Antimicrobial Properties of Copper and Copper Alloys for Infection Control

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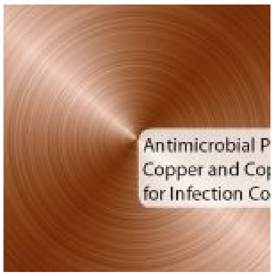

Abstract

Over the past decade the development of additional disinfecting methods has become increasingly important to prevent hospital acquired infections as antibiotic drug resistance has risen rapidly. One such method involves copper-impregnated self-sanitizing surfaces. Despite the overwhelming evidence that such devices decrease the microbial burden in hospitals, their introduction to clinical settings has been slow.

Introduction

Copper was used in medicinal preparations in ancient civilizations, long before the concept of microbes arose in the 19th century (1). In past centuries it was known that water stored in copper vessels or transported in copper systems was of superior quality to water stored or transported by other mechanisms. Such knowledge resulted in its use in baths, healthcare facilities, spas, taps, and brewery coppers.

The antimicrobial activities of copper are due to multiple factors. Elevated cellular copper levels cause oxidative damage. Excess copper also results in the loss of membrane integrity, which causes essential nutrients, including potassium and glutamate to leak from cells and cause death. Copper also binds proteins, which either inhibits enzymatic activity or leads to protein degradation (2-4).

The antimicrobial activities of copper against Gram-positive and Gram-negative bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile*, vancomycin-resistant enterococci (VRE), and ESBL-producing species, as well as adenoviruses, influenza A, and fungi has been known for decades (5). Nevertheless, medical students routinely cite silver as a primary metal with bacteriostatic or bactericidal activity. This is often in reference to the intra-urethral application of silver for the treatment of gonorrhoea in the pre-antibiotic era (6).

The use of copper materials to reduce environmental contamination on contact surfaces was first postulated over 30 years ago. During a training session to promote hygiene awareness, cleaning staff in a U.S. hospital obtained environmental swabs from multiple locations and assessed the quantities of bacteria that were present on each surface. That assessment revealed that brass doorknobs (an alloy of 67% copper and 33% zinc) contained substantially fewer bacteria than stainless steel doorknobs (7).

Since environmental surfaces are reservoirs for pathogen growth and transmission, and the microbial burden of frequently touched surfaces in healthcare facilities may play a significant role in hospital-acquired infections (HAIs) (8), investigations of environmental surfaces have been increasing.

To standardize the assessment of hospital cleanliness, aerobic colony counts (ACC) on hand-touch sites should not exceed 250 colony forming units (CFU)/cm^2 (9). Investigations of terminal room cleaning using a fluorescent indicator showed that sufficient decontamination occurred only 49% of the time following hospital discharge and that less than 30% of toilet handholds, bedpan cleaners, doorknobs, and bathroom light switches were adequately cleaned (10). It is known that the environment may facilitate the transmission of several important healthcare-associated pathogens, including VRE, *C. difficile*, *Acinetobacter* spp., MRSA, and norovirus (11-15). Such pathogens are frequently shed by hospital patients, visitors, and staff, and can survive on stainless steel surfaces for days, which increases the risk of transfer to other patients (16). Multiple studies showed that EPA-registered copper surfaces are effective at lowering the microbial burden and augmenting existing infection control strategies (17-26).

In a 2016 study by Schmidt *et al*., copper surfaces were found to be equally antimicrobial in paediatric settings and adult intensive care units. In that study, the microbial burden on copper bed rails was reduced by 1.996 log (99%). Moreover, the introduction of copper items in eight study rooms was found to reduce the microbial burden recovered from subjects in control rooms by 1.863 log (73%). Thus, it was concluded that copper surfaces warrant consideration for the introduction of no-touch disinfection technologies for reducing HAIs (17).

Schmidt *et al*. also revealed that the introduction of copper surfaces on objects formerly covered by plastic, wood, stainless steel, or other materials reduced the microbial burden by 83%. Notably, that reduction was maintained over 21 months (18). Similarly, a 2017 study by Coppin *et al.* showed that copper impregnated tray tables had lower microbial burdens than tray tables made of standard materials. The microbial burden was 81% lower on copper surfaces after 30 hours, compared to levels on non-copper surfaces (19). Copper-impregnated stethoscopes also exhibited up to 91% fewer CFU/cm^2, compared to non-copper impregnated stethoscopes (191 vs. >300 CFU/cm^2, respectively) (26).

Such findings led to the question of whether the reduced microbial burden observed with copper surfaces could also reduce HAIs. Salgado *et al*. found that patients cared for in ICU rooms containing copper alloy surfaces had a 58% reduction in the rates of HAIs and/or colonization with MRSA or VRE, compared to patients treated in standard rooms. Based on those data, the authors concluded that additional studies with larger patient populations were warranted to determine the clinical impact of copper alloy surfaces in hospital rooms (27).

A 2015 review by Michaels and Salgado discussed the difficulties with performing large, prospective, longitudinal randomised controlled trials (RCTs) for the use of copper surfaces in hospitals, including the increasing costs of copper (28). Recently, Sentara's Leigh Hospital in Norfolk tested the use of copper linens. That study revealed an 83% decline in *C. difficile* infections within 10 months. The rates of MRSA and VRE infections were also reduced by 78%; however, the study failed to implement a control group or well-defined endpoints (29). Conversely, a Chilean study failed to identify any reductions in HAIs, mortality, or antimicrobial costs when copper surfaces were implemented in hospital settings. However, the lack of beneficial effects may have been due to the limited sample size (30).

A similar study involving the use of copper linens in a long-term care facility for patients with brain injuries found a 24% reduction in the HAIs per 1,000 hospitalization days, a 47% reduction in the number of fever days, and a 32% reduction in the total number of antibiotic administrations per 1000 hospitalization days. Thus, a 27% reduction in the costs of antibiotics, X-rays, disposables, labour, and laundry was observed (31).

Overwhelming evidence exists to favour the effects of copper surfaces on reducing the microbial burden for infectious disease control. Despite an the existence of a registered U.S. Environment Protection Agency copper surface system, and subsidies provided by the Canadian Government, the introduction of copper to hospital settings remains difficult (33). The question remains whether copper surfaces should adhere to the FDA criteria for new drug using RCTs in the absence of investments by pharmaceutical companies.

Copper has two key properties that are exploited in consumer products and medical devices. Copper has potent biocidal properties, and is critical for most tissues in the body, including the skin. In the skin, copper is involved in the synthesis and stabilisation of extracellular matrix skin proteins and angiogenesis (32). Thus, those properties were leveraged for the use of copper oxide-impregnated wound dressings, in which wound closure increased due to increased blood vessel formation, and the increased production of pro-angiogenic factors, including placental growth factor and vascular endothelial growth factor (34). A study involving copper oxide containing diapers in elderly patients revealed similar results (35).

Conclusion

In an era of rapidly evolving multidrug resistant bacteria, it is unsurprising that substantial attention has been given to the development of additional disinfecting methods to prevent hospital-acquired infections. One such method is the use of copper-impregnated self- sanitizing surfaces. However, despite the overwhelming evidence that such surfaces significantly decrease the microbial burden, the implementation and introduction of these devices in hospitals has been unacceptably slow. One reason for this is the lack of clinical trials. Additionally, bacterial resistance to metallic copper is known; however, this should be considered a minor concern (36) since copper allergies are rare, particularly in intra-uterine device users (37).

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