

BACKGROUND

Silver in medicine – past, present and future

Silver has been associated with human medicine and healthcare for over two millennia. The ‘father of modern medicine,’ Hippocrates, wrote of using silver to improve wound care around 400 BC, and during the intervening years silver has featured in a wide range of writings, most of which highlight its capabilities particularly with regards to limiting inflammation and infection. The interest in silver in medicine was probably spurred by long-held knowledge that silver kept many perishable items fresher for longer periods of time – for example, silver coins were often dropped into barrels of water and milk on long journeys to slow their degradation. While it was not understood at the time, under these conditions silver ions are formed which interrupt many microbial processes associated with spoilage. It is this relatively simple piece of science which ultimately drove the medical community’s interest in silver.

‘Modern day’ medical uses of silver began at the turn of the 19th century when surgeons used silver sutures to help minimize post-operative inflammation. Later in the 1800s, silver nitrate eyedrops were introduced as an antiseptic (to reduce neonatal conjunctivitis). The following century saw World War I soldiers take silver leaf into battle to help fight infection if they were injured in the trenches, and silver was increasingly used to treat common ailments such as sore throats and tonsillitis. This increase in usage was accompanied by the identification of argyria, a rare condition associated with the gradual accumulation of silver compounds in the body and characterized by discoloration of the skin in the most extreme cases.

Alexander Fleming’s discovery of antibiotics in the late 1920s saw a reduction of interest in silver’s use in medicine for a short period, but this was reignited in the 1960s by the work of Professor Carl Moyer, who was Chairman of the Department of Surgery, Washington University, Missouri. Moyer recognized the potential of silver salts to be used in the treatment of severe burns injuries. In a paper presented at the 69th annual convention of the U.S. National Medical Association in 1964, Moyer described: “A personal experience during 25 years with applying dressings continuously wet with 0.5% silver nitrate to chronically infected open wounds and to thin split-grafts on surfaces that rejected them repeatedly, had demonstrated that silver nitrate in this concentration cleared the ulcers of organisms such as pseudomonas, staphylococci, streptococci and proteus quickly, and that small stamp-type skin grafts would take and proliferate rapidly when covered continuously with 0.5% silver nitrate.”¹

¹ C A Moyer. Some effects of 0.5 per cent silver nitrate and high humidity upon the illness associated with large burns. *J. Natl. Med. Assoc.* 1965, 57(2), 95.

Moyer published widely on his experiences with silver nitrate, which spurred further research and subsequent improvements to silver-based treatments for burns.

Soon after Moyer published his silver nitrate work, a surgeon based in New York, Charles Fox, developed silver sulfadiazine (SSD), which is a topical antibiotic formulated to contain an atom of silver in place of a hydrogen atom found in the standard antibiotic molecule (see figure 1).

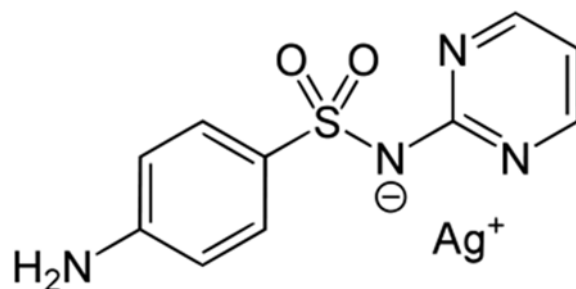


Figure 1: The chemical structure of silver sulfadiazine

Fox spent years researching SSD, and was particularly interested in its mechanism of action; that is, the specific route by which silver and the sulfadiazine combined to offer an effective and safe way to treat severe burns. In the mid-1970s, he published a paper which stated: “The efficacy of silver sulfadiazine is thought to result from its slow and steady reactions with serum and other sodium chloride-containing body fluids, which permits the slow and sustained delivery of silver ions into the wound environs.”²

Until very recently, SSD remained one of the most widely-used substances of its type in the treatment of burns. A 2016 review concluded that some newly developed non-silver burn dressings can result in faster healing than SSD, but it remains a worthy alternative if treatment with more modern dressings is not an option for any reason.³ This underlines the ongoing value of a fifty-year-old silver-based medical technology in the modern world.

SSD may have been partially usurped by more modern treatments, but the research of Fox, Moyer and their peers has undoubtedly paved the way for other silver technologies to reach market. Today, dozens of different silver-containing dressings are commonly available from specialist wound care companies around the world such as Smith & Nephew, J&J, Hartmann and B. Braun. Beyond wound care, silver is used in a range of applications to minimize or prevent infection. In 2007 the U.S. Food & Drug Administration (FDA) cleared a silver-coated breathing tube for sale. The tube, which is manufactured by C. R. Bard, helps to reduce the risk of Ventilator-Associated Pneumonia (VAP). Given that 15% of patients on ventilators develop VAP on a yearly basis, and over 25,000 of them die because of this infection, this was an important development. Catheters are often also silver-coated to help limit a variety of infections.

² Fox & Modak. Mechanism of Silver Sulfadiazine Action on Burn Wound Infections. *Antimicrob. Agents Chemother.* 1974, 5(6), 582.

³ Heyneman et al. The role of silver sulphadiazine in the conservative treatment of partial thickness burn wounds: A systematic review. *Burns*, 2016, 42(7), 1377.

But what of the future? Silver continues to be the subject of intense R&D efforts, particularly with respect to limiting and preventing infection. As mentioned above, infections associated with implantable medical devices adversely affect patient health and quality of life, and the overall healthcare costs. The emergence of antibiotic-resistant pathogens has made the search for both new antibiotics and non-antibiotic alternatives even more critical. As discussed, silver is one such alternative and significant efforts are being made to improve the actual ionization of the metal which is central to its effectiveness as a tool to tackle infection. Recent research has focused on nanomaterials, chemical and electrical activation-based strategies to enhance silver ionization.

One example of this type of research is work being undertaken at North Carolina State University under the direction of Assistant Professor Rohan Shirwaiker. His team has been developing an electrically-activated silver-based antimicrobial implant system. They have engineered the application of low intensity direct and alternating current mechanisms to a silver-titanium implant system to release silver ions that kill or neutralize bacteria on and around the implant. A small power circuitry that can be integrated into the implant design creates a potential difference between the implant's silver and titanium components, and the conductive body fluids surrounding the device result in a small electrical current via the release of antimicrobial silver ions. Such a system can be utilized in implants for prophylaxis or for treatment of device-associated infection. With the growing number of implant procedures including total hip and knee joint arthroplasties, such innovations in silver-based antimicrobial technology can have a significant impact on improving patient outcomes while reducing medical expenditure.

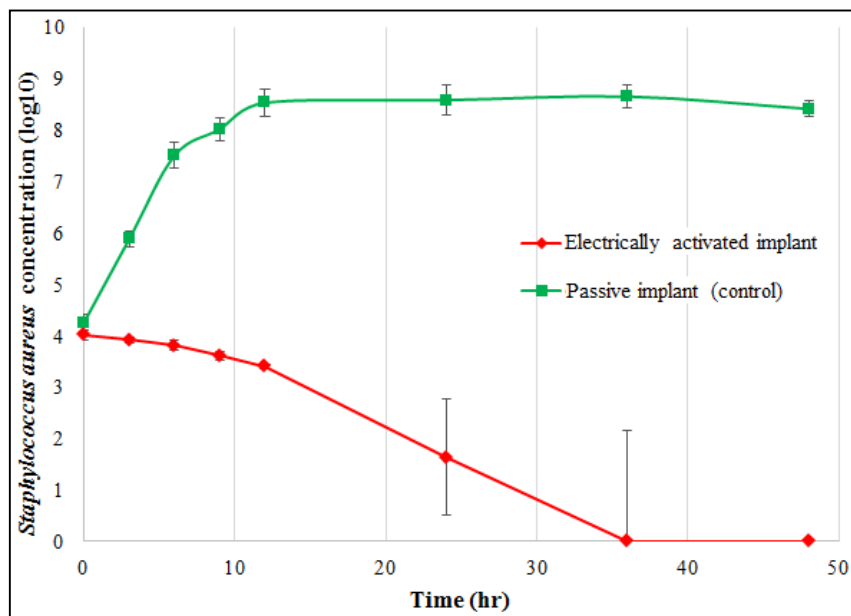


Figure 2: The effectiveness of the electrically-activated silver-titanium system in reducing the concentration of pathogenic *Staphylococcus aureus* bacteria is illustrated over a 48-hour period in comparison to a passive control device.

Silver has also been shown to directly enhance antibiotic activity against certain gram negative bacteria. In 2013 researchers from Boston published a paper⁴ which demonstrated that silver effectively sensitizes gram negative bacteria to the gram positive-specific antibiotic vancomycin, thus expanding the antibacterial spectrum of this drug. Using silver in combination with established antibiotics may offer a significant boost to the ongoing fight to identify and develop new ways to fight infection. Another promising field of research is investigating how silver nanoparticles may be developed into healthcare solutions. One such example is the efforts of researchers in Canada and Sweden who are working to stabilize and incorporate silver nanoparticles into cornea replacements and contact lenses to take advantage of their antimicrobial and anti-inflammatory properties.⁵

According to the GFMS team at Thomson Reuters, the current silver offtake from the silver antimicrobial coating market (which includes medical devices, textiles and wound dressings as key application areas) is estimated to be between 3 - 10 Moz annually. When compared to most other silver-based applications this is relatively low, however the market is expected to grow at a double-digit pace over the coming 5 - 10 years, and the evolution of new applications is likely to support this growth. Most of the major chemical companies such as BASF, PPG, DuPont and Dow all manufacture silver coatings, and have active R&D programs in place to develop the next generation of products.

Beyond coatings, the quantities of silver used in other areas of medicine such as nanotechnology and drug development are very small. However, the impact these types of applications have in society can be very significant. Recently, the World Health Organization has stated that antimicrobial resistance is putting the gains of the Millennium Development Goals at risk and endangers achievement of the Sustainable Development Goals.* As detailed above, silver potentially has a role to play in tackling both antimicrobial resistance and improving common antibacterials, but for these efforts to positively impact communities around the world applications must be cost-effective. Small quantities of silver help to enable this requirement.

⁴ Morones-Ramirez et al., Silver Enhances Antibiotic Activity Against Gram-Negative Bacteria, *Science Translational Medicine*. 2013, 5(190), 190ra81

⁵ Alarcon et al., Coloured cornea replacements with anti-infective properties: expanding the safe use of silver nanoparticles in regenerative medicine. *Nanoscale*, 2016, 8, 6484.

* The United Nation's Millennium Development Goals (UN's MDGs) are the world's time-bound and quantified targets for addressing extreme poverty in its many dimensions-income poverty, hunger, disease, lack of adequate shelter, and exclusion-while promoting gender equality, education, and environmental sustainability. The MDG era came to a conclusion in 2015, and was replaced with the UN's 2030 Agenda for Sustainable Development. The Sustainable Development Goals (SDGs) are a universal call to action to end poverty, protect the planet and ensure that all people enjoy peace and prosperity.