods are accessible using the links we provided above. To grade evidence in this report, we consider seven domains that may affect strength of evidence: risk of bias, consistency, directness, precision, magnitude of effect, dose-response gradient, and plausible confounders that would reduce a demonstrated effect. For each selected outcome, we assign a grade of "high," "moderate," "low," or "very low." The definitions of the grades are provided in Table A-2.

Table A-1. Strength-of-evidence Grade Definitions

Grade	Definition
High	We have high confidence in the findings for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable (i.e., another study would not change the conclusions).
Moderate	We have moderate confidence in the findings for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence in the findings for this outcome. The body of evidence has major or numerous deficiencies. We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Very low	We have no confidence in the findings for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies.

We assessed each comparative study as having low, medium, or high risk of bias using the items in Table A-2.

Table A-2. Items Used for Risk-of-bias Assessment

Item	Comment
Were patients randomly or pseudorandomly (e.g., using instrumental variable analysis) assigned to the study groups?	Instrumental variable analysis can account for both measured and unmeasured confounders as long as the chosen variables have a strong association with treatment choice but no association with health outcomes. Studies using this method received a "yes" for this item. Studies using propensity scoring or multivariate regression received a "no."
Was there concealment of group allocation?	—
Were data analyzed based on the intention-to-treat-principle?	—
Were the patients blinded to the group assigned?	—
Were those who treated the patient blinded to the group to which the patients were assigned?	—
Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	—
Was the outcome measure of interest objective, and was it objectively measured?	All outcomes (i.e., rate of HAIs, length of stay, mortality rate) reported in the study included in our analysis were objective.
Was there a 15% or less difference in the length of follow-up for the 2 groups?	—
Did 85% or more of enrolled patients provide data at the time point of interest?	—
Was there fidelity to the protocol?	—

Appendix B. Results of Risk-of-bias and Strength-of-evidence Assessment

Table B-1. Results of Risk-of-Bias Assessment

Study Author/Year	Outcome(s)	Q1. Were patients randomly assigned to treatment groups?	Q2. Was there concealment of group allocation?	Q3. Were data analyzed based on the intention-to-treat-principle?	Q4. Were the patients blinded to the group assigned?	Q5. Were those who treated the patient blinded to the group to which the patients were assigned?	Q6. Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	Q7. Was the outcome measure of interest objective, and was it objectively measured?	Q8. Was there a 15% or less difference in the length of follow-up for the 2 groups?	Q9. Did 85% or more of enrolled patients provide data at the time point of interest?	Q10. Was there fidelity to protocol?	Risk-of-bias Category
Salgado et al. 2013[104]	Rate of healthcare-acquired infections	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Medium
	Mortality rate	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Medium

Table B-2. Results of Strength-of-evidence Assessment

Comparison/ Reference	Outcome	Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
Antimicrobial copper alloy surfaces vs. standard surfaces Salgado et al. 2013[104]	Rate of HAIs	Moderate	Consistency unknown (single study)	Direct	Imprecise	Inclusive	Very low
	Mortality rate	Moderate	Consistency unknown (single study)	Direct	Imprecise	Inclusive	Very low

SOE: Strength of evidence

Appendix C. Impact Ratings Definitions

Reimbursement Status

Definition: The extent to which third-party payer coverage and coding are in effect to enable insured patients' access to the intervention.

(4) Wide coverage: Medicare has a positive national coverage determination and/or ≥8 private payers provide coverage.

(3) Expanding coverage: Medicare has no national coverage determination; some local Medicare carriers provide coverage; 4 to 7 major private payers provide coverage; others deny coverage, have no published policy in place, or decide coverage on a case-by-case basis.

(2) Limited coverage: Medicare has no national coverage determination or provides coverage only in the context of a clinical trial (i.e., coverage with evidence development); 1 to 3 major private payers provide coverage.

(1) No coverage: Medicare has a national coverage determination that denies coverage. Most private third-party payers explicitly state that they do not cover the technology because they consider the technology or intervention to be "investigational" or "experimental" or consider the evidence insufficient.

Diffusion Status

Definition: The extent to which the technology or intervention has been adopted into clinical care at this time. Considerations include the proportion of clinicians or healthcare facilities that report or advertise using the technology or intervention.

(4) Wide: Adopted by ≥50% of healthcare providers and facilities expected to use this technology.

(3) Middle: Adopted by >25% and up to 50% of healthcare providers and facilities expected to use this technology.

(2) Early: Adopted by about >10% and up to 25% of healthcare providers and facilities expected to use this technology.

(1) Innovative: use limited to clinical trials or adopted by <10% of healthcare providers and facilities that would be expected to use this technology after it is clinically and commercially available.

Effect on Staffing and Care Processes

Definition: The extent to which most providers need to change their staffing model and/or care processes if adopting this technology. Staffing impacts include need for additional staff or different model/team. Process impacts include shifts in amount of care delivered, care setting, and changes in patient volume and/or throughput.

(4) Substantial: Significant staffing changes and/or care process changes needed.

(3) Moderate: Some staffing changes and/or care process changes needed.

(2) Low: Limited staffing changes and/or care process changes needed.

(1) Negligible: Current staffing and/or care processes are probably sufficient.

Infrastructure Needs

Definition: The extent of new or expanded infrastructure that most providers will need if adopting the technology (e.g., new or expanded existing facilities, new capital equipment, supplies).

(4) Substantial: Significant additional infrastructure needed to adopt the technology.

(3) Moderate: Some additional infrastructure needed to adopt the technology.

(2) Small: Limited additional infrastructure needed to adopt the technology.

(1) Negligible: No additional infrastructure needed to adopt the technology.

Technology Cost Impact on Providers

Definition: The costs to implement and use the technology initially and ongoing; considers acquisition and maintenance, additional staff and training, additional infrastructure needed.

(4) Substantial costs associated with acquisition, implementation (estimated >$100,000).

(3) Moderate costs associated with acquisition, implementation (estimated >$50,000 up to <$100,000).

(2) Small costs associated with acquisition, implementation (estimated <$25,000 up to $50,000).

(1) Negligible costs associated with acquisition, implementation, and ongoing use. Resources and supplies required to use the technology are on hand at most healthcare facilities that would use the technology (estimated <$25,000).

Technology Cost Impact on Payers

Definition: The costs to payers (health plans and patients) for use of the new technology (drug, device, procedure). Considerations include cost per patient, size of the patient population expected to use it, and patient copay scenarios.

(4) Substantial per-patient costs (estimated >$50,000) and copays or substantial number of patients expected to use the technology.

(3) Moderate per-patient costs (>$25,000 to $50,000) and copays or moderate number of patients expected to use the technology

(2) Small per-patient costs ($5,000 to <$25,000) and copays or small number of patients expected to use the technology.

(1) Negligible per-patient costs (<$5,000) and copays or negligible number of patients expected to use the technology.

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