**Antimicrobial coatings for reduction of hospital acquired infection and associated specialised cleaning: Opinion of the COST Action Network AMiCI (CA15114)**

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**Summary:**

**Background:** The recognized issue with poor hand hygiene compliance among healthcare workers, and reports of re-contamination of previously chemically disinfected clinical surfaces through hand contact, emphasize a need for novel hygiene methods in addition to those currently available. One such approach involves antimicrobial (nano)-coatings (AMC), in which integrated active ingredients are responsible for the elimination of microorganisms that come into contact with treated surfaces. These coatings have been widely studied under laboratory conditions with promising results. However, efficacy studies on real life conditions in healthcare settings are relatively scarce.

**Aim**: This study collated views of 75 participants from 24 European countries regarding introduction of new hospital cleaning methods and their potential efficacy against HCAI.

**Methods:** Using a modified World Café model, facilitated sessions determined awareness regarding new cleaning approaches that may impact the effectiveness of antimicrobial coatings, the generation of effluent or waste water that may contain coating-derived antimicrobial agents, and the potential for generation of antimicrobial resistance.

**Findings:** There was unanimous agreement that the generation of scientific guidelines for cleaning of antimicrobial coatings, using traditional or new processes, are needed. Specific topics included: understanding the mechanisms of action of cleaning materials and their physical interactions with conventional and antimicrobial coatings; that assessments mimic the life-cycle of coatings to determine the impact of repetitive cleaning and other aspects of ageing (e.g., exposure of surfaces to sunlight, etc.); determining the concentrations of AMC-derived biocides in effluents, and development of effective de-activation and sterilisation treatments for cleaning effluents.

**Conclusion:** A consensus view that prior to widespread implementation of AMCs, the varying responsibilities of involved clinical, healthcare management, cleaning services, and environmental safety stakeholders should be clarifed.

**Introduction:**

Healthcare-associated infections (HCAI), also termed nosocomial infections, are complications of healthcare that result in elevated patient morbidity and mortality (1). HCAI increase healthcare costs for patients, hospitals and insurers due to extended hospitalization and unanticipated reduction of hospital capacity. There are further impacts on efficiency of healthcare, consequential associated care including opportunity costs subsequent to patients’ and their carers’ inability to work, attend school, etc., and the psychological burdens placed on patients, their carers and families (2, 3, 4). It has been estimated that, in the US alone, HCAI affect approximately 2 million patients annually, of whom approximately 90,000 patients die, with an annual cost estimated to range from US$ 28 billion to 45 billion (5). Similarly, in the European Union, the European Centre for Disease Prevention and Control (ECDC) advise that approximately 4.1 million acute care patients acquire a HCAI annually, with 37,000 deaths directly attributed to HCAI (6). Monitoring of outbreak incidence and individual cases has shown that HCAI are increasing (e.g., *Escherichia coli*, *Klebsiella pneumonia and Staphylococcus epidermidis*) (6, 7, 8). Such monitoring, including pan-European surveillance, has been expanded to encompass long term care facilities (LTCF) in addition to hospitals (European Centre for Disease Prevention and Control 2014). Further to that, more comprehensive data are emerging across Europe; for example, in Ireland, where a recent national median HCAI prevalence of 4.2% in long-term care facilities was reported (9) albeit not consistently (10).

HCAI are, however, to some extent preventable (11). Hand hygiene is widely regarded as the most effective preventative measure for healthcare workers (11) when complementing effective hospital hygiene practices that ensure proper cleaning and appropriate use of disinfectants and antimicrobials. The recognized issue with poor hand hygiene compliance among healthcare workers (12), and reports of re-contamination of previously chemically disinfected clinical surfaces through hand contact (13), emphasize a need for novel hygiene methods in addition to those currently available. One such approach involves antimicrobial (nano)-coatings (AMC) (14), in which integrated active ingredients are responsible for the elimination of microorganisms that come into contact with treated surfaces. Many different chemical strategies and technologies for antibacterial coatings have been described that utilise active eluting agents (e.g. ions or nanoparticles of silver, copper, zinc, or antibiotics, chloride, iodine, etc.), immobilized molecules that become active upon contact (e.g. quaternary ammonium polymers or peptides), or light-activated molecules (e.g. TiO2 or photosensitizers). These coatings have been widely studied under laboratory conditions with promising results (13, 15, 16), bolstered by reports describing successful delay and/or prevention of recontamination following conventional cleaning and disinfection by problematic microbes such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant enterococci (VRE), amongst others (15). However, efficacy studies performed under real life conditions in healthcare settings are relatively scarce.

More broadly, a 2016 comprehensive systematic review by Muller *et al* reported a paucity of studies evaluating non-copper antimicrobial surfaces in clinical environments, and a lack of peer-reviewed data relating to successful implementation of materials other than copper on clinically relevant outcomes (including HCAI) (17). Researchers have demonstrated successfully that copper touch surfaces in Finnish facilities such as hospital patient rooms and kindergartens lowered total bacterial counts and reduced occurrence of *S. aureus* when compared to non-copper touch surfaces (18). Michels and colleagues described efficacy of copper alloy based on compelling data generated in sequential laboratory and clinical trial assessments (19). Molling et al. (20) have reported a dominance of nanosilver in nanoparticle-based coatings, and associated adequate *in situ* performance. However, (21) reported prudently that while coating of hospital surfaces with substances containing silver ions may reduce bacterial growth, the effectiveness of the coating agent is affected by application method, environmental conditions and the type and cleanness of the surface.

Therefore, caution is needed. The introduction of (nano)-coatings with novel active components (e.g. nanosilver), some of which may be affected by varying end-user cleaning methods, could possibly cause emission of bioactive agents into the environment and, thereby, facilitate potential exposure of humans, livestock and microorganisms to low concentrations of these. Directly relevant to the One Health Initiative (http://www.onehealthinitiative.com), these agents (e.g. AgNP, Ag+, CuNP, ZnO2 and TiO2) may have potential to impact organisms living in water and soil compartments, specifically. In addition, the slow infusion of active ingredients may induce antimicrobial resistance that differs from antibiotic-driven mechanisms (22, 23). The widespread introduction of such coatings should be subject to expert risk-benefit analyses that incorporate objective assessment of available coatings and guidance for hospital systems regarding their use, for example the Scientific Committee on Emerging and Newly Identified Health Risks of nano-silver specifically (https://ec.europa.eu/health/scientific\_committees/emerging/docs/scenihr\_o\_039.pdf) or the EU-COST Action AMiCI (AntiMicrobial Coating Innovations) CA15114 regarding antimicrobial coating technologies and their use more broadly (24, 25) . More specifically, AmiCI is an initiative funded by the European Commission through its Cooperation in Science and Technology program (COST). In this case, the four-year initiative has established a network of stakeholders involved in development, regulation and use of novel anti-microbial coatings for prevention of HCAI. The network (AMiCI) comprises participants of more than 60 universities, research institutes and companies across 29 European countries and, to-date, represents the most comprehensive consortium targeting use of these emergent technologies in healthcare settings. In particular, the network prioritises coordinated research on the effects (both positive and negative) of antimicrobial coatings in healthcare sectors; know-how regarding availability and mechanisms of action of (nano)-coatings; possible adverse effects of such materials (e.g., potential emergence of microbial resistance or emission of toxic agents into the environment); standardised performance assessments for antimicrobial coatings; identification and dissemination of best practices by hospitals, other clinical facilities, regulators and manufacturers.

The aim of this study, performed in parallel with and following a design published previously that determined the opinions of expert stakeholders regarding safe use of antimicrobial coatings (26), was to collate views regarding introduction of new hospital cleaning methods and their potential efficacy against HCAI. Particular emphasis was placed on awareness of new cleaning approaches that may impact the effectiveness of antimicrobial coatings, the generation of effluent or wastewater that may contain coating-derived antimicrobial agents, and the consequent potential for generation of antimicrobial resistance.

**Methods:**

**Setting**

The aim of this study was to determine perceived or encountered practical challenges and suggested approaches when introducing new cleaning processes into healthcare settings. Wold Café fora were utilised to allow feedback to predetermined open-questions. These fora, a form of group consultation with larger numbers than usually involved in focus groups, are designed to enable a facilitated discussion on specific topics, whereby participants were enabled to share and contribute to a wider discussion through a process of guided facilitation [27]. Such discussions have advantages for researchers in the field of health and medicine such that they encourage participation by people reluctant to be interviewed on their own or who feel they have nothing to say [28].

AMiCI consortium members (n = 85) were invited to facilitated discussions having already registered to attend the initial conference hosted by COST Action CA15114 AMiCI in Heerlen (The Netherlands) in November 2016. Two weeks prior to the conference, participants were asked to familiarize themselves with questions circulated to them via email. The discussions were preceded by a keynote lecture on the broad topic of current hospital cleaning practices in the United Kingdom.

In total, 75 participants from 24 European countries shared their opinions in the discussion fora. Approximately 90% of the participants were from universities or research institutes, while the remainder represented other stakeholders such as hospital-based clinical microbiologists, infection prevention & control nurses, hygiene product suppliers, professional hygiene consultants, and antimicrobial coating producers.

**Development of study instrument**

Discussions were based on 3 primary questions, with sub-questions, relevant to the topic of COST AMiCI working group 4 (WG4), which focuses specifically on new cleaning methods for use in healthcare environments and their potential interactions with antimicrobial coatings when applied in those settings (24, 25). The questions were trialed on graduate entry medical students with prior degrees in microbiology or biochemistry, professional nurses, and clinical microbiologists (n=10) for clarity of meaning and understandability.

The questions were:

* What new (non-traditional) cleaning methods are being introduced into healthcare settings?
* Is there belief or confidence in their effectiveness?
* When choosing cleaning methods, are cost in use, shelf-life (or length of time they will be effective), special cleaning or training, and other considerations including antimicrobial resistance taken into consideration?

**Discussion forum**

For the discussions, the participants were divided into four subgroups and discussion of each question lasted for approximately thirty minutes facilitated by one members of AMiCI WG4 (authors of this paper – CPD, JG, NHO’C and MM).

In each case, the facilitator introduced the questions. Answers and comments were recorded on flip-chart(s). After thirty minutes, the groups moved on to the next question in sequence. Thus, all participants had the opportunity to share their opinions on all four questions. Following the 4 discussions, the results were summarized and all participants allowed the opportunity to add additional comments. Subsequent to the conference, all of the participants’ recorded comments were transcribed from the flip-charts. These were not attributed to specific individuals.

**Results:**

Responses provided by the participants are detailed below, and are presented in the context of each of the individual questions posed.

**Question One:** What new (non-traditional) hygiene methods are being introduced into healthcare settings?

The 75 participants represented a pan-European perspective, with commonalities and differences in healthcare facility cleaning practices. However, there were few novel, non-detergent, non-disinfectant hygiene practices known to be in current use. These are listed below:

**H2O2:** Used ubiquitously but not regularly and, typically, to reduce the microbial burden of surfaces in a room following an incidence of HCAI or discharge of a patient known to be a carrier of a problematic MDR (multidrug-resistant) microorganism.

**Ultra Violet light:** As above. However, not allowed in The Netherland due to unacceptable efficacy versus chemical cleaning in addition to concern regarding potential damage to plastic surfaces.

**Ultrasonically-activated water:** Not common. When used, they are perceived as suitable for use on all surfaces due to absence of resulting chemical residue and gentle action. The effect is physical removal but not killing of microbes.

**Nanofibre materials:** Used ubiquitously. Effective at removal of microorganisms (and physical dirt). In the Netherlands and Germany used with water alone, while used with detergents/disinfectants elsewhere. Also used with detergents and/or disinfectants in Germany and Switzerland

**Plant oils and acids:** Not common (for example, lauric acid and peracetic-acid is commonly used for disinfection of instruments or equipment (if no automatic processing can be done).

**Formic acid in water:** Not common

**Bacteriophage (“phage”):** Not common.

**Question Two:** Is there belief or confidence in their effectiveness?

The dominant view expressed was one of caution. The reputational damage to a healthcare facility, in addition to the actual effects on patient and staff health, due to outbreak of a HCAI can be significant. Consequently, there is reticence to adopt new approaches in place of existing, recognized cleaning procedures. Where new cleaning processes are adopted, they seem to be introduced into practice in parallel with and even complementary to traditional detergent-, disinfectant-based systems.

Surprisingly, in an era when confidence in a process or product should, ideally, be based on evidence and scientific data, most participants stated that decision-making stakeholders placed considerable credence on products that had a “clean smell”. In other words, there appears to be a psychological association between the smell of alcohol, disinfectant and detergent and their perceived effectiveness. For that reason, perhaps, there was unanimous lack of confidence regarding steam cleaning, while strong odours (such as formic acid acetic acid/chlorine) would perhaps be more widely accepted. Worryingly, there was also a general lack of confidence in the adequacy of training provided to cleaning staff and an unawareness of accreditation such as, for example, that provided by the British Institute of Cleaning Science (https://www.bics.org.uk). More specifically, there was consensus regarding poor quality of training provided to hospital cleaning staff who, irrespective of country, appear to be relatively poorly educated and of lower socio-economic status. Typically, these workers are employed on temporary contracts and are not, usually, integrated fully into medical teams and instead represent “invisible” support staff. As such, views were expressed that these support staff may not be considered capable (by clinicians or hospital management) of implementing innovative or technologically-advanced cleaning processes beyond the “mop and bucket” approaches traditionally used. Consequently, the perceived risk of potential failure may dissuade decision-makers from adopting new cleaning methods.

**Question Three:** When choosing cleaning methods, are cost in use, shelf-life (or length of time they will be effective), special cleaning or training, and other considerations including antimicrobial resistance taken into consideration?

Proof of efficacy was a consistent need for all participants, as was regulatory approval or license for use in their country. Similarly, there was consensus that new cleaning approaches would not be implemented, or even trialed, at their respective facilities unless:

* promoted by credible, well-established supply companies with good reputations;
* evidence demonstrated that their use did not damage existing surfaces;
* there would not be significant training requirements for clinical and facility management staff and, especially, not for cleaning staff;
* that new cleaning products were compatible with existing cleaning processes and chemicals;
* additional or specialist equipment was not needed, especially personal protective equipment; and
* crucially, that cost effectiveness had been documented.

Another, but not consistently expressed, perspective was the fact that while cost in use was an important consideration, there should also be some estimation made regarding cost avoidance as a result of reduced risk of HCAI due to the enhanced effectiveness of cleaning and subsequent decreased clinical care expenditure. However, there was general agreement that this calculation may not be persuasive when facility managers are looking at short-term budgeting.

An interesting problem was also identified with respect to proof of efficacy. Most participants stated that new cleaning approaches would not be introduced in their hospital unless proven to work elsewhere. This represents a “Catch-22” situation with clear challenges regarding potential sites at which to assess innovations.

Generation of antimicrobial resistance was discussed at length and acknowledged as a major challenge for use of antimicrobial coatings in general, and cleaning processes in particular. More specifically, all participants were aware that cleaning processes would be likely to remove small amounts of biocides from antimicrobial coatings when applied to hospital surfaces (25-29). Such chemicals are inherently toxic and may be harmful to humans and animals (26). Indeed, compounds containing silver, copper and zinc (described previously in this article) are covered within EU by the Biocidal Product Regulation (BPR, Regulation (EU) 528/2012) and by the Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH). Therefore, appropriate treatment of hospital wastewater and cleaning effluent, potentially containing either biocides or multidrug-resistant bacteria, requires clarification. Effluent-free cleaning would present significant benefits for risk-reduction.

There was unanimous agreement that the generation of scientific guidelines for cleaning of antimicrobial coatings, using traditional or new processes, are needed. There should be particular emphasis on:

1. understanding the mechanisms of action of cleaning materials (chemicals and textiles) and their physical interactions with conventional and antimicrobial coatings;
2. evaluation of these cleaning processes on newly-applied coatings, and that assessments further mimic the life-cycle of coatings to determine the impact of repetitive cleaning and other aspects of ageing (e.g., exposure of surfaces to sunlight, etc.);
3. determining the concentrations of biocides in effluents, based on interactions with cleaning chemicals and materials, and their residual antimicrobial activity also be determined;
4. development of effective de-activation and sterilisation treatments for cleaning effluents. These may also involve removal of biocides and/or multidrug-resistance microorganisms.
5. That all of the above apply equally to cleaning materials such as textiles and other physical cleaning equipment.

**Discussion:**

Participants of this study spanned clinical practice, academic research, industry, and regulatory agencies. However, despite this diversity, there was general consensus and acknowledgement of analogous experiences regarding hospital cleaning practices across more than 20 countries. Agreeing with the perspectives on hospital cleaning “Dos and don’ts” described by Dancer (34), each of the participants detailed resource constraint-driven changes to hospital hygiene practices. These included outsourcing of cleaning services to commercial providers, and subsequent infection prevention & control failures or perceived detrimental effects on effectiveness, knowledge, attitudes and practices of relatively low-paid and typically poorly educated workers (35-38). The participants believed these factors to be important determinants of potential success or failure for AMCs. Specifically, irrespective of their antimicrobial properties, coatings are unlikely to impact incidence of nosocomial infections if they are not thoroughly cleaned and bioburden, molecular or cultivable material are not effectively removed. This has been discussed previously with credible arguments presented regarding poor training and motivation of cleaning staff (36, 39-41).

It was especially notable that during discussion of Question One, none of the participants referred to practical experience of AMC use at clinical facilities, other than in experimental settings. Indeed, there was consensus regarding a need for clarity regarding the potential efficacy claims for AMCs or “expectation management”. Put more simply, that if those who have responsibility for clinical facility management are to adopt their use, to be convinced of their benefit, AMC products need to have credible, unambiguous trial data relevant to the intended environment in which they are to be used and the microbes targeted (e.g., vegetative cells or spores). However, in the context of associated specialized AMC-related cleaning practices, the participants recognised that with notable exceptions (42) there was a paucity of prospective, appropriately controlled, crossover trials of hygiene products or practices irrespective of whether used on standard or enhanced surfaces.

Participants reiterated concerns regarding the potential of AMCs to promote development of antimicrobial resistance mechanisms, as described elsewhere (26). Multidrug-resistant bacteria have been identified in waterways contaminated by effluent of ineffective hospital waste water treatment (43). While these reports relate to antibiotic resistance, there is potential for non-antibiotic leachates from AMCs borne in cleaning equipment (e.g., mops and buckets) to introduce non-inhibitory levels of antimicrobial agents into sewage and ground water. For that reason, AMC cleaning procedures should stipulate suitable, and possibly dedicated, disposal processes to reduce or negate the risk of such environmental contamination.

Therefore, the recommendations of this group, derived from disparate but complementary expertise, acknowledge the potential benefit of AMCs and the strong likelihood that such products will enter into use. This is almost an inevitability due to pressures on the healthcare industry to adopt attractive propositions claiming reduction of infection risk in their facilities and the increasing marketing pressure from manufacturers and distributors. However, we recommend the use of AMCs as part of suites of practices that include availability of well-characterised cleaning materials and processes, training (and accreditation) of cleaning staff, and environmental monitoring. In particular, the latter should take into consideration potential impact on organisms living in water and soil compartment, in addition to potential slow infusion of active antimicrobial agents that may induce resistance that differs from antibiotic-driven mechanisms. Furthermore, our consensus view is that prior to widespread implementation of AMCs, the varying responsibilities of the involved stakeholders should be clarified. Specifically:

* analogous to European Directives stipulating the level of scientific evidence required for food supplement claims or drug efficacy, there should be minimal data requirements regarding proof of efficacy for specific AMC formulations that have been assessed in appropriate environments;
* instructions for care of AMCs following deployment for use should include evidence-based directions regarding their cleaning with specified cleaning material types (chemical, textiles materials, etc);
* appropriate and understandable information should be provided to allow effective training of clinical, management and cleaning staff prior to use of the AMCs;
* environmental monitoring protocols should be adopted to allow efficient and effective detection and measurement of potential presence or effects of AMC-derived active agents. Actions for remediation and those responsible for their implementation should be explicit.

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