burns 40s (2014) s3–s8

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/burns

Silver in medicine: A brief history BC 335 to present☆

David J. Barillo [a,*], David E. Marx [b]

[a] Disaster Response/Critical Care Consultants, LLC, Mount Pleasant, SC, USA
[b] Department of Chemistry, University of Scranton, Scranton, PA, USA

ARTICLE INFO

Keywords:
Silver
Antimicrobial
Burn
Wound healing
Acute wound
Chronic wound

ABSTRACT

Silver is a naturally occurring element. Similar to other metals, the ionized form of silver (Ag^{+1}) has known antimicrobial properties. A number of wound dressings incorporating silver ion or silver compounds have recently been developed and marketed. In addition, the antimicrobial effects of silver are currently being promoted in consumer products such as clothing and household appliances.

The present use of silver in medical and consumer products has prompted concerns for potential toxicity and ecological effects, including induction of microbial resistance to antibiotics. These concerns ignore the fact that silver has been used for medicinal purposes for several thousand years. A historical review of the uses of silver in medicine is presented.

1. Introduction

Silver is a naturally occurring element that has been used for millennia for currency and jewelry; for food serving; for water purification; and, more recently, for electrical and industrial applications. Ionized silver (Ag^{+1}) has known antimicrobial properties and has been employed in burn wound care for over 200 years. More recently, the health-promoting properties of silver have been touted in a number of consumer products, including silver-containing clothing, refrigerators, and washing machines that claim to deodorize or sanitize by 'killing germs'. Several new wound dressings and gels containing silver ion or silver compounds are currently being marketed.

The rediscovery of silver for medicinal uses has prompted exaggerated claims by both proponents and detractors of silver therapy. The Internet, which was not available during the last wave of silver popularity in the 1960s, has only added to the confusion. Oral colloidal silver solutions, although outlawed by the US Food and Drug Administration, are still advocated, advertised and available over the Internet. Claims are made that the consumption of colloidal silver can treat or cure 650 different diseases or disease organisms including HIV, cancer, tuberculosis, malaria, lupus, syphilis, typhus, tetanus, bubonic plague, cholera, warts, Menieres Disease, hemorrhoids, ringworm, prostatism, acne, sinusitis, appendicitis, anthrax, Hanta, Ebola, and flesh-eating bacteria [1–4]. The lack of data supporting these claims is matched by equally unscientific concerns raised by detractors of silver therapy. The widespread adoption of new silver dressings, in their view, will cause skin to turn blue, result in universal cross-species resistance of bacteria to all known antibiotics, and irrevocably destroy ecosystems.

The truth obviously belongs somewhere in between these two extremes, and common sense has been sorely lacking. Silver is not a new product or laboratory-manufactured

☆ Presented at a symposium on "Silver in Medicine: Customs and Controversies" held in Association with the 24th Annual Southern Region Burn Conference, Winston-Salem, NC, December 2, 2011.

* Corresponding author at: Disaster Response/Critical Care Consultants, LLC, PO Box 683, Mount Pleasant, SC 29465, USA.
E-mail address: dbarillo@gmail.com (D.J. Barillo).

http://dx.doi.org/10.1016/j.burns.2014.09.009

superdisinfectant. People have used silver in various forms for at least 5000 years, including jewelry and body piercing. There is evidence that humans learned to separate silver from other metals as early as 3000 BC [5]. The use of silver for currency and food handling (drinking cups) is mentioned in the first book of the Old Testament (Genesis Chapters 13:2, 20:16, 23:15, 24:35, 24:53, 33:19, 37:28, 42:25, 42:27, and 44:2) [5,6]. While manufacturers of silver dressings claim the medical applications of silver as a new idea, in truth, silver has been used for medicinal purposes for thousands of years. In this article, the history of the medicinal uses of silver is reviewed.

2. Review

From the authors standpoint, the history of silver in medicine may be conveniently divided into the eras of ancient history; the 1800s and Germ Theory of disease; the silver renaissance of the 1960s; the second generation of silver dressings in the late 20th century; and current uses.

Prior to the establishment of the Germ Theory of disease, the use of silver for medicinal purposes was based on folklore or tradition. Probably the earliest medical use of silver was for water disinfection and storage [7]. Alexander the Great (335 BC) stored and drank water in silver vessels when going on campaigns [7–10]. The Greeks and Romans also stored water in silver vessels to keep it fresh. Ancient Mediterranean and Asiatic cultures used silver flasks and storage containers to prevent spoilage of liquids, and placed silver foil into wounds to prevent infection [11]. The Romans included silver in their official book of medicines and were known to have used silver nitrate [8]. Ambrose Pare (1510–1590) was a pioneer of battlefield surgery and served as royal surgeon to Kings Henry II, Francis II, Charles IX and Henry III. Among other innovations, he championed the use of silver clips for facial reconstruction [12].

The Germ Theory of disease postulated that microorganisms were responsible for certain diseases. Evidence to support this theory came from Semmelweis in 1847 (hand washing), John Snow in 1854 (epidemiology of a cholera outbreak), Davaine in 1865 (identification of anthrax bacteria in blood), Louis Pasteur in 1880 (isolation and culture of chicken cholera bacteria), Robert Koch in 1876 (isolation of *Bacillus anthracis* and Koch's Postulates; and others [13]. The idea that microbes could cause disease and the fact that silver ion had strong antimicrobial properties provided a rational basis for the medicinal uses of silver that were already in place.

On the other side of the ocean, silver was finding niche medical applications. Americans traveling west during the 1880s placed silver coins in water barrels because this practice was known to retard the growth of bacteria and algae [14,15]. Perhaps the most unique application, however, was the use of a silver plate for a cranioplasty performed by Dr Georgia Arbuckle Fix [16].

Dr. Fix was the only women in the founding class of eight students at the College of Medicine of Omaha in 1881 [17]. Following graduation, she started a practice in western Nebraska in 1886, where she was the only physician for a 75-mile radius [17]. In 1890, she was called to attend on a man with an open skull injury resulting from a farming accident [16]. She successfully closed the skull defect with a plate created from a silver coin, which, according to legend, she hammered into a thin sheet using a fencing hammer and piece of rail iron.

In the 1880s, the German obstetrician Karl Crede in found that dilute solutions of silver nitrate reduced the incidence of neonatal eye infections from 10.8% to under 2% [12]. The application of silver nitrate solution to the eyes of newborns to prevent ophthalmia neonatorium became mandatory by state law in most United States jurisdictions by the early 1900s. In the late 1970s both the US Centers for Disease Control (CDC) and the American Academy of Pediatrics still advocated silver nitrate as one of three antibiotic choices (erythromycin, tetracycline or silver nitrate) for this indication. Erythromycin 0.5% ointment is now the only regimen recommended by CDC, as the other two eye preparations are no longer available [18].

William Halstead, MD became the first Chief of Surgery at the Johns Hopkins Hospital in 1889. In this capacity, he established the first surgical residency program in the United States. Halstead advanced the field of wound healing, and was an advocate of careful hemostasis, aseptic technique, meticulous anatomic dissection and tension-free closure. Among his other surgical innovations, Halstead employed silver wire suture for hernia repair and found silver foil an effective means of controlling postoperative wound infections [12,19].

Silver in its numerous forms has been used for over 200 years in the treatment of burn injury [15,20] and silver nitrate solutions in 5% and 10% concentrations were used as caustics or escharotics in the early 20th century [21]. The true renaissance of silver in medicine, however, occurred in the 1960s, when silver compounds revolutionized burn wound care and then found application in manned space flight.

In 1964, the value of mafenide acetate (Sulfamylon®) as a topical burn treatment was established in human clinical trials [21]. In the following year Moyer et al. pioneered the use of 0.5% silver nitrate solution as a topical therapy for burn patients [21,22]. His work was influenced by the experiences of one of his co-authors, who had been using topical silver nitrate solutions as an adjunct for the management of necrotizing fasciitis since 1941 [21,22]. The original article described a dressing methodology, and included a recommendation that burn units be constructed of black floors and walls because of the dark staining that the use of silver nitrate produced [21,22]. In the initial 7 months of use, there was no new emergence of bacterial resistance noted in over 1300 wound cultures [21,22].

With the successes of sulfamylon and silver nitrate demonstrated, the next logical step was a combination of the two drug classes. Dr. Charles Fox, working at Columbia University in New York had previously studied soluble sulfonamides for burn wound care. He mixed silver nitrate with a weakly acidic sulfadiazine to create silver-sulfadiazene [21]. His initial report on silver sulfadiazine, published in 1968 described success in a mouse model followed by ongoing human studies [23]. The mouse model utilized a scald burn seeded with *Pseudomonas aeruginosa* and had an expected mortality of over 80%. The once-daily application of silver sulfadiazine decreased mortality to 'between 5% and 20% in 8 days or longer in numerous experiments involving approximately 1280 mice' [23]. Silver-sulfadiazene was also applied to

16 human patients with burns between 20% and 85% body surface area as part of an ongoing study [23], however, detailed results were not reported. A second paper by describing use of silver sulfadiazine on 24 burn patients treated in New York City and 33 patients treated at the Can Tho Provincial Hospital, Republic of Vietnam was published in 1969 [24]. Fox and Modak further investigated the mechanism of action of silver-sulfadiazene and found that silver, but not sulfadiazine was bound by bacteria [25]. They postulated that the combination of both drugs, in the presence of serum and sodium containing body fluids, allowed slow and sustained release of silver ion [25]. Silver sulfadiazine is sparingly soluble in water but readily ionizes in body fluids to release ionic silver.

In addition to silver, rare-earth elements are also known to have antimicrobial activity in vitro [26]. In 1977, Fox and colleagues evaluated the combination of cerium salts added to silver sulfadiazine and found better suppression of wound bacterial growth [26]. This was later developed commercially as Flammacerium®, a combination of 1% silver sulfadiazene and 2.2% cerium nitrate. In addition to antimicrobial effect, the cerium ion is claimed to reduce inflammatory changes and reduce mortality [12,27]. Flammacerium® is widely used in Europe but is not approved by the U.S Food and Drug Administration for use in the United States.

Despite the availability of newer topical antimicrobials, both 0.5% silver nitrate solution and 1% silver sulfadiazine cream continue to be used in contemporary burn care [21]. Silver nitrate at 0.5% is highly effective against *P. aeruginosa* and may to be superior to chlorhedixine against more resistant strains of *Streptococcus pyogenes* and *Staphylococcus aureus* [12].

At the same time that silver nitrate and silver sulfadiazine were being developed for burn care, the National Aeronautics and Space Administration was studying the use of silver for extra-terrestrial applications [28,29]. In the midst of the Cold War, the launch of the Soviet satellite Sputnik in October, 1957 started a race between the Soviet Union and the United States to land humans on the moon. The technologic challenges involved included life-support systems for astronauts living for extended periods in space. Water is the most critical life-support element aboard spacecraft [30]. Birmele et al. note that the per-capita water requirements (4.5 L/day as either liquid or water in food) represents twice the mass required for food and oxygen combined [30]. Bacterial contamination of drinking water would pose a serious health risk, and one can imagine the problems of gastroenteritis, diarrhea and vomiting in a zero-gravity environment.

The original United States space program consisted of Mercury, Gemini and Apollo missions. Mercury missions (1959–1963) were a series of six manned flights of 15 min–34 h duration, each carrying one astronaut. The water supply consisted of one bladder filled with tap water before launch. The purity of the water depended on the chlorine added to the public water system in Cocoa Beach, Florida, where the flights originated [31]. The Gemini program (1965–1966) had 10 manned flights, each carrying two astronauts in low earth orbit for durations of 5 h to 14 days. Gemini spacecraft carried 7.3 l water bladders, with chlorine added prior to launch [31]. The Apollo program (1966–1972) consisted of 11 manned missions that included six moon landings. Because Apollo spacecraft were designed to carry three astronauts for long missions, water requirements were higher. A NASA-funded study in the mid 1960s investigated the use of silver for control of microbial contamination in water supply subsystems and concluded that a silver-ion concentration of 50 parts-per-billion was sufficient for water disinfection [28]. A simple electrode device was designed to pass a weak direct current thru a silver anode to add ionic silver to water [28], followed by development of a self-contained flight-rated water sterilization cell measuring 2.5×4 inches and weighing 0.6 pounds, including the battery [29]. The final Apollo spacecraft design consisted of three separate modules (service, command and lunar-landing) and used combinations of chlorine, iodine and ionic silver to purify water in different subsystems [7,31].

Soviet spacecraft also utilized silver for water purification. The Vostok, Voskhod and Soyuz series of spacecraft added a silver preparation to the (boiled) drinking water supply before launch [31]. The Salyut and Mir spacecraft used ionic silver at 0.2 mg/L to purify water [31]. Ionic silver was also used for purifying and storing water on the US Space Shuttle fleet, and is currently used on the International Space Station [31].

NASA has licensed their water purification metal ion technology for commercial development, and water filters based on silver-ion, copper-ion or combined technologies are now used to disinfect water in swimming pools, spas, decorative fountains, and animal habitats for dolphins, sea lions and sea turtles. Copper/silver filters are also used in hospital water supplies to prevent Legionella infection [12,32].

The last two decades of the 20th century saw the development of silver-based textiles for burn and wound dressings. A number of centers investigated the antimicrobial properties of silver-coated nylon, a fabric which was originally developed as a flexible electrical shield or radar reflector [33,34]. Deitch et al. examined the antimicrobial properties of silver-nylon in vitro and showed effectiveness against *P. aeruginosa*, *S. aureus* and *Candida albicans* [33]. Spadaro et al. demonstrated that weak electric current delivered thru silver electrodes was ‘extremely bacteriostatic’ against agar plate bacterial cultures of *S. aureus*, *Escherichia coli*, *Proteus vulgaris* and *P. Aeruginosa* [35]. The US Army Institute of Surgical Research (US Army Burn Center) extensively researched the combined effects of silver-nylon fabric and weak electric (direct) current on wound healing and published at least 13 studies between 1988 and 2005 [34,36–47]. A variety of animal models of partial and full-thickness burns, infected burn wounds, excised burn wounds, donor sites, and skin flaps evaluated the utility of silver-nylon with and without direct current on wound healing, microcirculation, wound edema, plasma protein extravasation, and wound closure using split thickness skin grafts, autograft/allograft composite grafts, and dermal replacement/meshed autograft techniques [34,36–47]. Two human trials were carried out, including one study of donor site healing [47]. Independently, Huckfeld et al. demonstrated that weak direct current applied to silver-nylon dressings could accelerate wound closure after split thickness skin grafting in humans [48].

In the 21st century, the medicinal use of silver extends beyond burn care or wound dressings. Nosocomial infection, particularly urinary tract infections and catheter-associated bloodstream infections are common in hospitalized patients, and increase patient morbidity, mortality, hospital length of stay and healthcare costs [49]. Central venous lines and foley catheters are prone to the development of biofilms, which are densely adherent polysaccharide structures that shelter bacteria [50]. Biofilms change bacteria from a free swimming state to a sessile state, where they are sheltered from antimicrobial drugs [50]. Biofilm production and microorganism adhesion can be reduced by coating catheters with antiseptics or antimicrobial agents [49]. Central venous and indwelling bladder catheters treated with silver metal, silver oxide, silver sulfadiazine, platinum, chlorhexidine, rifampin and tetracyclines have been evaluated in vitro and in vivo in animal and human studies [12,49]. In general, in vitro results are superior to those seen in animal and human models [12,51,52], however, chlorhexidine (CHG) and silver sulfadiazine (SSD) have synergistic antibacterial action, and central venous catheters coated with chlorhexidine/silver sulfadiazine have proven effective in clinical trials [49,53]. Maki et al. [53] prospectively studied 158 patients (403 catheters) randomized to receive either a standard CVP catheter or an antibiotic coated (CHG/SSD) catheter at the University of Wisconsin Hospital. Antibiotic catheters had a fivefold decrease in bloodstream infection rates ($p = 0.03$) and were significantly less likely to be colonized at the time of removal ($p = 0.005$) [53]. Borschel et al. evaluated central venous catheters coated with CHG/SSD in a pretest–posttest cohort study at the University of Michigan [54]. A 35% relative risk reduction in the catheter-related bloodstream infection rate was seen after introduction of the coated catheters, with an associated cost reduction of $100,000 annually [54]. Antibiotic-coated central venous catheter use was also associated with a 22% reduction in the use of vancomycin, presumably prescribed for Gram positive bloodstream infections [54].

Silver-coated endotracheal tubes designed to lower the risk of ventilator-associated pneumonia have shown efficacy in both animal and human studies [55,56]. The NASCENT Randomized Trial prospectively evaluated 2003 patients requiring endotracheal intubation as a multicenter study involving 54 centers. Patients were randomized to receive either silver-coated or conventional endotracheal tubes. Patients receiving a silver-coated endotracheal tube had a statistically significant reduction in the incidence of ventilator associated pneumonia (VAP) compared to those intubated with conventional tubes [55]. Silver-coated endotracheal tubes also delayed time to onset of VAP compared to uncoated controls [55].

Urinary tract infections are the most common hospital acquired infections, comprising approximately 40% of all nosocomial infections [50]. Up to 25% of hospitalized patients have urinary catheters placed during their hospital stay [50], and more than 80% of hospital urinary tract infections are associated with the use of a urinary catheter [50]. A urinary tract infection in a patient with an indwelling catheter is termed a catheter-associated urinary tract infection (CAUTI), which, by definition, becomes a complex UTI. Biofilm formation commonly occurs on urinary catheters, making treatment difficult. In addition to patient discomfort and morbidity, catheter-associated urinary tract infections are a financial concern for hospitals, in that the US Centers for Medicare and Medicaid Services (CMS) refuses to pay additional reimbursement for this condition.

Silver-coated urinary catheters have been commercially available for over 20 years [57]. Multiple publications suggest that silver-alloy coated catheters are effective in reducing CAUTI rates by up to 45% [50,57]. Silver-oxide coated catheters do not work as well as silver-alloy catheters [50,57]. Parker et al. in a evidence-based literature review, recommend the use of silver-alloy coated catheters in patients requiring short-term (up to 2 weeks) bladder catheterization as a method to reduce bacteria and the risk of CAUTI [50].

While not strictly a medical application, the antimicrobial effects of silver ion are now finding application in home appliances. Samsung Electronics produces refrigerators using silver trays, and washing machines containing nanosilver particles that generate silver ions. The claimed benefit is to deodorize and sanitize clothes against germs as well as to keep the internal parts of the machine germ-free [7]. LG Electronics markets refrigerators using a nanosilver compound for antimicrobial properties [7]. Hitachi markets a silver-containing dishwasher [8].

Finally, the original use of silver in medicine (water storage and purification) continues to find utility. In 2009, Shrestha et al. [58] published a study examining the ability of common household metal pots constructed of silver, copper or brass to kill enteric pathogens isolated from drinking water in Nepal. Isolates of *E. coli*, multidrug resistant *E. coli*, *Salmonella paratyphi*, *Shigella* species, and *Vibrio cholerae* were placed in metal pots and assayed at 4 h intervals. *Salmonella* and *E. coli* were completely inhibited by 24 h in all pots tested and *Shigella* were completely inhibited at 24 h by copper and 48 h by brass and silver vessels [58]. Multidrug resistant *E. coli* was completely inhibited by silver and brass at 24 h and by copper at 48 h [58]. The use of silver to purify water has thus traveled over 23 centuries from Macedon to Nepal, traversing the moon along the way.

3. Discussion

The medicinal use of silver is not a new idea. Silver ion has been employed as an antimicrobial for several millennia, the discovery of this indication preceding the discovery of microbes or the Germ Theory of Disease by several centuries. True allergy is rare, and resistance has never become clinically significant. Silver is not an eye or skin irritant or skin sensitizer, human carcinogen or mutagen [4,59]. Adverse effects such as argyria are almost always related to inappropriate use, usually from oral ingestion of colloidal silver solutions. There is no accepted medical indication for the use of oral colloidal silver. Ionic silver, on the other hand, is routinely added to drinking water for disinfectant purposes without any harm to health.

When the safety of silver is debated, common sense must prevail. There are few, if any compounds in contemporary medical practice with as lengthy a history as silver.

Conflict of interest statement

The authors have received research support or consulting fees from Argentum Medical, LLC and are members of the Argentum Medical Advisory Board.

REFERENCES

[1] US Department of Health and Human Services, Food Drug Administration. 21 CFR Part 310 – Over-the-counter drug products containing colloidal silver ingredients or silver salts: Proposed Rule. Federal Register Volume 61; October 15, 1996, 200 pages, 53685–53688.

[2] Wadhera A, Fung M. Systemic argyria associated with ingestion of colloidal silver. Dermatol Online J 2005;11(1):12.

[3] US Department of Health and Human Services, Food Drug Administration. 21 CFR Part 310. Over-the-counter drug products containing colloidal silver ingredients or silver salts: final rule. Federal Register V64; August 17, 1999, 158 pages, 44653–44658.

[4] Marx DE, Barillo DJ. Silver in medicine: the basic science. Burns 2014;40:s9–18.

[5] Weast RC. Handbook of chemistry and physics. 51st ed. Cleveland: The Chemical Rubber Co.; 1970: B29–30.

[6] St. Joseph Edition of the New American Bible. New York: Catholic Book Publishing Co.; 1992.

[7] Melaiye A, Youngs WJ. Silver and its application as an antimicrobial agent. Expert Opin Ther Pat 2005;15(2):125–30.

[8] Silver S, Phung LT, Silver G. Silver as biocides in burn and wound dressings and bacterial resistance to silver compounds. J Ind Microbiol Biotechnol 2006;33(7):627–34.

[9] Russell AD, Hugo WB. Antimicrobial activity and action of silver. Biol Met 1994;31:351–70.

[10] White RJ. An historical overview on the use of silver in modern wound management. J Br J Nurs 2002;15(10):3–8.

[11] Addicks L. Silver in industry. New York: Reinhold Publishing Company; 1940.

[12] Lansdown. ABG: silver in health care: antimicrobial effects and safety in use. Curr Prob Dermatol 2006;33: 17–34.

[13] Kruger RG, Gillham NW, Coggin JH. Introduction to microbiology. New York: Macmillan Co.; 1973.

[14] Hermans MH. Silver-containing dressings and the need for evidence. AJN 2006;106(12):60–8.

[15] Klasen HJ. Historical review of the use of silver in the treatment of burns. Burns 2000;26:117–30.

[16] Rollings NB. Georgia Arbuckle Fix: silver dollar surgeon. Am Hist Illus 1985;20(5):20–1.

[17] Enss C. The doctor wore petticoats: women physicians of the old west. Helena, MT: Globe Pequot Press; 2006.

[18] US Department of Health and Human Services Centers for Disease Control and Prevention. Morbidity and Mortality Weekly Report – Sexually transmitted diseases treatment guidelines, 2010. Volume 59 # RR-12; December 17, 2010.

[19] Halstead WS. The operative treatment of hernia. Am J Med Sci 1895;110:13–7.

[20] Gravante G, Caruso R, Sorge R, Nicoli F, Gentile P, Cervelli V. Nanocrystalline silver. A systematic review of randomized trials conducted on burned patients and an evidence-based assessment of potential advantages over older silver formulations. Ann Plast Surg 2009;63(2):201–5.

[21] Barillo DJ. Topical antimicrobials in burn wound care: a recent history. Wounds 2008;20(7):192–8.

[22] Moyer CA, Brentario L, Gravens DL, Margraf HW, Monafo Jr WW. Treatment of large human burns with 0.5% silver nitrate solution. Arch Surg 1965;90:812–67.

[23] Fox Jr CL. Silver sulfadiazine – a new topical therapy for Pseudomonas in burns. Therapy of Pseudomonas infections in burns. Arch Surg 1968;96(2):184–8.

[24] Stanford W, Rappole BW, Fox Jr CL. Clinical experience with silver sulfadiazine, a new topical agent for control of pseudomonas infection in burn patients. J Trauma 1969;9(5):377–88.

[25] Fox CL, Modak SM. Mechanism of silver sulfadiazine action on burn wound infections. Antimicrob Agents Chemother 1974;5(6):582–8.

[26] Fox CL, Mofano WW, Ayvazian VH, Skinner AM, Modak S, Stanford J, et al. Topical chemotherapy for burns using cerium salts and silver sulfadiazine. Surg Gynecol Obstet 1977;144:668–72.

[27] Lansdown ABG, Myers S, Clarke J, O'Sullivan P. A reappraisal of the role of cerium in burn wound management. J Wound Care 2003;12:113–8.

[28] Shankle JD, Lechtman MD. Final report – investigation of silver for control of microbial contamination in a water supply subsystem. In: Apollo Applications Program. Prepared for Manned Spacecraft Center, National Aeronautics and Space Administration; 1966. NASA Accession # X67-37915.

[29] Albright CF, Nacham R, Lechtman MD. Development of an electrolytic silver ion generator for water sterilization in Apollo spacecraft water systems. Final Report 67-2158. NASA Accession # N69-14494; June, 1967.

[30] Birmele MN, McCoy LE, Roberts MS. Disinfection of spacecraft potable water systems by passivation with ionic silver. American institute of Aeronautics and Astronautics; 2011, http://ntrs.nasa.gov/archive/nasa/casi.ntrs.nasa.gov/20110014435.pdf.

[31] Daues K. A history of spacecraft environmental control and life support systems. NASA Johnson Space Center; January, 2006.

[32] Lansdown ABG, Silver I. Antibacterial properties and mechanism of action. J Wound Care 2002;11:125–30.

[33] Deitch EA, Marino AA, Gillespie TE, Albright JA. Silver-nylon: a new antimicrobial agent. Antimicrob Agents Chemother 1983;23(3):356–9.

[34] Chu CS, Matylevich NP, McManus AT, Pruitt Jr BA, Goodwin CW. Direct current reduces accumulation of Evans Blue albumin in full thickness burns. J Trauma 1999;47(2):294–9.

[35] Spadaro JA, Berger TJ, Barranco SD, Chapin SE, Becker RO. Antibacterial effects of silver electrodes with weak direct current. Antimicrob Agents Chemother 1974;6(5):637–42.

[36] Chu CS, McManus AT, Pruitt Jr BA, Mason Jr AD. Therapeutic effects of silver nylon dressings with weak current on *Pseudomonas aeruginosa*-infected burn wounds. J Trauma 1988;28:1488–92.

[37] Chu CS, McManus AT, Okerberg CV, Mason Jr AD, Pruitt Jr BA. Weak direct current accelerates split-thickness graft healing on tangentially excised second degree burns. J Burn Care Rehabil 1991;12:285–93.

[38] Chu CS, Matylevich NP, McManus AT, Mason Jr AD, Pruitt Jr BA. Direct current reduces wound edema after full thickness burn injury in rats. J Trauma 1996;40(5):738–42.

[39] Matylevich NP, Chu CS, McManus AT, Mason Jr AD, Pruitt Jr BA. Direct current reduces plasma protein extravasation after partial thickness burn injury in rats. J Trauma 1996;41(3):424–9.

[40] Chu CS, Matylevich NP, McManus AT, Pruitt Jr BA, Goodwin CW. Optimized mesh expansion of composite skin grafts in rats treated with direct current. J Trauma 1997;43(5):804–12.

[41] Chu CS, McManus AT, Mason Jr AD, Okerberg CV, Pruitt Jr BA. Multiple graft harvestings from deep partial thickness scald wounds healed under the influence of weak direct current. J Trauma 1990;30(8):1044–50.

[42] Chu CS, McManus AT, Matylevich NP, Mason Jr AD, Pruitt Jr BA. Enhanced survival of autoepidermal–allodermal composite grafts in allosensitized animals by use of silver-nylon dressings and direct current. J Trauma 1995;39(2):273–8.

[43] Chu CS, Matylevich NP, McManus AT, Goodwin CW, Pruitt Jr BA. Accelerated healing with a mesh autograft/allodermal composite skin graft treated with silver nylon

dressings with and without direct current in rats. J Trauma 2000;49(1):115–25.
[44] Chu CS, McManus AT, Matylevich NP, Goodwin CW, Pruitt Jr BA. Integra as a dermal replacement in a meshed composite skin graft in a rat model: a one-step operative procedure. J Trauma 2002;52:122–9.
[45] Chu CS, McManus AT, Mason AD, Pruitt Jr BA. Topical silver treatment after escharectomy of infected full thickness burn wounds in rats. J Trauma 2005;58:1040–6.
[46] Barillo DJ, McManus AT, Chu CS, Pruitt Jr BA. Effect of silver-nylon dressings and weak direct current on skin microcirculation. Shock 1995;3(Suppl.):42.
[47] Shirani KZ, McManus AT, Robertson F, Walton G, Barillo DJ, McManus WF, et al. Silver-nylon dressings promote painless healing. Proc Am Burn Assoc 1993;25:66.
[48] Huckfield R, Flick AB, Mikkelson D, Lowe C, Finley PJ. Wound closure after split thickness grafting is accelerated with the use of continuous direct anodal microcurrent applied to silver nylon wound contact dressings. J Burn Care Res 2007;28:703–7.
[49] Frasca D, Dahyot-Fizelier C, Mimoz O. Prevention of central venous catheter-related infection in the intensive care unit. Crit Care 2010;14:212–9.
[50] Parker D, Callan L, Harwood J, Thompson DL, Wilde M, Gray M. Nursing interventions to reduce the risk of catheter-associated urinary tract infection. Part 1: catheter selection. J Wound Ostomy Cont Nurs 2009;36(1):23–34.
[51] Darouiche RO. Anti-infective efficacy of silver-coated medical prostheses. Clin Inf Dis 1999;29:1371–7.
[52] Saint S, Veenstra RH, Sullivan SD. The potential clinical and economic benefits of silver alloy urinary catheters in preventing urinary tract infection. Arch Intern Med 2000;160:2670–3.
[53] Maki DG, Stolz SM, Wheeler S, Mermel LA. Prevention of central venous catheter-related bloodstream infection by use of an antiseptic-impregnated catheter – a randomized controlled trial. Ann Intern Med 1997; 127:257–66.
[54] Borschel DM, Chenoweth CE, Kaufman SR, Vander Hyde K, VanDerElzen KA, Raghunathan TE, et al. Are antiseptic-coated central venous catheters effective in a real-world setting? Am J Infect Control 2006;34:388–93.
[55] Kollef MH, Afessa B, Anzueto A, Veremakis C, Kerr KM, Margolis BD, et al. Silver-coated endotracheal tubes and incidence of ventilator-associated pneumonia. The NASCENT Randomized Trial. JAMA 2008;300(7): 805–13.
[56] Rello J, Afessa B, Anzueto A, Arroliga AC, Olson ME, Restrepo MI, et al. Activity of a silver-coated endotracheal tube in preclinical models of ventilator-associated pneumonia and a study after extubation. Crit Care Med 2010;38(4):1135–40.
[57] Denstedt JD, Cadieux PA. Eliminating biofilm from ureteral stents: the holy grail. Curr Opin Urol 2009;19: 205–10.
[58] Shrestha R, Joshi DR, Gopali J, Piya S. Oligodynamic action of silver, copper and brass on enteric bacteria isolated from water of Kathmandu Valley. Nepal J Sci Technol 2009;10:189–93.
[59] US Environmental Protection Agency: EPA 738-F-93-005. R.E.D. Facts: Silver. Washington, DC: EPA Office of Prevention, Pesticides and Toxic Substances; 1993.