Reduce Infections in Military and Disaster Medicine with a New Weapon: Continuously Active Antimicrobial Copper Alloy Surfaces

Copper Development Association Inc. Copper Alliance

MUSC

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Modula S

Antimicrobial Copper

Summary of Technology and Application

Antimicrobial copper surfaces are proven to inactivate lethal viruses and kill infectious bacteria that cause healthcare-associated infections (HAIs) responsible for substantial patient morbidity and mortality. These continuously active metal surfaces can be integrated into rapidly deployable military medical clinics and military medical treatment facilities to reduce the risk of infectious outbreaks thereby increasing productivity and improving mission effectiveness.

Impact of Infections and Antibiotic Resistance

Infection prevention and control is one of the World Health Organization's strategic objectives in their Global Action Plan on Antimicrobial Resistance[1]. HAIs are the most frequent adverse event in healthcare delivery worldwide – affecting hundreds of millions of patients each year[2]. In military health systems, the risk of HAI is even higher. An estimated 36% of deployed personnel become ill due to infection of common contagious diseases. In addition, an estimated 80% of all military hospital admissions result from diseases and non-battle injuries[3].

From an infection prevention and control perspective, best practices typically deployed in conventional treatment facilities may not be feasible in the military theater of operations or disaster settings. Infectious microbes which cause HAIs have an intrinsic ability to survive on common touch surfaces, for many months in some cases, where acquisition and transport from surfaces to humans is common[4]. This resident, microbial burden in the built environment is believed to play a significant role in HAI acquisition[5]. Even when best practices are rigorously followed, hand hygiene, routine surface disinfection, isolation, and antimicrobial stewardship have been unable to significantly mitigate infection complications of combat trauma[6].

Pathogens can survive on conventional surface materials for a long time

- Rotavirus: 60 days
- VRE: 4 months
- *Acinetobacter spp*: 5 months
- *C.diff* spores: 5 months
- MRSA: 7 months
- *E. coli*: 16 months
- *S. typhimurium*: 4.2 years

Kramer, A et al. (2006). How long do nosocomial pathogens persist on inanimate surfaces? A systematic review. BMC Infectious Diseases. 6, 130.

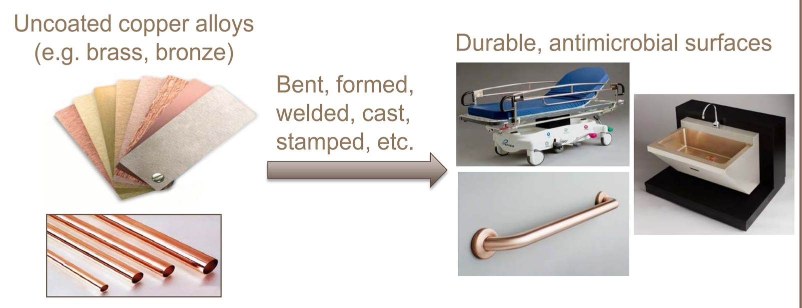
Furthermore, pathogens are developing resistance to antimicrobial treatments at an alarming rate. According to a joint UK Government/Wellcome Trust review on the potential impact of antimicrobial resistance[7], 10 million people a year could die across the world by 2050 if no radical action is taken. The associated economic costs have been estimated at $100 trillion due to a forecast reduction in GDP of between 2 and 3.5%. It is incumbent upon healthcare providers to deploy evidence-based solutions to reduce preventable infections and mitigate the spread of antimicrobial resistance in military and disaster medicine.

Copper Alloys – Inherently Antimicrobial Engineering Materials

Copper has long been recognised for its intrinsic antimicrobial properties, which have been confirmed in modern, peer-reviewed literature[8,9]. It shares this efficacy with a wide range of copper alloys – including brasses and bronzes – collectively called 'antimicrobial copper'. These solid materials are antimicrobial through and through, with no surface coating or treatment to wear away. Hard-wearing and durable, antimicrobial copper is fully recyclable and typically contains a high percentage of recycled material. The inherent and broad-spectrum antimicrobial activity of copper surfaces offers a solution to infection control as its action is continuous rather than episodic.

What is "Antimicrobial Copper"?

Solid metals with intrinsic antimicrobial properties



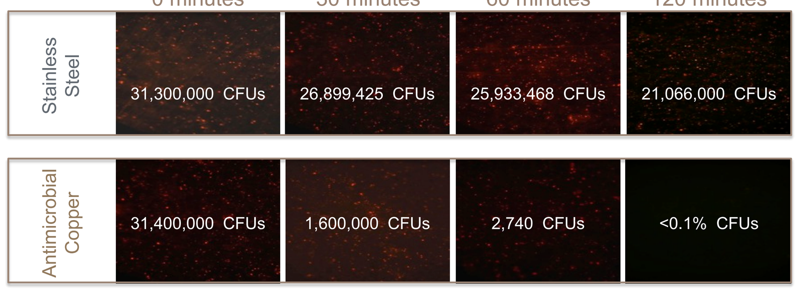
Not a coating or surface treatment!

Laboratory Efficacy Testing

Preliminary research was initiated at the Southampton University in the UK in the early 2000s. A wide range of copper alloys were challenged with *Escherichia coli* O157:H7 at or above 10 million CFUs (colony forming units)/in², which is orders of magnitude higher than typical levels found on contaminated surfaces in hospitals. All tested copper alloys were found to markedly reduce the number of viable bacteria after just a few hours on their uncoated surfaces. Stainless steel served as the experimental control. Thus *E. coli* O157:H7 was killed simply by being placed on the copper alloy surface, as shown in the figure below.

Time lapse of test as seen through microscope:

***E. Coli* O157:H7 on stainless steel and copper surfaces**



Epifluorescence Images after Staining with Viability Fluorophore CTC. Red dots indicate viable bacteria colonies
CFU = Colony Forming Unit (Keevil, unpublished)

These findings led to additional studies investigating the efficacy of copper against a range of human pathogens including many multi drug resistant organisms. Copper alloys have subsequently demonstrated efficacy in published studies against many bacteria, viruses and fungi. A partial list of organisms that are killed or inactivated by copper alloy surfaces is provided below and the supporting peer-reviewed studies are catalogued in a recent review by Michels and Michels[10] .

Partial list of organisms killed or inactivated by copper alloys:

- *Acinetobacter baumanii*
- Adenovirus
- *Aspergillus spp.*
- *Campylobacter jejuni*
- *Candida albicans*
- Carbapenem-resistant *Enterobacteriaceae* (CRE)
- *Clostridium difficile*
- *Fusarium spp*
- Influenza A (including H1N1)
- *Klebsiella pneumoniae*
- *Legionella pneumophila*
- *Listeria monocytogenes*
- *Mycobacterium tuberculosis*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Norovirus
- *Penicillium chrysogenum*
- Rhinovirus
- Rotavirus
- *Salmonella enterica*
- *Salmonella typhi*
- Vancomycin-resistant *Enterococcus faecalis* (VRE)
- *Vibrio cholerae*

And more…

Efficacy Against High Threat Pathogens and Biothreat Agents

In addition to the laboratory studies referenced above, a large-scale study at the Bundeswehr Institute of Microbiology demonstrated that copper surfaces can rapidly inactivate highly pathogenic bacterial and viral agents of risk group 3 (*Burkholderia pseudomallei* and *B. mallei*, *Brucella melitensis*, *Yersinia pestis*, *Francisella tularensis*, vaccinia- and monkeypox-viruses). All of these pathogens cause high fatality rates in humans and thus have the potential to be used as terrorist bioweapons[11].

Efficacy data on viruses suggests that copper alloy surfaces will inactivate Ebola virus which can be transmitted through direct contact with body fluids/substances of an infected person with symptoms, or through exposure to objects that have been contaminated with infected fluids.

The US Centers for Disease Control and Prevention (CDC) has instructed hospitals to use disinfectants with proven efficacy against the following viruses: norovirus, rotavirus, adenovirus and poliovirus as these viruses have a similar genetic structure to Ebola[12]. Laboratory testing has demonstrated that copper alloys are effective against norovirus[13], rotavirus and adenovirus. Based on CDC's recommendation, and proven efficacy against viruses with similar genetic structures, copper alloys are expected to inactivate Ebola virus.

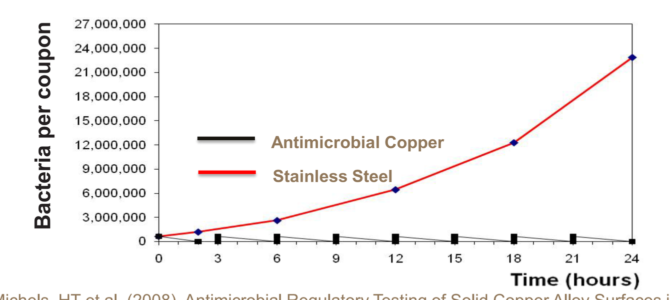
Preventative measures are particularly important for diseases such as Ebola for which there is currently no causative cure. Here, antimicrobial copper surfaces might make a meaningful contribution, e.g. in barrier-nursing. Medical missions abroad including stationary or mobile patient isolation-units aimed at diminishing the spread of biothreat agents may benefit from the use of copper surfaces.

US Environmental Protection Agency Registration

In the US, products advertised with antimicrobial claims are regulated by the US Environmental Protection Agency (EPA). Claims against specific pathogens must be substantiated through rigorous laboratory efficacy testing under EPA-approved protocols. Over 500 copper alloy compositions are currently registered with EPA which permits products made from registered alloys to make claims of killing six bacteria including MRSA and VRE[14]. The chart below shows data from an EPA test protocol which demonstrates the ability of copper alloy surfaces to continuously reduce >99% of MRSA bacteria deposited eight times in three hour intervals with no cleaning. In contrast, the stainless steel control surface accumulates bacteria throughout the duration of the test.

EPA testing: continuous reduction of MRSA

>99% kill on copper after 8 exposures over 24 hours with no cleaning in between



Michels, HT et al. (2008). Antimicrobial Regulatory Testing of Solid Copper Alloy Surfaces in the USA. Metal Ions in Biology and Medicine. Vol 10, 185-190.

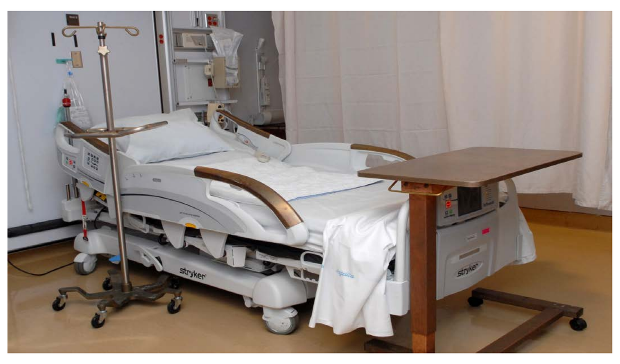
The EPA registration represents an independent assessment and approval of antimicrobial efficacy claims for uncoated copper alloy materials against six prominent bacteria that cause HAIs. Outside the US, this registration represents an independent, official recognition of the laboratory data presented and provides the quantified efficacy claims applicable to all registered alloys for the organisms tested.

Clinical Trials and Impact on Infections

With a foundation of laboratory evidence and EPA registration, testing in the clinical environment was required to determine if the antimicrobial properties of copper alloys can provide a meaningful benefit in real world applications. As such, a multi-site clinical trial, sponsored by the US Department of Defense was conducted in the Intensive Care Units (ICUs) of three hospitals: Memorial Sloan Kettering Cancer Center, Medical University of South Carolina, and Ralph H. Johnson Medical VA Medical Center. This was a multi-year study carried out in three phases.

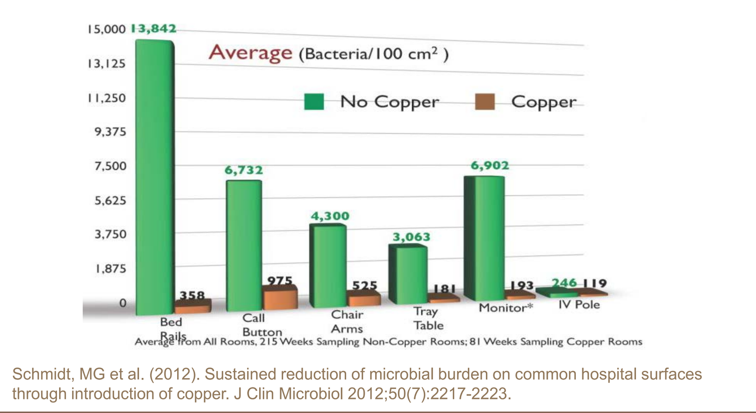
In Phase 1, the baseline microbial burden on components in existing patient rooms was determined with a standardized sampling protocol and the surfaces of components to be converted to copper were identified and prioritized. Surfaces found to be the most contaminated and closest to the patient were fabricated from copper alloy materials. In Phase 2, a total of six components made from copper alloys, including bed rails, nurses' call buttons, arms of the visitor's chairs, over-bed tray tables, IV poles, and data input devices, were installed in half of the study rooms as shown in the image below. The existing cleaning and infection control practices at each institution remained unchanged throughout the study.

Antimicrobial copper components in Ralph H. Johnson VA Medical Center



The microbial burden found on the components made from copper alloys was reduced by 83% on average compared to control surfaces after two years of weekly sampling at random times as shown in the chart below[15].

83% fewer bacteria on copper items after 2 years



Schmidt, MG et al. (2012). Sustained reduction of microbial burden on common hospital surfaces through introduction of copper. J Clin Microbiol 2012;50(7):2217-2223.

In Phase 3, infection rates were measured and compared over a one-year period between ICU rooms containing copper items or conventional surfaces. At the end of the study period, patients treated in copper rooms had 58% fewer infections compared to the control population (p=0.013; N=614)[16]. Infections were reduced by more than 50% simply by converting less than 10% of the touchable surface area in ICU rooms to copper.

Salgado and colleagues also empirically demonstrated the link between the level of microbial burden on surfaces and the propensity to acquire an infection as shown in the following chart.

Patients treated in ICU rooms with copper surfaces had significantly fewer infections (HAIs)

Copper Rooms: 10 HAIs in 294 patients

Control Rooms: 26 HAIs in 320 patients

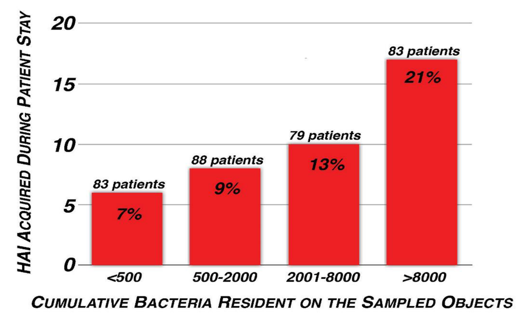
Normalize populations →24 Infections in control rooms

= 14 infections prevented in copper rooms

= 58% reduction in HAI (N=614, p=0.013)

Salgado, C, et al. (2013). Copper surfaces reduce the rate of healthcare-acquired infections in the intensive care unit. Infection Control and Hospital Epidemiology. 34(5), 479–486.

Contaminated surfaces increase infection risk



Salgado, C, et al. (2013). Copper surfaces reduce the rate of healthcare-acquired infections in the intensive care unit. Infection Control and Hospital Epidemiology. 34(5), 479–486.

A business case for deploying antimicrobial copper can be derived from the data reported in the Salgado study. Taking conservative estimates for the additional cost to treat an infection, the time to recoup the cost of outfitting the interventional rooms with copper items based on prevented infections was between 29 and 44 days as shown below. This rapid payback is confirmed using the Salgado study infection reduction data in a fully referenced model developed by York Health Economics Consortium[17].

Basic ROI calculation from US clinical trials

- **Low Cost Scenario ($29K/HAI)**
  - 14 infections prevented X $29,000/Infection = **$406,000 Savings**
  - $406,000 ÷ 338 days = **$1,201/day**
  - $52,000 (cost of copper products) ÷ $1,201/day
    = **43.3 day payback period**
- **High Cost Scenario ($43K/HAI)**
  - 14 infections prevented X $43,000/Infection = **$602,000 Savings**
  - $602,000 ÷ 338 days = **$1,781/day**
  - $52,000 (cost of copper products) ÷ $1,781/day
    = **29.2 day payback period**

*HAI cost projections based on AHRQ estimates
*Estimated $52,000 to "copperize" 8 ICU Rooms (prototype pricing)

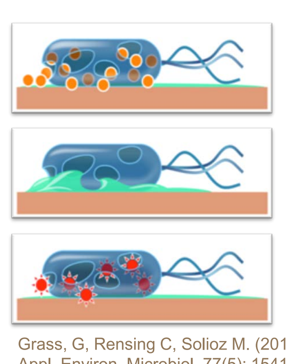
In addition to the Salgado study, other clinical studies have also reported the ability of copper alloy surfaces to reduce microbial burden and infection. Von Dessauer and colleagues recently reported a 19% relative risk reduction in infections for pediatric patients treated in ICU rooms with antimicrobial copper surfaces[18]. Hinsa-Leasure and colleagues found that 93% of rooms outfitted with copper surfaces in the medical-surgical unit at Grinnell Regional Medical Center remained at or near the recommended threshold for terminal cleaning during 18 months of sampling[19]. Karpanen et al also reported significantly fewer microorganisms including methicillin-susceptible *Staphylococcus aureus* and VRE found on copper furnishings (e.g. door handles, grab rails, sink fittings, light switches, etc.) vs. control surfaces in an acute care medical ward[20].

This evidence suggests that antimicrobial copper surfaces can provide a public health and economic benefit in diverse care settings. Efficacy observed in conventional healthcare facilities is expected to translate to military and disaster medicine settings.

Mechanism of Action

The mechanisms by which solid copper surfaces damage and destroy human pathogens are still being studied. By interacting with the cell structure, copper initiates a series of cascading events, including rapidly interrupting normal functions and compromising cell membrane integrity. This allows copper to enter the microbe structure and overwhelm the metabolism. The final stage is the breaking down of genomic material. These numerous and complex reactions mean that resistance to copper alloys is unlikely to develop. Copper is also an essential nutrient for most pathogens and required for several metabolic functions, but is toxic when internal copper levels become excessive. Michels and Michels summarized the latest research on copper's mechanism of action in a recent review[10].

How does copper kill bacteria?



1) Copper ions on the surface are recognized as an essential nutrient, and enter the cell

2) A lethal dose of copper ions interferes with normal cell functions and membrane integrity

3) Copper ions impede cell respiration/metabolism, sometimes causing DNA damage

Grass, G, Rensing C, Solioz M. (2011). Metallic copper as an antimicrobial surface. Appl. Environ. Microbiol. 77(5): 1541 -1547.

Combating Antibiotic Resistance With Copper Surfaces

Antibiotic resistance (AR) arises when bacteria survive exposure to the antibiotics that would normally kill them. AR threatens the effective prevention and treatment of infections caused by pathogens encountered in civilian, military and disaster settings. Importantly, bacteria are developing resistance to existing antibiotics faster than the rate at which new antibiotics are being developed, thus threatening a post-antibiotic era.

Horizontal gene transfer (HGT) in bacteria plays an important role in the evolution of AR. Research shows that, while HGT can take place in the environment – on frequently-touched surfaces such as door handles, trolleys and tables made from inert materials – copper prevents this process from occurring by rapidly killing bacteria on contact and destroying plasmid and genomic nucleic acid[21]. Strategic deployment of antimicrobial copper touch surfaces can therefore mitigate the transfer of AR between bacterial species.

Global Supply Chain and Adoption

Growing laboratory and clinical evidence supporting the deployment of antimicrobial copper materials led to the commercialization of products utilizing these continuously active metals for infection control. An international supply chain of over 200 companies now offer a wide range of antimicrobial copper alloys and touch surface products including fixtures and fittings, medical equipment and furniture. Installations are taking place around the world in healthcare facilities and other hygiene sensitive environments such as mass transit and education.

Products have also been developed with specific relevance for military and disaster medicine. For example, a rapidly deployable Emergency Treatment Unit (ETU) featuring antimicrobial copper alloy interior walls, equipment, fixtures and furnishings follows.

Application: Modula S Rapidly Deployable Emergency Treatment Unit (ETU)

Modula S applied copper technology to their Emergency Medical Treatment Units - rapidly deployable, autonomous and netzero energy facilities that provide state-of-the-art technologies to help support a healthy environment of care. The design is in response to the recent Ebola Grand Challenge Award, granted by USAID, the White House OSTP, the Centers for Disease Control and the US Dept. of Defense.

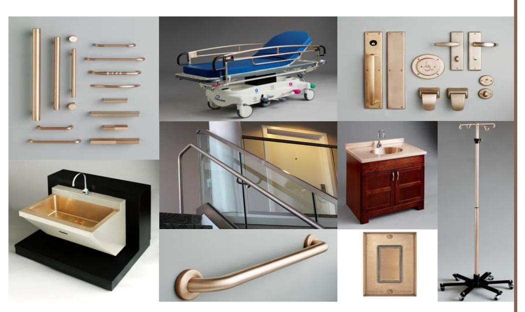
Winner: USAID Ebola Grand Challenge

FIGHTING EBOLA: A GRAND CHALLENGE FOR DEVELOPMENT — USAID FROM THE AMERICAN PEOPLE — CDC CENTERS FOR DISEASE CONTROL AND PREVENTION

The units are ideally suited for infection isolation, promoting safe, clean and comfortable buildings for patients and caregivers. The solar and ground-source powered, antibacterial, thermally resilient, netzero energy buildings can maximize healthcare worker efficacy in treating patients while mitigating the risk of transmitting infections.

Products supplied in the Ebola ETU

- Diverse applications
  - Hardware
  - Healthcare
  - Fitness
  - Residential
  - HVAC
- Design options
  - Color selection
  - Surface finish
  - Various forms



Business Case for Military and Disaster Medicine

The projected business case for antimicrobial copper in military and disaster medicine is compelling. Among military personnel deployed to Iraq or Afghanistan in 2003-2004 that received medical treatment, an average of 3.8 days was required for hospitalization and confined quarters[22]. According to the Congressional Budget Office, the estimated cost of a soldier is $656 per day[23]. With 1.32 million active-duty service members, the projected productivity loss due to days of hospitalization and days subject to quarters alone can be calculated to be over $3 billion. If one day could be recovered across the active-duty force, then a savings of almost $1 billion in productivity could be gained.

Inclusion in National Guidelines

National guidelines and accreditation schemes for hygiene, infection control and well-being now recognize copper as an effective antimicrobial material for touch surfaces. Bodies that have recognized copper include the Ministry of Health's National Centre for Quality Assessment in Healthcare (CMJ)[24], Poland, The International WELL Building Institute™'s WELL Building Standard®[25], US, the Building Information Foundation[26], Finland, and the Indian Green Building Council[27].

Conclusion

Copper alloys are continuously active metals with broad-spectrum antimicrobial efficacy verified by extensive laboratory and clinical testing, supported by US EPA registration and recommended in several national guidelines. The unique and continuous efficacy of copper can supplement best practices to reduce the risk of infectious outbreaks thereby increasing productivity and improving mission effectiveness, especially in settings where the ability to execute well-established hygienic procedures is limited. Antimicrobial copper technology is poised for rapid implementation in military and disaster medicine with over 200 manufacturers worldwide offering a wide array of product applications.

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References

1. Global Action Plan on Antimicrobial Resistance. (2015.) World Health Organization.
2. Allegranzi, B et al. (2011). Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. Lancet. 377(9761):228-41.
3. Agudelo, JJ. (2015). Preventative medicine and its role in the Special Operation Forces medical team. Preventative Medicine. June.
4. Kramer, A et al. (2006). How long do nosocomial pathogens persist on inanimate surfaces? A systematic review. BMC Infectious Diseases. 6, 130.
5. Boyce, JM (2007). Environmental contamination makes an important contribution to hospital infection. The Journal of Hospital Infection. 65, 50–54.
6. Hospenthal, DR et al. (2011). Prevention of Combat-related Infections Guidelines P. Infection prevention and control in deployed military medical treatment facilities. J Trauma. 71(2 Suppl 2):S290-8.
7. Review on Antimicrobial Resistance. Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations. 2014.
8. Dollwet, et al. (1985). Historic uses of copper compounds in medicine. Trace Elem. Med. 2:80-87.
9. Gould, et al. (2009). The antimicrobial properties of copper surfaces against a range of clinically important pathogens. Annals of Microbiology. 59, 151–156.
10. Michels, HT and Michels, CA. (2016). Copper alloys – the new 'old' weapon in the fight against infectious disease. Current Trends in Microbiology. 10(1);23-45.
11. Bleichert, P et al. (2014). Inactivation of bacterial and viral biothreat agents on metallic copper surfaces. Biometals. 27(6):1179-89.
12. Interim Guidance for Environmental Infection Control in Hospitals for Ebola Virus. (2014). US Centers for Disease Control and Prevention. http://www.cdc.gov/vhf/ebola/healthcare-us/cleaning/hospitals.html.
13. Warnes, SL et al. (2013). Inactivation of norovirus on dry copper alloy surfaces. PLOS One. 8(9): e75017.
14. United States Environmental Protection Agency. EPA registers copper-containing alloy products https://www3.epa.gov/pesticides/chem_search/ppls/082012-00002-20130321pdf. 2008.
15. Schmidt, MG et al. (2012). Sustained reduction of microbial burden on common hospital surfaces through introduction of copper. Journal of Clinical Microbiology. 50(7), 2217–2223.
16. Salgado, C, et al. (2013). Copper surfaces reduce the rate of healthcare-acquired infections in the intensive care unit. Infection Control and Hospital Epidemiology. 34(5), 479–486.
17. Cost-Benefit Model (2012). YHEC.
18. Von Dessauer, B et al. (2016). Potential effectiveness of copper surfaces in reducing health care associated infection rates in a pediatric intensive and intermediate care unit: A nonrandomized controlled trial. American Journal of Infection Control. 44(8):133-139.
19. Hinsa-Leasure, SM et al. (2016). Copper alloy surfaces sustain terminal cleaning levels in a rural hospital. American Journal of Infection Control. doi: 10.1016/j.ajic.2016.06.033. [Epub ahead of print].
20. Karpanen, TJ, et al. (2012). The antimicrobial efficacy of copper alloy furnishing in the clinical environment: A crossover study. Infection Control and Hospital Epidemiology. 33(1):3-9.
21. Warnes, SL et al. (2012). Horizontal transfer of antibiotic resistance genes on abiotic touch surfaces: implications for public health. mBio. 3(6):e00489-12.
22. Sanders, W et al. (2005). Impact of illness and non-combat injury during operations Iraqi Freedom and Enduring Freedom (Afghanistan). Am. J. Trop. Med. Hyg. 73(4), 713–719.
23. Long-term Implications of the 2014 Future Years Defense Programme. (2013). Congressional Budget Office. November.
24. Hospital Accreditation Standard (2015). Chapter IX 'Infection Control', NCQA (CMJ).
25. WELL Building Standard®. (2016). International WELL Building Institute™.
26. Draft Indoor Hygiene Environment Guidelines (2016). Building Information Foundation, Finland.
27. Green Healthcare Facilities Rating System (2016). Indian Green Building Council.