Health Protection Scotland

NHS National Services Scotland

Literature Review and Practice Recommendations: Existing and emerging technologies used for decontamination of the healthcare environment

Antimicrobial Copper Surfaces

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Contents

Topic

The use of antimicrobial copper surfaces for decontamination of the healthcare environment and reusable non-invasive patient care equipment.

Background

Current microbiological and epidemiological evidence indicates that contaminated surfaces in hospital settings can contribute to the transmission of nosocomial pathogens.[1] In particular, there appears to be a risk of pathogen acquisition from prior room occupants for methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), *Clostridium difficile* and *Acinetobacter baumannii*.[2] Accordingly, existing research implies that improved surface cleaning and disinfection can reduce healthcare-associated infections.[3]

Manual processes for surface cleaning are frequently sub-optimal, suggesting that automated decontamination processes might offer an opportunity to improve cleaning efficacy and consistency.[4] Antimicrobial surfaces have been proposed as a method for inhibiting the accumulation of micro-organisms on hospital surfaces without the need for an increased frequency of cleaning.[5] However, these surfaces are only recommended as a supplemental measure, rather than a replacement for standard cleaning processes, due to their limited capacity to remove microbial bioburden.[6]

The need for studies evaluating long-term antimicrobial potency, practicality and cost-effectiveness of copper-coated surfaces has been highlighted.[7] Concerns have similarly been expressed over the durability of these surfaces and whether antimicrobial activity is influenced by other factors such as temperature, humidity, frequency of cleaning, and the presence of organic load.[8] A systematic review of antimicrobial surfaces, covering published literature up to 2014, failed to identify any clinical studies on antimicrobial surfaces published before 2010.[9]

A recent literature review by Health Protection Scotland (HPS) summarised existing evidence supporting the use of antimicrobial copper solutions for decontamination of the environment and equipment in healthcare settings, but excluded those studies concerning antimicrobial copper surfaces at the outset.[10] To address this gap, the following review intends to assess the evidence base on the appropriateness of using antimicrobial copper surfaces for decontamination of the healthcare environment and patient care equipment.

Aim

To review the evidence for using antimicrobial copper surfaces for decontamination of the healthcare environment and reusable non-invasive patient care equipment.

Objectives

- To provide a generic description of antimicrobial copper surfaces, including the proposed or actual mechanism of action and the procedure for use.
- To assess the scientific evidence for effectiveness of antimicrobial copper surfaces.
- To explore practical and safety considerations related to the use of antimicrobial copper surfaces.
- To explore the costs associated with antimicrobial copper surfaces.
- To produce a concise evidence summary for antimicrobial copper surfaces to assist the Equipment and Environmental Decontamination Steering Expert Advisory Group in making practical recommendations on the use of antimicrobial copper surfaces for NHSScotland.

Research questions

The following research questions will be addressed:

1. Are antimicrobial copper surfaces currently in use in UK healthcare settings?
2. What is the actual or proposed mechanism of action of antimicrobial copper surfaces?
3. What is the procedure for using antimicrobial copper surfaces?
4. What is the scientific evidence for effectiveness of antimicrobial copper surfaces for decontamination of the healthcare environment?
5. Are there any safety considerations associated with using antimicrobial copper surfaces in the healthcare setting?
6. Are there any practical or logistical considerations associated with using antimicrobial copper surfaces in the healthcare setting?
7. What costs are associated with using antimicrobial copper surfaces in the healthcare setting?
8. Have antimicrobial copper surfaces been assessed by the Rapid Review Panel?

Methodology

Search Strategy

The following databases and websites were searched to identify relevant academic and grey literature:

- MEDLINE
- CINAHL
- EMBASE
- NHS Evidence (http://www.evidence.nhs.uk/)
- Health Technology Assessment (HTA) database (http://www.crd.york.ac.uk/CRDWeb/)
- Database of Abstracts of Reviews of Effects (DARE) (http://www.crd.york.ac.uk/CRDWeb/)
- National Patient Safety Agency (NPSA) (http://www.npsa.nhs.uk/)
- National Institute for Health and Care Excellence (NICE) (http://www.nice.org.uk/)
- Medicines & Healthcare products Regulatory Agency (MHRA) (http://www.mhra.gov.uk/)
- Rapid Review Panel (RRP): production evaluation statements (http://www.gov.uk/government/groups/rapid-review-panel/)

Search terms were developed and adapted to suit each database/website. Literature searches were run on 31/03/17. See Appendix 1 for an example search run in the MEDLINE database. Monthly Ovid auto-alerts were arranged to identify further studies published subsequent to this date.

Exclusion Criteria

Academic and grey literature was excluded from the review on the basis of the following exclusion criteria:

- Article was published before 2010 (a comprehensive systematic review on antimicrobial surfaces by Muller *et al.*[9] failed to identify any clinical studies published prior to 2010)
- Article was not published in the English language
- Article does not concern antimicrobial copper surfaces (off-topic)
- Article is an opinion piece, a literature review or a conference abstract
- Article does not present evidence compatible with the McDonald-Arduino evidentiary hierarchy[11]

- Article concerns a study that did not have an appropriate comparison in the form of a standard surface (e.g. plastic, wood)
- Article concerns a study that was not conducted in a clinical setting

Screening

There was a two-stage process for screening the items returned from the literature searches. In the first stage, the title/abstract was screened against the exclusion criteria by the lead reviewer. Items that were not excluded at the screening stage progressed to the second screening stage. In the second stage of the screening process, the full text of remaining items was screened against the exclusion criteria by the lead reviewer. Items that were not excluded at the second screening stage were included in the review.

Critical Appraisal

Critical appraisal of the studies included in this review and considered judgement of the evidence was carried out by the lead reviewer using the Scottish Intercollegiate Guidelines Network (SIGN) methodology.[12] The McDonald-Arduino evidentiary hierarchy was used as a framework for assessing the evidence.[11]

Results

The search found 2,742 articles. After the first stage of screening this was reduced to 35 articles, and after the second stage there were 18 articles, describing 14 studies, to critically appraise. The 14 studies included: two randomised controlled trials,[13-16] six non-randomised controlled trials,[17-23] one randomised cross-over study,[24] two non-randomised cross-over studies[25-27] and three before-and-after studies.[28-30] Eight of the studies concerned copper alloy environmental surfaces, two studies evaluated copper alloy equipment surfaces and two studies examined copper oxide-impregnated textiles. One study combined both copper alloy and copper oxide-impregnated composite environmental surfaces as an intervention. Another study combined copper oxide-impregnated composite environmental surfaces and copper oxide-impregnated textiles as a single intervention.

None of the studies were conducted in Scotland, although two were performed in the UK while the others were mainly confined to high-income countries (e.g. USA, Germany, Greece and Israel). A broad range of settings were involved, including intensive care units, outpatient infectious disease clinics, rural primary care walk-in clinics, head injury wards and geriatric wards. There was also significant variation in the placement of antimicrobial surfaces: from high-touch sites (e.g. bed rails) to low-touch sites (e.g. windowsills).

Studies were frequently funded or supported by organisations and manufacturers that may have a financial interest in the promotion of antimicrobial copper surfaces. These included: Cupron (two studies), the Copper Development Association (four studies), the German Copper Institute (one study), the Hellenic Copper Development Institute (one study), EOS Surfaces (one study) and GBC Metals, Olin Brass (one study). It is to some extent inevitable that the conduct of expensive, high-quality studies will depend upon financial support from these companies. However, this should be interpreted as a potential source of both reporting and publication bias, and consideration should be given to the role these organisations played in study design, data collection and analysis, manuscript writing, and the decision to submit the manuscript for publication.

Research Questions

1. Are antimicrobial copper surfaces currently in use in UK healthcare settings?

There is no mention of antimicrobial copper surfaces in the NHSScotland National Cleaning Services Specification,[31] the National Patient Safety Agency (NPSA) Revised Healthcare Cleaning Manual,[32] the Association of Healthcare Cleaning Professionals (AHCP) Revised Healthcare Cleaning Manual[33] or the NHSScotland National Infection Prevention and Control Manual.[34] This suggests that antimicrobial copper surfaces are not widely in use within UK healthcare settings.

2. What is the actual or proposed mechanism of action of antimicrobial copper surfaces?

Antimicrobial copper surfaces demonstrate biocidal activity via multiple mechanisms. Both metallic copper and copper oxide particles are known to release copper ions in the presence of humidity, including that of air.[35] Copper ions are able to alter the membrane integrity of micro-organisms via electrostatic forces, influencing membrane permeability.[35] Interaction of unbound copper cations with reactive oxygen species in Fenton-like reactions produces hydroxyl radicals, which are capable of damaging cellular constituents.[17] In addition, copper cations bind to thiol groups, e.g. of proteins, disrupting homeostatic balance of redox reactions and displacing cations of other transition metals from enzyme binding sites.[17] Finally, copper and copper oxide particles can kill micro-organisms by direct contact in the absence of humidity.[35] The USA Environmental Protection Agency (EPA) approved testing protocols for antimicrobial surfaces require 2 $\log_{10}$ (>99.9%) reduction in microbial bioburden within two hours of exposure.[35]

3. What is the procedure for using antimicrobial copper surfaces?

Dancer[5] states that there is a lack of consensus over which sites, surfaces and clinical equipment in healthcare settings would be the most efficacious should antimicrobial surfaces be applied. In the clinical trials identified by this review, high-touch surfaces were the most frequently targeted, including: bed rails, over-bed tables, intravenous stands, nurse call buttons, handles/levers, grab bars, light switches and nurse workstations. Yet, there was a broad variety of surfaces, equipment and textiles evaluated for antimicrobial copper surfaces.

4. What is the scientific evidence for effectiveness of antimicrobial copper surfaces for decontamination of the healthcare environment?

As detailed in the protocol, the McDonald-Arduino evidentiary hierarchy was used as a framework for assessing the evidence, and has been integrated into the critical appraisal process.[11]

Level V – Demonstration of reduced microbial pathogen acquisition (colonisation or infection) by patients via *non-outbreak* surveillance testing and clinical incidence:

Copper alloy surfaces

Von Dessauer *et al.*[18] and Schmidt *et al.*[19] undertook a non-randomised controlled trial (SIGN level 2+; tertiary hospital, Chile) across a paediatric intensive care unit and a paediatric intermediate care unit, allocating copper alloy-surfaced items to eight rooms, with another eight control rooms in alternating style. The items surfaced with copper alloy included bed rails and levers, cradles, intravenous poles, sink faucet handles and the surface of the nurses' workstation. In the control rooms, bed rails and faucet handles were fabricated from polypropylene and stainless steel, respectively. Over a 12-month period, the rate of healthcare-associated infections was measured according to standard definitions used by the National Surveillance System of the Ministry of Health of Chile. A sample size calculation was performed to identify a 50% reduction in infection rate with 85% statistical power and a two-sided type I error of 0.05. Of the intervention arm, 12.3% (32/261) developed an infection, whereas 13.0% (33/254) developed an infection in the control arm; however, the number of patient-days was higher in the intervention group. Crude analysis showed an infection rate of 10.6 versus 13.0 per 1,000 patient-days for copper- and non copper-exposed patients, respectively. There was also a non-significant relative risk reduction of 0.19 (90% confidence interval: -0.22–0.46). When potential confounding factors, such as age and number of days with an invasive catheter, were included as covariates in the regression model, the relative risk reduction continued to be non-significant. The pragmatic nature of the trial entailed that, where medical opinion became paramount, some patients were moved from intervention rooms to control rooms, or vice-versa.

Salgado *et al.*[13], Schmidt *et al.*[14] and Schmidt *et al.*[15] describe a randomised controlled trial (SIGN level 1+; tertiary and veterans hospitals, USA) carried out in eight medical intensive care units, randomly assigning patients to either one of eight intervention rooms with copper-surfaced items or one of eight control rooms with standard items. The items included: bed rails, over-bed tables, intravenous poles and the arms of visitors' chairs. Other items varied by hospital but included the nurses' call button, a computer mouse, a touch-screen monitor and the palm rest of a laptop. The copper alloys used were copper-nickel, brass, silicon bronze, naval brass, aluminium bronze, cartridge brass and phosphor bronze, with a copper content ranging from 60 to 99.99% – most frequently being copper-nickel with 90% copper). A sample size calculation estimated that 620

patients would be required for a study with 90% power (and a two-sided significance test of $p<0.05$) to detect a 50% difference in healthcare-associated infections and/or acquisition of methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant enterococci (VRE). Characteristics of the intervention and control groups were comparable at baseline. Over an 11-month follow-up period, the primary outcome measure was the incident rate of healthcare-associated infections and MRSA or VRE colonisation, using National Healthcare Safety Network definitions. Weekly samples were taken from six objects in each room to measure microbial bioburden over a period of 44 months (23 months before, and 21 months after, installation of the copper surfaces). In total, 7.5% (46/614) of patients developed healthcare-associated infections and 4.2% (26/614) became colonised with MRSA or VRE. The proportion developing infections was significantly lower among those assigned to intervention rooms (3.4% vs. 8.1%; $p=0.013$). Over the full 43-month period, copper surfaces were found to cause a significant reduction (83%; $p<0.0001$) in the average microbial bioburden found on the objects (465 colony-forming units [CFU] /100 cm^2) compared to the controls (2674 CFU/100 cm^2). To control for bias toward cleaning objects differently in intervention versus control rooms, a non-copper object was sampled in each room unbeknownst to participating study clinicians, environmental services or healthcare teams. The mean burden on this object was not significantly different between intervention and control rooms. Randomisation was not performed via a standard procedure, e.g. randomised number generation with masking using sealed opaque envelopes. Notably, there was a 64% reduction in microbial bioburden between the pre-intervention and intervention phases in the control rooms. The authors account for this with three explanations: (i) the presence of copper might have resulted in better cleaning by environmental services staff; (ii) the presence of copper might have resulted in an “antimicrobial halo” that limited the transfer of microbes between control rooms, as staff were common to both types of room; or (iii) variations in compliance with other infection control measures such as hand hygiene might account for the difference.

Copper oxide-impregnated surfaces

Sifri *et al.*[28] conducted a before-and-after study (SIGN level 3; community hospital, USA) in which 16% copper oxide-impregnated composite hard surfaces and woven linens were implemented in an intensive care unit and an intermediate medical care unit. In total, 204 beds were included in the baseline period, 72 beds in the intervention group and 84 beds in the control group. Over the 12-month baseline period 13,928 patients were hospitalised, whereas 4,704 and 5,257 patients were hospitalised in the intervention and control wings, respectively. The surfaces included sinks, vanities, patient room desks, computer stations, soiled utility room surfaces, nurse workstations, over-bed tray tables and bed rails. The linens featured patient gowns, pillowcases, fitted and flat sheets, washcloths, bath towels, bath blankets and thermal blankets. The primary outcome was the incident rate of hospital-onset infections, using National Healthcare Safety Network definitions,

due to multi-drug resistant organisms (MDROs; including MRSA, VRE, extended-spectrum beta-lactamase [ESBL]-producing organisms, *Acinetobacter* spp. and carbapenem-resistant *Enterobacteriaceae* [CRE]) or *Clostridium difficile*. Secondary outcomes included incident rates of MDRO infections, *C. difficile* infection (CDI), central line-associated bloodstream infection (CLABSI) and catheter-associated urinary tract infection (CAUTI). On completion of the 10-month follow-up period, the intervention wing had 78% (p=0.023) fewer infections due to MDROs or *C. difficile* and 83% (p=0.048) fewer cases of CDI. There were fewer infections due to MDROs but this difference was non-significant. No changes in rates of infection were observed in the control hospital wing. Notably, the admission types of the intervention wing and the control wing were markedly different: a majority of admissions to the intervention wing were surgical patients, whereas those hospitalised in the control wing were nearly exclusively medicine patients. Patients admitted to the control wing were more likely to have medical co-morbidities, more likely to have been admitted to the hospital in the previous 180 days and more likely to have a history of CDI in the previous six months.

Lazary *et al.*[30] completed a before-and-after study (SIGN level 3; hospital, Israel) of copper oxide-impregnated linens introduced into a head injury ward for long-term care patients, mainly confined to beds or wheelchairs. The linens included bed sheets, pillowcases, patient shirts and trousers, patient gowns, towels, under-pads and personnel robes. The six-month baseline period was followed by a six-month intervention period. Healthcare-associated infection rates were measured, in addition to which 40 copper oxide-impregnated bed sheets and 40 regular bed sheets were swabbed six or seven hours after use to determine the presence of micro-organisms. There was a 24% reduction in infection rate from 27.4 to 20.8 per 1,000 patient-days (p=0.046). Also, the copper oxide-impregnated bed sheets had a significantly lower bacterial titre for both Gram-positive bacteria (p=0.005) and Gram-negative bacteria (p=0.047). However, the authors note that the patients hospitalised in the head injury ward were highly susceptible to infection and the ward had a particularly high incidence of infections.

Level IV – Demonstration of reduced microbial pathogen acquisition (colonisation or infection) by patients via *outbreak* surveillance testing and clinical incidence:

No evidence identified (antimicrobial copper surfaces are not suitable for use in an outbreak management strategy).

Level III – Demonstration of in-use bioburden reduction that may be clinically relevant:

Copper oxide-impregnated surfaces

Marcus *et al.*[27] designed a non-randomised cross-over study (SIGN level 2+; long-term care hospital, Israel) for chronic ventilator-dependent patients over two wards. For three months, one

ward received copper oxide-impregnated textiles while the other received untreated textiles. After a one-month wash-out period, the wards were alternated for another three-month period. Staff members were masked to the treatment and control groups by colour-coding the textiles, which included linen, patients' clothes and towels. Healthcare-associated infection indicators were assessed: antibiotic treatment initiation events, fever days (axillary temperature >37.6°C), days of antibiotic treatment and antibiotic defined daily dose (DDD) per 1,000 hospitalisation days. There were reductions of 29.3% (p=0.002), 55.5% (p<0.0001), 23.0% (p<0.0001) and 27.5% (p<0.0001) in antibiotic treatment initiation events, fever days, days of antibiotic treatment and antibiotic DDD per 1,000 hospitalisation days, respectively.

Level II – Demonstration of in-use bioburden reduction effectiveness:

Copper alloy surfaces

Souli *et al.*[24] engaged in a randomised cross-over study (SIGN level 1; tertiary hospital, Greece) in an intensive care unit, endemic with multidrug-resistant organisms, where patients were randomly assigned to either a compartment with copper-coated surfaces or a compartment with non copper-coated surfaces. Those surfaces included: bed rails, bedside tables, intravenous stands, side-cart handles and antiseptic dispenser covers. Randomisation was not performed via a standard procedure, e.g. randomised number generation with masking using sealed opaque envelopes, and the study was supported by a grant from the Hellenic Copper Development Institute. For a six-month period, copper items were placed next to non-copper items in both compartments, after which copper and non-copper items were situated in different compartments for a further nine months. In total, 24 patients were admitted during the first phase (eight in copper beds) and 22 during the second phase (12 in copper beds). 685 samples were collected (347 and 338 during the first and second phases, respectively), of which 311 were derived from copper surfaces and 374 from non-copper surfaces. There was a significant reduction in the percentage of colonised surfaces (55.6% vs. 72.5%; p<0.0001) as well as the percentage colonised by Gram-negative bacteria (13.8% vs. 22.7%; p=0.003) or by enterococci (1.3% vs. 4.5%; p=0.014). In addition, there was a non-significant reduction in the percentage of surfaces colonised by multidrug-resistant Gram-negative bacteria.

Coppin *et al.*[23] describe a non-randomised controlled trial (SIGN level 2+; veterans hospital, USA) in which copper-alloyed over-bed tray tables in 11 occupied patient rooms were compared with standard tray tables in another 11 patient rooms, each sampled for aerobic bacterial colony count three times per day over a two-day period. By the second day, there was a statistically significant reduction (p=0.002) in microbial bioburden. The copper-alloyed tray tables were donated by EOS Surfaces under a cooperative research and development agreement. However, EOS Surfaces did

not participate in the study design; data collection, analysis or interpretation; writing the report; or in the decision to submit the manuscript for publication.

Hinsa-Leasure *et al.*[29] performed a before-and-after study (SIGN level 3; regional hospital, USA) where copper-nickel alloy surfaces, containing 90% copper by weight, were compared with plastic, metal and porcelain control surfaces in six single rooms and five double rooms. The items included: toilet levers, bath grab-bars, bathroom sinks, faucet handles, soap dispenser push-plates, door levers, door handles, alcohol gel dispenser push-plates, light switches, bedside tables, over-bed tables and intravenous poles. In addition, four objects outside the patient rooms were included: sinks and faucet handles in staff lounges, keyboards at work stations, and automatic door opener push-plates. Weekly samples from a total of 20 surfaces and objects were analysed for microbial bioburden over a 12-month period. After installation, there was a significant reduction (p<0.0001) in bacterial concentrations on the copper surfaces. The average concentration on copper surfaces was 117 CFU/100 cm^2, whereas the average concentration on standard surfaces was 6,172 CFU/100 cm^2. The copper components were provided at no cost through a cooperative arrangement between GBC Metals, Olin Brass. Different disinfectants were used on copper and control surfaces, purportedly as an attempt to maintain appearance of the copper surfaces and minimise bias as a consequence of appearance imperfections. The authors report that there was no difference in efficacy between the two disinfectants, although they do not show this data. All samples taken during the pre-intervention period were from occupied patient rooms, while samples taken following installation of copper components were taken from both occupied and unoccupied rooms. The medical centre had a low bed occupancy rate of 26.5%. However, when unoccupied rooms were excluded from the analysis, the difference between the copper and control samples was still significant.

Rai *et al.*[20] outline a non-randomised controlled trial (SIGN level 2+) conducted in an outpatient infectious disease clinic over a 15-week period, evaluating copper alloy (90% copper, 10% nickel) arm tops and trays on phlebotomy chairs against wooden and plastic composite controls. Samples were collected twice per week in the mid-afternoon, and demonstrated an 88% (p<0.0001) and 90% (p<0.0001) median reduction for the total aerobic bacteria of copper-surfaced trays and copper-surfaced arms, respectively. The authors reported an “antimicrobial halo” effect around the vicinity of the copper surfaces, in that the microbial bioburden associated with the wooden side arms of the copper-surfaced chair arms was significantly lower (by 70%) than the control surfaces.

Karpanen *et al.*[25] and Casey *et al.*[26] designed a non-randomised cross-over study (SIGN level 2+; tertiary hospital, UK) in an acute care medical ward. 14 frequently-touched items made of copper alloy or copper oxide-impregnated composite were installed, including door push-plates, door pull-handles, door lever handles, grab rails, toilet seats, toilet cistern levers, commode seats and arm pads, tap handles, sink waste traps, light switch rockers, light pull-toggles, socket rockers, dressing

trolleys and patient over-bed tables. The copper alloy composition varied from 58% to 99.9%, and was typically either copper-zinc or copper-tin alloys. The medical ward was engaged in the study for 12 weeks before and after cross-over, with a four-month wash-out period in between. Surfaces were assessed for total aerobic microbial counts and the presence of indicator organisms (e.g. VRE, MRSA, methicillin-sensitive *Staphylococcus aureus* [MSSA], *C. difficile* and coliforms) from samples taken once weekly. Eight of the 14 items demonstrated significantly lower (p<0.02) median CFU counts on the copper surfaces than on the standard materials. In addition, significantly fewer copper surfaces were contaminated with VRE, MSSA and coliforms, none of which showed evidence of resistance to copper. Comparing the two study periods, there were no statistically significant differences in hand hygiene compliance, staffing levels or bed occupancy levels.

Mikolay *et al.*[17] embarked on a non-randomised controlled trial (SIGN level 2+; hospital, Germany), comparing copper-alloy push-plates, doorknobs and light switches with aluminium and plastic control surfaces in an oncological/pneumological ward and a geriatric ward. Over 32 weeks (16 weeks in the Summer and 16 weeks in the Winter), microbiological sampling for aerobic, heterotrophic colony-forming units was taken once or twice a week, and found that the total number on copper surfaces was reduced by 37%. The reduction was highly significant for doorknobs, although the effect of push-plates and light switches was considerably lower.

Marais *et al.*[21] completed a non-randomised controlled trial (SIGN level 2+; rural primary clinic, South Africa) across a six-month period, forming a comparison between copper sheets (99.9% copper) fitted to desks, trolleys, cupboard tops and windowsills, and control surfaces of wood, stainless steel or ceramic tiles. Five high-touch surfaces were sampled every six weeks: two trolleys, one desk, one cupboard and one windowsill. There was a 71% reduction in overall mean total colony count for copper surfaces compared with control surfaces. Significantly lower mean total colony counts (p<0.001) for all copper surfaces were evident.

Schmidt *et al.*[22] conducted a non-randomised controlled trial (SIGN level 2+; tertiary hospital, USA) evaluating a copper-alloyed stethoscope in a paediatric emergency division and an adult medical intensive care unit. 21 healthcare providers, including physicians and nurse practitioners, received either a control stethoscope or a copper-alloyed stethoscope and were masked to the purpose of the trial. After a one week follow-up period, the mean aerobic colony counts from stethoscope surfaces fabricated from copper alloy were significantly lower (11.7 vs. 127.1 CFU/cm^2; p<0.00001) than the control equivalents.

Casey *et al.*[16] performed a randomised controlled trial (SIGN level 1+; tertiary hospital, UK) to assess whether copper-containing pens (85% copper) were more effective at reducing microbial bioburden than stainless steel pens. 50 nurses working on two critical care units were randomly

allocated either copper alloy or stainless steel pens using a computer-generated randomisation table. After a 12.5-hour shift, there was no significant difference (p=0.25) between the contamination rate of stainless steel pens (17/25) and copper alloy pens (12/25). Yet, there was an 87.3% reduction in median number of colony-forming units for copper alloy pens compared with stainless steel pens (p=0.04).

Copper oxide-impregnated surfaces

As described above, Karpanen *et al.*[25] and Casey *et al.*[26] combined both copper alloy and copper oxide-impregnated composite environmental surfaces as an intervention in their study.

Level I – Laboratory demonstration of bioburden reduction efficacy:

No evidence identified (laboratory studies were excluded from this review as low-quality evidence that would not contribute to the formulation of graded recommendations).

5. Are there any safety considerations associated with using antimicrobial copper surfaces in the healthcare setting?

Lazary *et al.*[30] claim that copper oxide-impregnated products do not cause skin irritation, sensitisation or any other adverse reactions to both intact and broken skin. Similarly, Marcus *et al.*[27] retrospectively report no adverse reactions or skin irritation in their cross-over study of 58 ventilator-dependent patients exposed to copper oxide-impregnated textiles. Sifri *et al.*[28] prospectively assessed 4,704 patients exposed to copper oxide-impregnated textiles for the development of potential allergic reactions to copper. Those who developed possible skin hypersensitivity reactions due to the products were referred to dermatology for assessment. Of the ten patients who developed skin rashes, nine were found to have an alternative aetiology for their rash, while one was discharged before the reaction could be assessed.

6. Are there any practical or logistical considerations associated with using antimicrobial copper surfaces in the healthcare setting?

Copper alloy surfaces are prone to discolouration and the formation of verdigris through oxidation, which could potentially reduce the antimicrobial effectiveness of surfaces over time. Hinsa-Leasure *et al.*[29] found that copper alloy surfaces on sinks and over-bed tables were particularly liable to staining and had to be polished bimonthly to maintain their finish, necessitating additional labour for the cleaning staff. Some authors have expressed doubt over the durability and in-use biocidal activity of antimicrobial surfaces following prolonged surface wear.[5] In the case of copper oxide-impregnated composite surfaces, copper oxide particles are distributed throughout the material, enabling submerged particles to become exposed on surface loss.[35] Lazary *et al.*[30] report that

copper oxide-impregnated linen is able to be laundered in the same laundry as regular linen, under identical conditions. Since copper oxide is a non-soluble form of copper, the copper oxide particles do not wash out during laundry and the particles remain active for the entire life-span of the products. Microbial resistance to copper is a theoretical concern for infection prevention purposes; however, it is claimed that the development of resistance is unlikely due to copper exerting antimicrobial activity through multiple mechanisms.[35]

7. What costs are associated with using antimicrobial copper surfaces in the healthcare setting?

There was only one identified study that evaluated the cost-effectiveness of antimicrobial copper surfaces. Michels *et al.*[36] estimate that, on the basis of copper alloy environmental surfaces costing an additional US$52,000 over standard surfaces for six sites in three intensive care units, it would take 37 to 44 days to recover the cost of installation. This assumes that the average annual direct cost to treat a healthcare-associated infection ranges from US$28,400 to US$33,800.

8. Have antimicrobial copper surfaces been assessed by the Rapid Review Panel?

The Rapid Review Panel (RRP) is a panel of UK experts established by the Department of Health to review new technologies with the potential to aid in the prevention and control of healthcare-associated infections. The RRP has reviewed a number of antimicrobial copper surface products between 2005 and 2013:

- 2005: Copper alloy coating for floor and walls (Hi-bond AV)
- 2008: Cupron healthcare fabrics (Cupron Inc.)
- 2013: Copper infused pyjamas (Copper Clothing Ltd.)

The copper alloy coating for floor and walls (Hi-bond AV) and Cupron healthcare fabrics (Cupron Inc.) were both assigned a grade 3 recommendation:
"A potentially useful new concept but insufficiently validated; more research and development is required before it is ready for evaluation in practice."

The copper infused pyjamas (Copper Clothing Ltd.) were assigned a grade 7 recommendation:
"The product is not sufficiently related to infection control procedures to merit consideration by the panel."

No copper oxide-impregnated composite surfaces have been reviewed by the RRP.

Discussion

This systematic review incorporated the results of 18 articles (14 studies) into its findings. The quality of included studies was predominantly **SIGN level 2+ (moderate-quality)**; however, there were two studies classified as **SIGN level 1+ (high-quality)**. The study design of choice varied from randomised controlled trials to before-and-after studies. They primarily concerned in-use bioburden reduction **(McDonald-Arduino level III)** but sometimes demonstrated a reduction in microbial pathogen acquisition in a non-outbreak setting **(McDonald-Arduino level V)**. The findings identified by the review were used to develop the following recommendations for clinical practice.

Recommendations for Clinical Practice

This review makes the following recommendations based on an assessment of the extant scientific literature on antimicrobial copper surfaces:

- Copper alloy environmental and equipment surfaces may be considered for high-touch sites (e.g. bed rails) as an additional measure to supplement existing procedures for routine cleaning but does not replace the requirement for routine cleaning to be performed.
  (Grade C)
- The additional expenditure required for copper alloy surfaces should be considered before implementation.
  (Good Practice Point)
- The procedure for cleaning, disinfection and maintenance (e.g. polishing) of copper alloy surfaces should be considered before implementation.
  (Good Practice Point)
- A protocol should be implemented to ensure possible adverse effects of copper alloy surfaces (e.g. allergic reaction) are reported to Occupational Health services.
  (Good Practice Point)
- Manufacturers' advice on the durability of copper alloy surfaces should be requested to assess whether copper alloy surfaces will require more frequent replacement compared to standard surfaces.
  (Good Practice Point)
- There is insufficient evidence to support the use of copper oxide-impregnated surfaces and textiles.

Implications for Research

The review identified several gaps in the literature in relation to antimicrobial copper surfaces. Many of the relevant studies identified could not be included in this review as they did not make a suitable comparison in the form of standard surfaces. Further studies assessing the clinical effectiveness of antimicrobial copper surfaces should include suitable comparison groups to enable the results to be transferable to clinical practice within NHSScotland.

It was also notable that several of the studies combined multiple antimicrobial copper surface interventions in a variety of sites. Ideally, studies that evaluate the effectiveness of antimicrobial copper surfaces should minimise this variety in order to reduce the risk of confounding factors producing a spurious result.

Finally, very few studies thus far have evaluated the cost-effectiveness of antimicrobial copper surfaces. It can be seen from these studies that a comprehensive cost-effectiveness analysis for the use of antimicrobial copper surfaces in NHSScotland would be timely.

Conclusion

The contribution of environmental contamination in healthcare settings to the cross-transmission of nosocomial infections has been thoroughly demonstrated: firstly, by interventional studies in which improved surface cleaning has reduced the incidence of healthcare-associated infections[1]; and secondly, by observational studies which have evidenced the higher risk of pathogen acquisition in patients admitted to rooms where the prior occupant was known to be infected or colonised.[2]

Antimicrobial copper surfaces provide an example of a novel technology that may supplement standard cleaning practices and potentially further reduce the transmission of nosocomial pathogens. This review aimed to provide a concise evidence summary outlining: the evidence of effectiveness for, the practical and safety considerations of, and the costs associated with, the use of antimicrobial copper surfaces.

The review found that there was a larger quantity of evidence supporting the use of copper alloy environmental surfaces, although this evidence was typically of low to moderate quality. A considerably smaller volume of evidence supported the use of copper alloy equipment surfaces, copper oxide-impregnated composite environmental surfaces and copper oxide-impregnated textiles.

Antimicrobial copper surfaces appear to pose little risk of skin irritation, sensitisation or adverse events (e.g. allergic reactions). Similarly, the development of microbial resistance to copper seems to be a rare event and largely a theoretical concern. There is a lack of consensus over which sites should be targeted for environmental surfaces, although most clinical trials have evaluated a combination of high-touch sites, e.g. bed rails, intravenous stands and over-bed tables. Copper alloy environmental surfaces are prone to discolouration and require regular polishing to maintain their surface integrity. Copper oxide particles are non-soluble and, therefore, it is suitable for these textiles to be laundered alongside standard linens. Unfortunately, there has been little in the way of cost-effectiveness evaluation for antimicrobial copper surfaces in the UK.

The Rapid Review Panel (RRP) has evaluated three antimicrobial copper surface products: one copper alloy environmental surface product and two copper oxide-impregnated textile products. The copper alloy product and one of the copper oxide-impregnated textile products were assigned a recommendation grade of 3, indicating that further research is required before they are ready for evaluation in practice.

Appendix 1: MEDLINE Search

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)

Search date

31/03/2017

1 (all "OR")		2 (all "OR")
Copper/ copper.mp.	AND	Infection Control/ Cross Infection/ infection*.mp. antimicrobial.mp.

Limits

English language

Publication Year 2010 – Current

Results: 1,229

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