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 and Silver Solutions

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Contents

Topic

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

Background

There is strong scientific evidence that contaminated environmental surfaces contribute to the transmission of pathogens in healthcare settings. As such, environmental decontamination has an important role to play in the prevention and control of healthcare associated infection (HAI).[1-4]

Appendix 7 within the National Infection Prevention and Control (IP&C) Manual[1] for NHSScotland outlines the recommendations for the decontamination of reusable non-invasive care equipment.

The National Infection Prevention and Control (IP&C) Manual[1] for NHSScotland currently outlines the following recommendations on agents for **routine environmental decontamination** within the Standard Infection Control Precautions (SICPs chapter 1), which are the basic measures intended to be applied by all staff, in all care settings, at all times, for all patients:

> *A fresh solution of general purpose neutral detergent in warm water is recommended for routine cleaning. This should be changed when dirty or at 15 minutes intervals or when changing tasks.*
>
> *Routine disinfection of the environment is not recommended. However, 1,000ppm available chlorine should be used routinely on sanitary fittings.*[1]

The National IP&C Manual also makes recommendations on agents for environmental decontamination in the chapter outlining Transmission Based Precautions (TBPs), which are intended to be applied when caring for patients who are known to have or are suspected of having an infection.[1] The following recommendations are made in relation to **routine environmental decontamination** when applying TBPs:

> *Patient isolation/cohort rooms/area must be decontaminated **at least daily** using either:*
>
> - *a combined detergent/disinfectant solution at a dilution of 1,000 parts per million available chlorine (ppm available chlorine (av.cl.)); or*
> - *a general purpose neutral detergent in a solution of warm water followed by disinfection solution of 1,000 ppm av.cl.*[1]

In addition, the following recommendations are made in relation to **terminal cleaning** when applying TBPs:

The room should be decontaminated using either:

- *a combined detergent disinfectant solution at a dilution (1,000 ppm av.cl.); or*
- *a general purpose neutral detergent in a solution of warm water followed by disinfection solution of 1,000 ppm av.cl.*[1]

Chlorine releasing agents are recommended for decontamination of sanitary fittings and for environmental decontamination under TBPs based on substantial evidence of their effectiveness against pathogens of HAI significance including norovirus and *Clostridium difficile.*[5]

However, several issues and problems associated with the use of chlorine releasing agents such as corrosion of equipment and furnishings, release of toxic gas and respiratory irritation, has encouraged interest in alternative methods of decontamination.[6] There are numerous other existing technologies such as steam cleaners, and a growing list of novel technologies becoming available for decontamination of the healthcare environment.[7-9] Currently, these technologies have not been sufficiently assessed to advocate their use for environmental decontamination in NHSScotland. A review is required to assess the effectiveness of technologies of interest to the infection control community, to consider any practical and safety considerations related to their use, and to explore the associated costs.

Aim

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

Objectives

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

Research questions

The following research questions will be addressed for antimicrobial copper and silver:

1. Are antimicrobial copper and silver currently in use in UK healthcare settings?
2. What is the actual or proposed mechanism of action of antimicrobial copper and silver?
3. What is the procedure for using antimicrobial copper and silver?
4. What is the scientific evidence for effectiveness of antimicrobial copper and silver for decontamination of the healthcare environment?
5. Are there any safety considerations associated with using antimicrobial copper and silver in the healthcare setting?
6. Are there any practical or logistical considerations associated with using antimicrobial copper and silver in the healthcare setting?
7. What costs are associated with using antimicrobial copper and silver in the healthcare setting?
8. Have antimicrobial copper and silver 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 (http://www.npsa.nhs.uk/)
- NICE (http://www.nice.org.uk/)
- MHRA (http://www.mhra.gov.uk/)
- Rapid Review Panel Reports Archive (http://www.hpa.org.uk/ProductsServices/MicrobiologyPathology/RapidReviewPanel/ReportsArchive/)

Search terms were developed and adapted to suit each database/website. Literature searches were run on 10/12/15. See Appendix 1 for an example search run in the Medline database.

Exclusion criteria

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

- Item was published before 2005
- Item was not in English
- Item does not concern antimicrobial copper and silver (off topic)
- Item was an opinion piece or non-systematic review
- Item does not present evidence compatible with the McDonald-Arduino evidentiary hierarchy[10]
- Study did not have a comparison in the form of a standard cleaning methods

N.B. If the study has used rigorous methodology and includes comparisons in the form of positive and negative controls or has been conducted as a before and after study it may be considered for inclusion. If these studies are included, then these limitations must be highlighted in the report.

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 SIGN methodology.[11] The McDonald-Arduino evidentiary hierarchy[10] was used as the framework for assessing the evidence, and was integrated into the critical appraisal process.

Results

Antimicrobial copper

The search strategy found 357 articles. Following the first and second stage screening, five articles were critically appraised. Three of these were before and after studies and the remaining two were laboratory based studies. All studies constituted **level 3 evidence** (experimental or observational analytic studies).

Although a considerable number of articles were found on the topic of antimicrobial copper, the majority of these related to antimicrobial surfaces/materials. Since antimicrobial surfaces cannot be utilised as a method of decontamination without use of other cleaning interventions, these articles were excluded during second stage screening.

All identified studies for inclusion assessed the antimicrobial effect of copper-based inorganic biocidal formulations. The laboratory based studies investigated a number of HAI causing bacteria, including *Staphylococcus aureus*, *Acinetobacter baumannii*, vancomycin resistant enterococci (VRE), *Legionella pneumophilia* and *Clostridium difficile.* The before and after studies considered bacterial Total Viable Counts (TVCs) only.

- One study[12] demonstrated that three copper biocidal solutions were *more effective* than the respective individual components within each solution minus copper (considered as negative controls) at inhibiting various HAI associated bacteria.
- One study[13] demonstrated that various concentrations of two copper biocidal solutions were *as effective* as comparable concentrations of a quaternary ammonium compound (QAC) based cleaning solution, at inhibiting meticillin-resistant *S. aureus* (MRSA).
- Three studies[14-16] demonstrated that use of ultra-microfibre (UMF) cloths and mops with a copper biocide solution was *more effective* than use of UMF cloths with water, at reducing TVCs in hospital environments. In contrast, one study[12] found that use of ultra-microfibre cloths, with three different copper biocide solutions was *as effective* as use of a UMF cloth and water at reducing bacterial numbers on laminate surfaces. It should be noted that the first three studies used copper biocide solutions at 300 ppm, in comparison to 150 ppm used in the fourth study.
- One study[14] demonstrated that use of UMF cloths and mops with a copper biocide solution at 300 ppm (contact time not stated) was *more effective* than use of UMF cloths and mops with a Hospec detergent solution (concentration not specified), in reducing TVCs in hospital environments.

- One study[15] demonstrated that use of UMF cloths and mops with a copper biocide solution at 300 ppm (contact time not stated) was *as effective* as use of UMF cloths and mops with an Actichlor Plus solution at 1000 ppm of available chlorine, at reducing TVCs in hospital environments.

Antimicrobial silver

The search strategy found 366 articles. Following the first and second stage screening, three articles were critically appraised. All of these were laboratory based studies and constituted **level 3 evidence.**

As with antimicrobial copper, the majority of articles on antimicrobial silver related to antimicrobial surfaces/materials and were excluded at second stage screening.

A number of articles on silver based solutions were also excluded due to a lack of suitable comparators within each study. All identified studies for inclusion assessed the antibacterial effect of silver nanoparticle solutions. Studies investigated the effect of these solutions on a variety of HAI causing bacteria including *S. aureus, Escherichia coli* and *Pseudomonas aeruginosa.*

- Two studies[17;18] demonstrated that silver nanoparticle solutions were *more effective* than the respective components within each solution minus silver (considered as negative controls), at inhibiting various HAI associated bacteria.
- One study[18] demonstrated that a silver nanoparticle solution (concentration not specified) was *more effective* than a 5% chlorine based disinfectant, at inhibiting *Vibrio cholerae* (a bacterium not associated with HAI in the UK).
- One study[19] demonstrated that silver nanoparticle solutions were *less effective* than comparable concentrations of phenol or sodium hypochlorite based disinfectant solutions at short contact times (≤ 10 minutes). At an increased contact time of ≥ 2 hours, silver nanoparticle solutions were *more effective* than comparable concentrations of phenol or sodium hypochlorite based disinfectant solutions.

All studies relating to antimicrobial silver took place outside of the UK. Studies relating to antimicrobial copper were conducted in the UK, other than one study which took place in the USA. The majority of studies relating to copper biocides were either funded by the product manufacturers or a number of the study authors were employed by the manufacturing company. It is worth considering this when assessing the results.

Research Questions

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

There is no mention of antimicrobial copper and silver in the Health Facilities Scotland (HFS) National Cleaning Services Specification,[20] the National Patient Safety Agency (NPSA) Revised Healthcare Cleaning Manual,[21] the Association of Healthcare Cleaning Professionals (AHCP) Revised Healthcare Cleaning Manual,[22] the NHSScotland National Infection Prevention and Control Manual[1] or the HPS Standard Infection Control Precautions Literature Review of Routine Cleaning in the Environment in the Hospital Setting.[23]

The Health and Safety Executive (HSE) issues Essential Use Authorisations for UK biocidal products under the Biocidal Products and Chemicals Regulations 2013/Biocidal Products. These currently exist for various copper based disinfectants used to control *Legionella* spp. in drinking and bathing waters as well as for the prevention of pipework biofouling of offshore oil and gas platforms and ships. Authorisation is essential for placing products on the UK market. There are no listed silver based biocidal products.

Various copper and silver based compounds are also currently under evaluation as potential disinfectants under the European Chemicals Agency (ECHA) Biocidal Product Regulation (BPR, Regulation (EU) 528/2012).

Although copper and silver containing solutions are not currently used for decontamination in UK healthcare settings, various other copper and silver containing products are routinely utilised due to their demonstrated antimicrobial effects. These include: copper alloys as a coating for various high touch surfaces,[24;25] silver ion treated products (doors, light switches, bins, blinds, etc.),[26;27] silver-coated catheters[28] and various silver impregnated wound care products.[29]

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

<u>Antimicrobial copper</u>

Various mechanisms have been suggested for the antibacterial activity of copper. There is general consensus that one of the key mechanisms involves the ability of copper to change its oxidation state between Cu(I) and Cu(II), allowing the generation of reactive oxygen species (ROS), including hydroxyl radicals and superoxide anions. These ROS are considered to cause oxidative damage to bacterial lipids and proteins, leading to inhibition/killing of various bacterial species.[12;30-32] A complete reduction in *C. difficile* spores has also been demonstrated following a 24 hour exposure to copper alloy surfaces containing > 70% pure copper.[33]

One study specifically discussed the antibacterial properties of copper based liquid biocides. The biocides were found to be effective at concentrations > 20 ppm, against a variety of HAI causing bacteria, in both stationary and exponential growth phases, suggesting a direct bacterial cytotoxic effect.[12]

Broad-spectrum virucidal activity is considered to be attributed to the ability of copper to bind to and disorder viral nucleic acids.[34] A recent study also reported that viral RNA destruction was proportional to the percentage of copper within a surface.[35] In addition to the demonstrated effect against nucleic acids, copper related destruction of viral capsids has also been reported.[36]

Antimicrobial silver

Various silver containing applications have been shown to be effective against bacteria, viruses, fungi and protozoa.[37;38] Although a number of mechanisms of action have been proposed, the primary mechanism is considered to involve the interaction of silver ions with various cellular proteins, leading to the inhibition of respiration and electron transfer in bacteria, fungi and protozoa.[29;37;39] The antiviral effect against a number of viruses is considered to be due to the binding of silver ions to viral surface proteins, leading to viral inactivation.[38]

The use of nano-materials has recently emerged as a method for the development of novel antimicrobials, with silver nanoparticles in particular being commonly utilised. The term ‘nano’ is used to indicate a dimension of 10^{-9} m.[17;38]

Liquid based silver formulations; also referred to as colloidal silver, are typically made up of silver nanoparticles and/or silver ions suspended in liquid form. Silver nanoparticles are generally non-reactive, requiring an oxidation reaction to occur upon contact with water, bodily fluids or other exudates, for the release of silver ions to occur. Silver ions exist in Ag+, Ag++ and Ag+++ forms, with only Ag+ considered to be reactive, leading to the broad-spectrum antimicrobial properties associated with silver. The majority of technologies utilising silver nanoparticles work by the gradual release of silver ions.[29;38;40-42]

Various methods for the synthesis of silver nanoparticles have been reported; using chemical, physical, photochemical and biological routes.[38;40] Antimicrobial properties of silver nanoparticles are considered to be dependent on the size, structure and synthesis conditions, with a smaller size being associated with increased antimicrobial activity.[19;38]

3. What is the procedure for using antimicrobial copper and silver?

Due to limited information being available on the use of antimicrobial copper and silver as disinfectants, instructions relating to the procedure of use are also limited.

Antimicrobial copper

A number of studies[14-16] outline once daily use of copper biocidal solutions as a method of decontaminating the healthcare environment, at a concentration of 300 ppm. Copper biocidal solutions were used with UMF cloths/mops within all studies.

Antimicrobial silver

No studies outlining the procedure for using colloidal nanosilver as a disinfectant were identified.

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

As detailed in the protocol, the McDonald-Arduino evidentiary hierarchy[10] was used as the framework for assessing the evidence, and has been integrated into the critical appraisal process.

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

No evidence identified.

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

No evidence identified.

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

No evidence identified.

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

Antimicrobial copper

A before and after study[16] conducted within a UK Trust assessed the antimicrobial effect of a copper biocidal solution (CuWB50), at a concentration of 300 ppm. A study by Gant *et al*.,[12] (outlined in the 'laboratory demonstration of bioburden reduction efficiency' section below) first described use of copper biocidal solutions which are formulated from copper sulphate as the source of copper. The CuWB50 biocidal solution was used in combination with UMF cloths/mops, in comparison to UMF cloths/mops with water. Pre-cleaning bacterial contamination was assessed by measuring total viable counts (TVCs) for 10 surfaces per ward (four wards in total). Microbiological sampling was undertaken three times a week, 1 hour prior to cleaning and 1 and 4 hours post cleaning, at the designated sampling sites. The UMF + CuWB50 TVC values were significantly lower than UMF + water TVCs at all time points over the 7 week trial period.

Collectively, cleaning with UMF + water reduced TVC on the test surfaces by 30%, whereas cleaning with TVC + CuWB50 reduced TVC by 56%. The authors state that a residual antimicrobial effect following cleaning with UMF + CuWB50 was demonstrated based on significantly lower TVC values found at the pre-cleaning time point in this group only (i.e. the 1 hour pre-cleaning time point equates to 23 hours post cleaning). This residual effect was not observed when switching from cleaning the same surfaces with UMF + CuWB50 to UMF + water. The cross-over design of the study (cleaning two wards with one intervention for one period of time followed by the other intervention for an equal period of time and vice versa) aimed to eliminate time- and place-dependent confounding variables.

A before and after study[14] conducted within a UK Trust also assessed the antimicrobial effect of a copper biocidal solution (CuWB50), at a concentration of 300 ppm. The solution was used in combination with UMF cloths/mops, in comparison to UMF cloths/mops used with Hospec detergent and UMF cloths/mops with water. A major limitation of the study was that no information was provided regarding the in-use dilution of detergent (manufacturer instructions state use at 1000 ppm.) An ATP bioluminescence assay was also utilised to measure cleaning efficacy. As with the study by Hamilton *et al*.,[16] TVCs were measured from 10 ward surfaces (1 hour pre-cleaning and 1 hour post cleaning within this study), using a cross-over study design. Pre-cleaning median TVC levels were similar for all three cleaning methods, although a slight reduction was seen with UMF + CuWB50 (considered to be due to a residual effect from cleaning 23 hours prior). The 1 hour post-cleaning median TVC levels were lower when using UMF + CuWB50 (resulting in a 75% bacterial reduction on surfaces), compared with UMF + detergent or UMF + water (45% and 35% reductions, respectively). In addition, post-cleaning ATP levels were significantly lower with UMF + CuWB50 only.

A before and after study[15] conducted within a UK Trust also assessed the antimicrobial effect of a copper biocidal solution (CuWB50), at a concentration of 300 ppm. The solution was used in combination with UMF cloths/mops, in comparison to UMF cloths/mops used with Actichlor Plus at 1000 ppm of available chlorine and UMF cloths/mops with water. An ATP bioluminescence assay was also utilised to measure cleaning efficacy. Furthermore, bacterial contamination of UMF cloths + water and UMF cloths + CuWB50 were also assessed. As with the studies by Hamilton *et al*.,[16] and Hall *et al*.,[14] TVCs were measured from 10 ward surfaces (1 hour pre-cleaning and 1 hour post cleaning within this study), using a cross-over study design. All three cleaning methods resulted in significant reductions in median TVCs. There was no significant difference in the median TVC reduction (approximately 70% for both methods) with UMF + CuWB50 and UMF + actichlor cleaning, suggesting both methods are comparable. In addition, UMF cloths impregnated with CuWB50 contained significantly fewer viable bacteria than UMF + water at both three hours and 24 hours after cleaning.

Level I – Laboratory demonstration of bioburden reduction efficacy:

<u>Antimicrobial copper</u>

A laboratory based study[12] assessed the antibacterial effect of three copper biocidal solutions (CuAL42, CuPC33 and CuWB50) against MRSA, VRE, *A. baumannii*, *L. pnuemophilia* and *C. difficile* in liquid culture. In addition, individual components within each solution were also evaluated to determine whether complete biocidal solutions, rather than their respective components, exhibited an antibacterial effect. Biocidal solutions were composed of copper sulphate and one of three inorganic binder components AL42, PC33, WB50 (individually considered as negative controls within the study). All three biocidal solutions were bactericidal at a concentration of 1 ppm, achieving a 2-3 $\log_{10}$ reduction in colony forming units (CFU) of all tested species after 120 minutes. In addition, time kill experiments using MRSA and *A. baumannii* and biocidal formulations at 150 ppm, resulted in a complete or near complete bactericidal effect after 60 minutes, other than for CuPC33 which required 120 minutes to be completely bactericidal against MRSA. Copper sulphate and the three inorganic binders alone had little or no effect on CFU. A secondary aim of the study was to assess the use of copper biocidal solutions at 150 ppm with UMF cloths, for cleaning of laminate surfaces pre-inoculated with bacteria. UMF cloths soaked in water and those soaked in biocidal solutions removed equivalent amounts of bacteria, although testing of the cloth solution after 16 hours resulted in no viable bacterial counts from UMF cloths with copper biocidal solutions only, suggesting a residual antibacterial effect.

A laboratory based study[13] assessed the antibacterial effect of two copper biocidal solutions (CuAL42 and CuWB50), in comparison to benzalkonium chloride (a QAC), against 169 hypervirulent isolates of MRSA 300. Bacterial growth was fully inhibited at concentrations of ≤ 18.75 ppm (with one isolate requiring 37.5 ppm of CuWB50), while the required active concentrations of the QAC disinfectant were more inconsistent; ranging from 0.1-40 ppm. Time kill experiments using a concentration of 150 ppm resulted in a complete or near complete bactericidal effect after 60 minutes for CuAL42 and 90 minutes for CuWB50, in comparison to 60 minutes for the QAC disinfectant. An increase in concentration to 300 ppm reduced the time required for a complete or near complete bactericidal effect to 30 and 45 minutes for CuAL42 and CuWB50, respectively, in comparison to < 15 minutes for the QAC disinfectant.

<u>Antimicrobial silver</u>

A laboratory based study[17] assessed the antibacterial effect of a silver nanoparticle solution (NP), a concentrated silver nanoparticle solution (CNP) and a silver nanoparticle solution containing additional sodium chloride (NPNaCl). Agar diffusion tests were used to evaluate various bacterial species, including common HAI causing organisms (*S. aureus*, *E. coli* and *P. aeruginosa).* The antimicrobial effect against spore forming organisms was also assessed by testing solutions against *B. cereus*. Individual components within each solution were also evaluated as negative controls, to determine whether complete biocidal solutions, rather than their respective components, exhibited an antibacterial effect. Although negative controls were found to inhibit bacteria; this was to a significantly lesser extent than the nanoparticle solutions. CNP resulted in a significantly higher antimicrobial effect for most bacteria, as compared to the other solutions. This was considered to be due to CNP containing the highest concentration of silver nanoparticles (60 ppm), as compared to 6 ppm in NP and NPNaCl. CNP was also the most effective in removing/killing *P. aeruginosa* (only organism tested) from stainless steel surfaces after both 30 and 60 minute contact times.

A laboratory based study[19] assessed the antibacterial effect of a silver nanoparticle (NP) solution against *S. aureus* and *E. coli* using agar and liquid culture based assays. A phenol and hypochlorite disinfectant were used as comparators. The NP solution exhibited full antibacterial activity after 120 minutes at 10 ppm, while the phenol and hypochlorite disinfectants demonstrated full antibacterial activity after 10 minutes at concentrations > 16 ppm.

A laboratory based study[18] assessed the antibacterial effect of a silver nanoparticle (NP) solution and the same solution minus the silver component (negative control), against *E. coli* and *V. cholera* using agar diffusion testing. NP concentrations of 3 and 6 ppm were found to be inhibitory against *E. coli* and *V. cholera*, respectively. The negative control solution resulted in no inhibition. In addition, a 5% chlorine based disinfectant was used as a comparator for fluorescence microscopy studies aimed at observing a bactericidal effect post treatment. A bactericidal effect by use of NP solution was observed after 15 minutes in comparison to the chlorine based disinfectant which required 60 minutes to result in an observed reduction in bacteria. This study was primarily aimed at the water industry and tested a chlorine based disinfectant used primarily within this industry. In addition, testing of *V. cholera* is not applicable for UK healthcare settings. Another major limitation was that the study did not specify the concentration of NP solution used when comparing this to the chlorine based disinfectant, meaning that no true comparisons could be made. This study only acts to provide further evidence to specify antibacterial concentrations of NP solutions.

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

Antimicrobial copper

Copper is considered to have a low level toxicity and is therefore selected for widespread use within the healthcare industry.[43;44] Specifically, copper sulphate containing solutions were found to be selectively toxic to bacterial cells but not human cells *in vitro*, at concentrations up to 1000ppm.[12]

Reports of severe adverse reactions related to contact with copper are very rare and are generally associated with systemic exposure only. This is typically attributed to copper used as part of intrauterine devices or prosthetic materials. Adverse reactions related to skin contact are also rare. These are typically mild and include contact urticaria and dermatitis.[44]

Antimicrobial silver

Similarly to copper, silver has also been used for decades within the healthcare industry, as toxicity associated with its use is considered to be insignificant compared to its attributed benefits.[29;40]

In a recently conducted study within an NHS Trust, the antimicrobial effect of silver coated surfaces was assessed. The authors concluded that there were no reports of contact allergy or any other adverse effects in outpatients attending the treated study unit.[45]

In terms of silver nanoparticles, toxicity in animal models has been demonstrated, although the majority of studies considered inhalation/ingestion over long-exposure times (< 28 days). It is considered that detrimental effects would be unlikely to occur with short-term use of silver nanoparticle based disinfectants, especially if gloves are worn.[40]

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

Antimicrobial copper

An observational study on the use of a copper based biocide (alongside UMF cloths/mops) for disinfection of the healthcare environment, obtained staff feedback relating to the utility of this method in practice. Responses indicated that this method was preferred to use of a chlorine based disinfectant, due to the option of supplying the biocide in a ready-to-use formulation, in addition to a perceived increased cleaning ability.[15]

In addition, the HPS literature review on microfibre for the decontamination of the healthcare environment,[46] states that standard disinfectants are typically not considered to be compatible with microfibre, unless specified by the manufacturer. The research group working on the topic of copper based biocides therefore concludes that use of these biocides with microfibre may have utility for standard cleaning of the healthcare environment.[14;15] In addition, a further study concluded that copper based biocides alone may be useful for the disinfection of hospital surfaces, due to a demonstrated antibacterial effect and lack of corrosive properties to metal surfaces.[13]

Antimicrobial silver

Due to early difficulties in generating stable and efficient metal nanoparticles, the application of these as a technology in the healthcare field has been limited to date.[19] Silver nanoparticle solutions have received much interest in the past decade, especially for surface disinfection applications. Other than antimicrobial properties, demonstrated benefits of use in colloidal form include a residual antimicrobial effect and long-term stability.[18;40]

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

Due to the majority of studies on liquid based copper and silver products being preliminary in design, cost considerations were not discussed.

8. Has antimicrobial copper and silver 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 technologies with potential to help in the prevention and control of HAI.[47]

A number of copper and silver containing products have been assessed by the RRP however none of these relate to decontamination of the environment/equipment and have therefore not been included.

Discussion

Based on an assessment of the extant professional literature: 5 publications relating to antimicrobial copper and 3 relating to antimicrobial silver were identified, all of which constituted **level 3 evidence.**

The evidence identified as part of this literature review was very limited. There was insufficient evidence to formulate any conclusions regarding the effectiveness antimicrobial silver as a disinfectant, although all evaluated studies were in agreement that tested nanosilver solutions were antibacterial at low concentrations (< 60 ppm).

Similarly, there was consensus between studies evaluating antimicrobial copper. All studies tested the same copper biocides which were shown to exhibit a direct bactericidal effect against various HAI causing bacteria, at concentrations < 20 ppm. Before and after studies conducted in UK healthcare settings also demonstrated that biocidal solutions at a concentration of 300 ppm were also shown to increase the efficacy of cleaning using UMF cloths/mops to a greater level than cleaning with a detergent and to a similar level to cleaning with a disinfectant recommended for decontamination within NHSScotland. Due to evidence indicating that copper biocide solutions are effective under laboratory conditions and in practice, there may be scope for assessing the utility of these within healthcare settings.

Other than the demonstrated direct antibacterial effects, biocidal copper solutions were found to exhibit a residual antibacterial effect on cleaned surfaces. A further study[48] has also found that this is a possible application of a nanosilver disinfectant sprays. This activity would have particular utility for high touch surfaces which are re-colonised rapidly after cleaning.

A major limitation of use of both copper and silver solutions was associated long contact times associated with use, which may not be applicable for use in practice.

Another limitation specific to the identified antimicrobial silver studies, was that all studies were directly relevant to the food and water industry, therefore tested bacterial species were in certain cases, not relevant to HAI.

It is important to note that the majority of the studies were undertaken in a laboratory environment which may not adequately represent use in clinical practice. In addition, none of the identified studies evaluated the antimicrobial effect against viruses or fungi.

Although the RRP evaluated several copper and silver containing products, none of the recommendations related to products used for decontamination of the healthcare environment and equipment.

Recommendations for practice

This review makes the following recommendations based on an assessment of the extant scientific literature on antimicrobial copper and silver.

If NHS boards use antimicrobial copper or silver products for decontamination of the healthcare environment and patient care equipment, the following must be considered:

- There was insufficient evidence to formulate any conclusions regarding the effectiveness antimicrobial silver, therefore the use of antimicrobial silver products for decontamination of the healthcare environment and patient care equipment is not currently advocated.
  (Good Practice Point)
- There was consensus in the evidence regarding use of copper biocidal solutions with microfibre/ultra microfibre cloths/mops at a concentration of 300 ppm as an alternative to current disinfection methods using hypochlorite at 1000 ppm.
  (Grade D recommendation)
- The majority of identified studies relating to both antimicrobial copper and silver stated that long contact times were necessary for full efficacy. This is an important consideration for determining the applicability for use in healthcare settings and may impact on acceptability as an alternative method.
  (Grade D recommendation)
- Manufacturer instructions should be followed regarding use of antimicrobial copper/silver products for decontamination.
  (Good Practice Point)
- The choice of antimicrobial copper disinfectant should always be cross checked with the manufacturers' instructions to determine if a detergent wipe is required pre disinfection.
  (Good Practice Point)

Implications for research

The limited evidence on this topic may reflect the fact that it is challenging to undertake well-designed studies to explore the effectiveness of different cleaning methodologies in the healthcare setting, due to both practical and ethical considerations. It may also reflect the fact that decontamination of the environment and equipment in healthcare settings has not been considered a priority area for research.

Future studies assessing the clinical effectiveness of antimicrobial copper and silver should include suitable comparisons to allow the results to be transferable into clinical practice. In addition, well designed experimental studies evaluating the antimicrobial effect on a wider range of HAI causing organisms would be beneficial. Furthermore, studies which include a cost analysis would also be useful for considering the potential future implementation of antimicrobial copper and silver.

Appendix 1: Medline Search

Ovid MEDLINE(R) 1946 to present with daily update

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 09, 2015

AND

Ovid MEDLINE(R) In-process & other non-indexed citations

Search dates

24/06/2014 and 25/06/2014

10/12/2015

AND

1 (all "OR")	2 (all "OR")
Silver/ Antimicrobial silver.mp	Sterilization/ Decontamination/ Disinfection/ Housekeeping, Hospital/ Clean*.mp

Limits

English language

Publication Year 2004-current

Results: 158

Publication Year 2014-current

Results: 42

References

(1) Health Protection Scotland. National Infection Prevention and Control Manual. Health Protection Scotland; 2014 Apr 4.

(2) Weber DJ, Rutala WA, Miller MB, Huslage K, Sickbert-Bennett E. Role of hospital surfaces in the transmission of emerging health care-associated pathogens: norovirus, Clostridium difficile, and Acinetobacter species. Am J Infect Control 2010 Jun;38(5 Suppl 1):S25-S33.

(3) Weber DJ, Anderson D, Rutala WA. The role of the surface environment in healthcare-associated infections. Curr Opin Infect Dis 2013 Aug;26(4):338-44.

(4) Weber DJ, Anderson DJ, Sexton DJ, Rutala WA. Role of the environment in the transmission of Clostridium difficile in health care facilities. Am J Infect Control 2013 May;41(5 Suppl):S105-S110.

(5) Health Protection Scotland. Transmission Based Precautions Literature Review: Environmental Decontamination and Terminal Cleaning. Health Protection Scotland; 2014.

(6) Rutala WA, Weber DJ. Disinfectants used for environmental disinfection and new room decontamination technology. Am J Infect Control 2013 May;41(5 Suppl):S36-S41.

(7) Weber DJ, Rutala WA. Self-disinfecting surfaces: review of current methodologies and future prospects. Am J Infect Control 2013 May;41(5 Suppl):S31-S35.

(8) Schneider PM. New technologies and trends in sterilization and disinfection. Am J Infect Control 2013 May;41(5 Suppl):S81-S86.

(9) Otter JA, Yezli S, Perl TM, Barbut F, French GL. The role of 'no-touch' automated room disinfection systems in infection prevention and control. J Hosp Infect 2013 Jan;83(1):1-13.

(10) McDonald LC, Arduino M. Climbing the evidentiary hierarchy for environmental infection control. Clinical Infectious Diseases 2013 Jan;56(1):36-9.

(11) Scottish Intercollegiate Guidelines Network. SIGN 50 A guideline developer's handbook. Scottish Intercollegiate Guidelines Network; 2011.

(12) Gant VA, Wren MWD, Rollins MSM, Jeanes A, Hickok SS, Hall TJ. Three novel highly charged copper-based biocides: Safety and efficacy against healthcare-associated organisms. Journal of Antimicrobial Chemotherapy 2007 Aug;60(2):294-9.

(13) Luna VA, Hall TJ, King DJ, Cannons AC. Susceptibility of 169 USA300 methicillin-resistant Staphylococcus aureus isolates to two copper-based biocides, CuAL42 and CuWB50. Journal of Antimicrobial Chemotherapy 2010;65:939-41.

(14) Hall T, Jeanes A, Coen P, Odunaike A, Hickok S, Gant V. A hospital cleaning study using microfibre and a novel copper biocide. I. Microbiological studies. Journal of Infection Prevention 2011 Sep;12(5):188-94.

(15) Hall T, Jeanes A, McKain L, Jepson M, Coen P, Hickok S, et al. A UK district general hospital cleaning study: a comparison of the performance of ultramicrofibre technology with or without addition of a novel copper-based biocide with standard hypochlorite-based cleaning. Journal of Infection Prevention 2011 Nov;12(6):232-7.

(16) Hamilton D, Foster A, Ballantyne L, Kingsmore P, Bedwell D, Hall TJ, et al. Performance of ultramicrofibre cleaning technology with or without addition of a novel copper-based biocide. Journal of Hospital Infection 2010;74(1):62-71.

(17) Araujo EA, Andrade NJ, da Silva LH, Bernardes PC, de CTA, de Sa JP, et al. Antimicrobial effects of silver nanoparticles against bacterial cells adhered to stainless steel surfaces. J Food Prot 2012 Apr;75(4):701-5.

(18) Le AT, Le TT, Nguyen VQ, Tran HH, Dang DA, Tran QH, et al. Powerful colloidal silver nanoparticles for the prevention of gastrointestinal bacterial infections. Advances in Natural Sciences: Nanoscience and nanotechnology 2012;3.

(19) Chamakura K, Perez-Ballestro R, Luo Z, Bashir S, Liu J. Comparison of bactericidal activities of silver nanoparticles with common chemical disinfectants. Colloids & Surfaces B: Biointerfaces 2011;84(88):96.

(20) Health Facilities Scotland. The NHSScotland national cleaning services specification. Health Facilities Scotland; 2014 Jul.

(21) National Patient Safety Agency. The Revised Healthcare Cleaning Manual. National Patient Safety Agency; 2009 Jun.

(22) Association of Healthcare Cleaning Professionals. Revised Healthcare Cleaning Manual. Association of Healthcare Cleaning Professionals; 2009 Jun.

(23) Health Protection Scotland. Standard Infection Control Precautions (SICPs) Literature Review: Routine cleaning of the environment in the hospital setting. Health Protection Scotland; 2014 Apr.

(24) Casey AL, Adams D, Karpanen TJ, Lambert PA, Cookson BD, Nightingale P, et al. Role of copper in reducing hospital environment contamination. Journal of Hospital Infection 2010;74(1):72-7.

(25) Karpanen TJ, Casey AL, Lambert PA, Cookson BD, Nightingale P, Miruszenko L, et al. The antimicrobial efficacy of copper alloy furnishing in the clinical environment: a crossover study. Infect Control Hosp Epidemiol 2012 Jan;33(1):3-9.

(26) Taylor L, Phillips P, Hastings R. Reduction of bacterial contamination in a healthcare environment by silver antimicrobial technology. Journal of Infection Prevention 2009 Jan 1;10(1):6-12.

(27) Taylor L, Phillips P, Hastings R. Reducing bacterial contamination using silver antimicrobial technology. Nursing Times 2009;105(7):24-7.

(28) Loveday HP, Wilson JA, Pratt RJ, Golsorkhi M, Tingle A, Bak A, et al. epic3: national evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England. Journal of Hospital Infection 2014 Jan;86:Suppl-70.

(29) Edwards-Jones V. The benefits of silver in hygiene, personal care and healthcare. Letters in Applied Miccrobiology 2009;49:147-52.

(30) Santo CE, Morais PV, Grass G. Isolation and characterization of bacteria resistant to metallic copper surfaces. Appl Environ Microbiol 2010 Mar;76(5):1341-8.

(31) Warnes SL, Green SM, Michels HT, Keevil CW. Biocidal efficacy of copper alloys against pathogenic enterococci involves degradation of genomic and plasmid DNAs. Applied & Environmental Microbiology 2010 Aug;76(16):5390-401.

(32) Warnes SL, Keevil CW. Mechanism of copper surface toxicity in vancomycin-resistant enterococci following wet or dry surface contact. Applied & Environmental Microbiology 2011 Sep;77(17):6049-59.

(33) Weaver L, Michels HT, Keevil CW. Survival of Clostridium difficile on copper and steel: futuristic options for hospital hygiene. Journal of Hospital Infection 2008;68:145-51.

(34) Sagripanti JL, Routson LB, Lytle CD. Virus inactivation by copper or iron ions alone or in the presence of peroxide. Applied Environmental Microbiology 1993;59(4374):4376.

(35) Warnes SL, Keevil CW. Inactivation of norovirus on dry copper alloy surfaces. PLoS One 2013;8(9):e75017.

(36) Warnes SL, Summersgill EN, Keevil CW. Inactivation of murine norovirus on a range of copper alloy surfaces is accompanied by loss of capsid integrity. Appl Environ Microbiol 2015 Feb 1;81(3):1085-91.

(37) Silvestry-Rodriguez N, Sicairos-Ruelas E, Gerba C, Bright K. Silver as a Disinfectant. Reviews of Environmental Contamination and Toxicology 2007;191:23-46.

(38) Galdiero S, Falanga A, Vitiello M, Cantisani M, Marra V, Galdiero M. Silver Nanoparticles as Potential Antiviral Agents. Molecules 2011;16(8894):8918.

(39) Feng Q, Wu J, Chen G, Cui F, Kim T, Kim J. A mechanistic study of the antibacterial effect of silver ions on Escherichia coli and Staphylococcus aureus. Journal of Biomedical Materials Research 2000;52(4):662-8.

(40) Quang HT, Van QN, Anh-Tuan L. Silver nanoparticles: synthesis, properties, toxicology, applications and perspectives. Adv Nat Sci : Nanosci Nanotechnol 2013;4.

(41) Lkhagvajav N, Yasa I, Celik E, Koizhaiganova M, Sari O. Antimicrobial activity of colloidal silver nanoparticles prepared by SOL-Gel method. Digest Journal of Nanomaterials and Biostructures 2011;6(1):149-54.

(42) Petrus EM, Tinakumari S, Chai LC, Ubong A, Tunung R, Elexon N, et al. A study on the minimum inhibitory concentration and minimum bactericidal concentration of Nano Colloidal Silver on food-borne pathogens. International Food Research Journal 2011;18:55-66.

(43) O'Gorman J, Humphreys H. Application of copper to prevent and control infection. Where are we now? Journal of Hospital Infection 2012 Aug;81(4):217-23.

(44) Hostynek J, Maiback H. Copper hypersensitivity: dermatologic aspects-an overview. Reviews on Environmental Health 2003;18(3):153-83.

(45) Taylor L, Phillips P, Hastings R. Reduction of bacterial contamination in a healthcare environment by silver antimicrobial technology. Journal of Infection Prevention 2009 Jan 1;10(1):6-12.

(46) Health Protection Scotland. Microfibre: Literature review and practice considerations. 2015.

(47) Public Health England. Rapid Review Panel. 2014 https://www.gov.uk/government/groups/rapid-review-panel

(48) Brady MJ, Lisay CM, Yurkovetskiy AV, Sawan SP. Persistent silver disinfectant for the environmental control of pathogenic bacteria. Am J Infect Control 2003 Jun;31(4):208-14.

(49) Health Protection Scotland. Standard Infection Control Precautions Literature Review: Management of patient care equipment. 2012.

(50) National Patient Safety Agency. The National Specifications for Cleanliness in the NHS: A framework for setting and measuring performance outcomes. 2007.