Copper - A Promising Antimicrobial Metal Having Potential Application to Reduce Healthcare Acquired Infections

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***Abstract** : Copper (Cu) and its alloys (brasses, bronzes, cupronickel, copper-nickel-zinc, and others) are known to have inherent antimicrobial properties since the dawn of civilization. It has been demonstrated by* in vitro *studies that copper has rapid, broad spectrum antimicrobial efficacy against some of the most pathogenic species of bacteria, fungi and viruses. The antimicrobial copper surfaces have been proven to harbor 83-100% less bacterial contamination than the conventional touch surfaces of stainless steel or plastic. Molecular mechanisms liable for the antibacterial activity of copper have been a subject of intensive research. Recently, the intrinsic efficacies of copper alloy "touch surfaces" to destroy a wide range of microorganisms which can cause healthcare acquired infections (HAIs) has been reported. In the year 2008, the US Environmental Protection Agency has confirmed copper as the first solid antimicrobial disinfectant. A renewed interest has been shown by researchers in few countries to explore the mechanism of antimicrobial properties of copper and their potential uses in the hospitals in order to reduce HAIs. This review provides a deep insight on the intrinsic values of copper and its alloys as solid antimicrobial material and their applications in wards and ICUs as supportive preventive measures to reduce the HAIs.*

INTRODUCTION

The widespread uses of metals in various fields have prompted many microbiologists to examine their bactericidal property. They have been historically shown to have antimicrobial effects even prior to the discovery of antibiotics. Recently, copper and its alloys have been incorporated into coatings, table tops, surfaces, and internally placed devices to prevent bacterial colonization and biofilm formation[1]. Since 1893, the oligodynamic properties of heavy metals are well-known[2]. Among the heavy metals, the most potent antimicrobial effects are shown by ions of gold, silver, copper, lead, iron, bismuth as well as aluminium. Recent evidence has shown that some metals can work synergistically with antibiotics (Cu with polycide)[3] and are effective against multi-drug resistant pathogenic bacteria including disruption of biofilms[4,5].

Recently, copper has been found to act as a rapid-killer of microorganisms on its surfaces. With this, the rapid "contact-killing" property has been explored to use copper and its alloys in utensils and furnitures in the hospital[6]. Healthcare-acquired infections (HAIs) play a significant role in socio-economic burden and suffering of infected patients throughout the world. These infections are mostly caused by methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-resistant *Enterococcus* (VRE) and *Clostridium difficile* which can thrive for many hours or days on objects subjected to frequent hand touch every day by patients and healthcare workers within the hospital and particularly in ICU facilities[7]. Antibiotic-resistant microorganisms can spread from the patients and hospital environments to other patients, healthcare workers and to the community through discharged patients. Despite aggressive hand washing campaigns and routine cleaning with effective disinfectants, infection rates remain unacceptably high, especially in developing countries. More stringent preventive measures are needed to reduce the risk of HAIs and improve patients' safety. Apparently, 99.9% of the hospital pathogens which can survive for many days or months on plastic and stainless steel surfaces can be rapidly killed on copper surfaces[8]. Some of the European companies have started manufacturing bed railings, tables and stands coated with copper for use in ICU's. Such innovative measures have shown marked reduction of HAIs-upto 58% compared to stainless steel surfaces[9,10]. In February 2008, United States Environmental Protection Act (USEPA) has confirmed copper as the first solid antimicrobial material and permitted 479 types of copper alloys to manufacture for the uses in hospitals and other healthcare facilities[11]. Very recently, copper was found to have most effective antimicrobial touch surfaces. This evidence has enhanced the uses of copper and its alloys to combat infectious microbes in healthcare facilities and crowded communities including educational institutions.

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HISTORY

Since the 5th and 6th millennia B.C, Copper has been used by human civilizations. Copper is found naturally as a native and metallic form that does not require smelting and is considered as the first solid metal to be used. Medical applications of copper were already described in the Egyptian Smith Papyrus, written between 2600 and 2200 BC. This medical text details the application of copper to disinfect chest wounds and drinking water. Greeks, Romans and Aztecs relied on copper compounds to treat burns, headaches and ear infections. Thousands of years later (21st century), the ancient therapeutic regime is being embraced by intensive research on copper due to its increased ability to rapidly kill bacteria and other microbes. Thus uses of copper items in the hospitals will lead to marked reduction of HAIs and related complications[12]. Copper utensils, cookware and drinking water containers have been used to prevent the spread of disease since the early Roman Empire. Copper, which belongs to the small groups of metallic elements are essential to human health. Living organisms requires lower concentrations of copper as

cofactors for metalloprorteins and enzymes; however, higher concentration induces an inhibition of growth in bacteria and has a toxic effect on most organisms[13-15]. This effect may involve substitution of essential ions and blocking of functional groups in proteins, inactivation of enzymes, production of hydro-peroxide free radicals by membrane bound copper and alterations of membrane integrity and DNA denaturation leading to cell death[16-18].

Some of the hospitals in US, Canada and Europe have already installed, or planning to install copper components on "high-touch" surfaces which can be contaminated with microbes - tables, bed railings, faucet handles on sinks, door knobs, cabinet pulls, toilet levers, call buttons and IV poles. On any given day, about 1 to 25 (average 10%) patients in acute-care hospitals develop HAIs according to the Center for Disease Control and Prevention, Atlanta. In US alone, two million patients acquire HAIs annually and about one lakh of them succumb to such infections[19].

MECHANISM

Metallic copper surfaces rapidly and efficiently kill micro-organisms. Bactericidal action of Copper follows two sequential steps: In the first step, the direct interaction between the outer membrane of the micro-organisms and the copper surfaces (Cu ions) produce short circuit current in the membrane, which leads to weakening and creation of holes. In the second step due to breaching of the defense, an unopposed stream of copper ions starts entering the cells. Now the copper ions overwhelm the internal parts of the cells and obstructs cell metabolism causing DNA damage leading to cell death[20]. This type of rapid "contact killing" of bacteria and other organisms are seen less with other metal and plastic surfaces as revealed by the *in-vitro* experiments. Within two hours of contact, ten to hundred million bacteria are killed per minute and no live microorganisms are recovered from copper surfaces. Over a dozen species of bacteria, yeast and viruses have been shown to be killed on copper and its alloy surfaces (99.99%), by *in vitro* experimental studies. The efficacy of copper and the rate of microbial inactivation are dependent on many factors like temperature, wet surfaces, copper ion concentration and the type or load of microorganisms attached to metal surfaces. Under optimal conditions, survival rates of 0% have been achieved for certain non-sporulated microbes within 2 hours of contact with copper surfaces[21].

APPLICATION

Copper and its uses have become constant throughout the centuries, marking a presence in the technological revolution by humans. Due to its physical and chemical properties, copper and its derivatives have shown durability and high resistance to corrosion leading to extended functionality[22]. Copper, in very small quantities, has the power to control multiplication of a wide range of bacteria, fungi, algae and other harmful microbes. It is also known to possess antimicrobial effects in aqueous and humid-air environments and has wide applications as an effective disinfectant. Recent research revealed that copper alloys having antimicrobial properties can be used for surfaces exposed to human touch or contact with food materials .This will contribute a substantial reduction in the quantity and transmission of potential pathogens. At present, the antimicrobial uses of copper have been expanded to include fungicides, anti-fouling paints, antimicrobial medicines, oral hygiene products, hygienic medical devices, antiseptics and a host of other useful applications. The use of copper also depends on their availability, cost, feasibility, longevity and toxicity. Certain metals, such as silver, copper and its alloys are known to be far more poisonous to bacteria than other metals like stainless steel and aluminum, which qualify them to be used in mineral sanitizers for swimming pools, water-coolers, air-conditioners, geysers and spas.

The problem of HAIs is a complex one requiring a multi-disciplinary approach from healthcare workers, microbiologists, administrators and hospital designers. There is no single solution, rather a raft of measures including improved hand hygiene, wearing personal protective equipments (PPEs) by health-care workers, pre-admission screening of patients, isolation of infected patients, review and monitoring of antibiotic regimes and improvements of hand hygiene and hospital environments. In practice, about 30% of healthcare workers do not observe strict hygiene on sterile precautions including hand washing. Hence copper having potential antimicrobial surfaces can play an important role in reducing hospital environmental contamination and limiting cross-infection. This emphasizes the re-introduction of copper and its alloys into the hospital to create antimicrobial surfaces[24]. During the past 20 years, emergence of multi-drug resistance (MDR) organisms has resulted in a dramatic increase in the incidence of HAIs around the world. In addition to the threatening lives, HAIs causes a huge financial burden on a nation's healthcare system. The potential hospital pathogens settle on many types of surfaces and get colonized. If they are not cleaned properly with effective disinfectants, the hands of the hospital staffs acquire and transmit them to other patients and contaminate surfaces of many hospital utility items. Furthermore, in the era of antimicrobial resistance, only few prospective antibiotics are in the pipeline to combat MDR strains of bacteria and fungi. Well planned investigations have demonstrated the efficacy of copper and its alloys in inactivating leading hospital pathogens like MRSA, VRE, *C.difficile, P.aeruginosa*, *E. coli* O157:H7, *K.pneumonia* and *Acinetobacter* species, which are multidrug resistant and are also responsible for most of the HAIs.

RESEARCH

The study of the antimicrobial properties of metallic copper surfaces is a relatively recent development and gained momentum. The USEPA registered almost 479 different types of copper and its alloys as solid antimicrobials in 2008[17]. It is well known that hospital pathogens like *S.aureus, C.difficile* and *Acinetobacter* spp. can persist on stainless steel, plastic or wooden surfaces for many days or months[24]. Frequent and efficient cleaning of hospital environments combined with proper hand washing and wearing PPEs will markedly reduce transmission of hospital pathogens and incidences of HAIs. Even after following various preventive measures, complete eradication of HAIs appear to be impracticable. Uses of copper surfaces, with their prolonged self-sanitizing properties, can play a significant role in markedly reducing HAIs. Hospital trials are now ongoing worldwide, and the results obtained have revealed marked reduction in surface bacterial counts, indicating that copper surfaces as a potential tool along with other hygienic measures to curb the number and severity of HAIs. Casey et al., (2010) have compared bacterial contamination of a copper-coated (70% Cu) composite toilet seat, brass tap handles (60% Cu), and a brass door push plate (70% Cu) with that of equivalent items with plastic, chrome-plated, or aluminum surfaces. They reported that MRSA, VRE and *E. coli* were found only on control surfaces but not on copper surfaces. In Israel, copper oxide incorporated textiles are being tried to reduce HAIs[25]. Biocidal

copper oxide textiles are being manufactured for many hospital utility items like linen, bed sheets, pillow covers etc. By using such kind of biocidal textiles, 24% reduction of HAI's has been achieved[26].

CONCLUSION

The antimicrobial properties of copper surfaces have now been firmly established by many experimental studies in United States, Canada and Europe. Controlled hospital trials have revealed a marked reduction in bacterial counts, indicating copper surfaces as a promising additional tool alongside other hygienic measures to curb the incidences and severity of HAI's. The increased cost of copper over stainless steel and other metals can compensate more than the investment because of the expected decrease in the incidences of HAIs which need high cost for the management of infected patients. It is also worthwhile encouraging further research on anti-microbial properties of copper and its alloys in India where as in many developing countries; the incidence rate of HAIs is very high with MDR hospital pathogens. The antimicrobial properties of copper surfaces must be integrated as an additional disinfectant measures within the hospitals. Thus, incorporating copper in the hospital hygienic regime as a supportive preventive measure will significantly bring down the incidences of HAIs and in particular among patients admitted in ICUs. Such measures will markedly reduce patients suffering, hospital admission days, added management costs and on the whole will deliver a quality assured healthcare services.

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